Nutritional Growth Retardation: Experimental Studies with Special Reference to Calcium

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A universal observation in vertebrate biology is that a low plane of nutrition in early life slows the rate of growth and, if it persists may result in small stature at maturity. The retardation in length of long bones can be attributed directly to diminished growth of epiphyseal cartilage, which becomes narrow with a decreased rate of chondrocyte proliferation (1-3). The synthesis of bone matrix collagen in particular appears to be depressed (4,5), although the incorporation of bone mineral is apparently unaffected (2-4) and resorption of bone mineral is similarly unimpaired (3,4). If the undernourished animals are subsequently rehabilitated, bone growth returns to normal, although in pigs, growth ceases at the same chronological age as in those animals that were adequately fed (6), so that the adults are stunted. Although bone structure is restored on rehabilitation, teeth may remain small, with permanent abnormalities in their fine structure (7). It has also been found that bones of pigs growing after protein deficiency may become bent and twisted, whereas such deformities are infrequent in recovery from deficiency of calories alone (8).

Young rats with maximum growth rate have been compared with those having a marginal degree of undernutrition by the simple technique of raising litters with large or small numbers of rat pups (9). Here the slower growth was associated with skeletons that were not only smaller but had poor structural development.

These changes in hard tissues are part of the general response of the whole body to gross nutritional deficiency and are inevitable consequences of cell malfunction when cells are starved of the molecules required for tissue growth. How much more likely are growth failure and abnormal development of bone with selective deficiency of the specific mineral elements required for bone structure itself? Experimental studies bearing on this question are reviewed in this chapter.

CALCIUM HOMEOSTASIS

One of the unifying characteristics among vertebrates is the presence in all of sensitive control mechanisms for maintaining a constant extracellular ionized cal-

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cium (Ca$^{2+}$) concentration (10). Although the mechanisms differ between aquatic and land vertebrates, in every species examined Ca$^{2+}$ concentration in serum is kept close to 1.25 mM. Any tendency for this level to rise causes excretory pathways to remove the excess. On the other hand, with a tendency for Ca$^{2+}$ concentration to decline, an adaptive capacity develops for enhanced absorption of calcium from the environment (diet), and sometimes internal calcium stores are mobilized as well. The sensitivity of nerve, muscle, and endocrine cells in particular to changes in extracellular Ca$^{2+}$ concentration requires that that concentration be kept constant.

When there is a deficiency of calcium during growth, competition exists between the calcium that is required for incorporation into bone and that required to maintain the extracellular ion pool. The importance of the latter for the function of all cells gives it precedence over bone mineralization. Hence, with a prolonged inadequate supply of calcium, either bone would be undermineralized or its growth would have to cease.

However, just as constancy of extracellular Ca$^{2+}$ concentration is important for cells in general, so also is it important for the bone-forming role of chondrocytes and osteoblasts. Deficiency of dietary calcium would not only starve bone of its substrate for growth but could lead to defective function of bone cells.

Thus, in principle, calcium deficiency could provoke two alternative responses:

1. Growth continues at a rate commensurate with the supply of other nutrients (energy and protein), but the bone is undermineralized with a defective structure.
2. Growth is retarded to a rate at which the limited calcium supply allows normally structured and mineralized (but smaller) bone to be formed.

EXPERIMENTAL INVESTIGATION OF THE CONSEQUENCES OF CALCIUM DEFICIENCY ON BONE GROWTH

Despite a large body of research accumulated over many years on the effect of variable calcium supply on bone growth in laboratory and other animals, very little of this has related the actual supply of calcium to the rate of growth. Most studies have created severe deficiency, suddenly imposed, and usually observed for a relatively short time of a few days or a few weeks. The long-term consequences of continuous deprivation of calcium during the total period of growth have seldom been investigated. Many of the published experiments have been concerned with the effect of calcium deficiency on the metabolism and function of vitamin D. Many were aimed at devising an experimental, diet-induced osteoporosis model to compare with the widespread osteoporosis of postmenopausal women (e.g., 11).

Any significance of a lack of calcium has been overshadowed by the observation that phosphorus deficiency has a much more striking effect on growth and development than does calcium deficiency. The importance of calcium supply is often assessed in relation to the dietary calcium : phosphorus ratio. For most species,
variation in the calcium : phosphorus ratio away from an optimum value leads to impaired growth and development of bones. However, because the influence of phosphorus on variable bone growth is more apparent than that of calcium, any specific effect of calcium may have been neglected. For growing children, phosphorus deficiency has not been identified as a practical problem, yet calcium intake well below recommended values is commonly found in malnourished communities.

Farm animal studies of undernutrition are often concerned with the efficiency of production rather than long-term consequences for adult life. Hence, the effect of calcium and phosphorus supply on food intake and the efficiency of food conversion are of prime importance (12). An undergrown farm animal is a poor economic unit, so interest lies in the optimization of diet and growth rate, and there is little incentive to follow the long-term consequences of malnourished curiosities, which predictably have low economic prospects.

Studies in Man

Poor growth in children is a characteristic of chronic illness, particularly in renal failure and inflammatory bowel disease. The etiology of stunting in renal disease is complex and multifactorial (13), and undernutrition is seldom the major cause of the problem. On the other hand, growth retardation in celiac disease can be more directly linked to intestinal malabsorption in the face of an apparently adequate diet. As Samuel Gee wrote in 1888 (14): "while the disease is active, children cease to grow; even when it tends slowly to recovery, they are left frail and stunted." Nevertheless, although calcium absorption can be markedly diminished with the abnormal intestinal mucosa, the bone of the affected children appears to be normally mineralized for their height and weight (15). Furthermore, analysis of all the many factors influencing growth in chronic malabsorption suggests that insufficiency of energy is of greater significance than protein, vitamin, or mineral deficiencies (16). Therefore, where there is an inadequate supply of several nutrients, it does appear that lack of calcium is not the limiting factor for growth.

One further complication in attempting to assess the role of nutrients on bone growth and mineralization is that nutritional and endocrine factors are not the only ones involved. Repetitive exercise and physical activity also enhance the density of bone (17). The influence of mineral nutrient supply on the long-term growth of bone in humans is not readily apparent from investigations so far.

Studies in Animals

Scattered in the earlier literature are reports of experiments in which dietary calcium was restricted for growing rats (18), puppies (19), and kittens (20). In each instance, the efficiency of retaining dietary calcium was much greater on a low-calcium diet, but bone abnormalities were surprisingly unspectacular. However,
severe calcium deficiency, with a dietary content of only 0.03 to 0.05% dry weight, did induce gross skeletal retardation in rats (18) and kittens (20,21), and marked osteopenia was observed (21).

The effect of calcium deprivation is clearly different between adult and growing animals. Adult rats fed a low-calcium, high-phosphorus meat diet survived with little or no sign of abnormality. On such a diet, weanling rats stopped growing after a few weeks and then died (22). The skeletons of these young rats with calcium deficiency had become severely demineralized and often showed fractures.

If, however, the diet were supplemented with 0.2% calcium for 14 days, the rats grew at almost the normal rate, and their bones were of similar size and shape to those given a continuous and adequate supply of calcium. Yet the bone mineral content of these calcium-deprived rats was only about 50% that of the controls (22). Only when the bone ash had decreased to 30% or less of the control values did the rate of growth decline. In the rat, therefore, it appears that growth takes precedence over the mineralization of bone and that bone continues to grow even though the incorporation of mineral is low.

Such a study relating calcium supply and bone mineralization to growth has apparently not yet been done in man. Nevertheless, the dimensions, composition, and density of bones from communities with a low calcium intake are reported to be similar to those where calcium supply is deemed to be adequate (23). Furthermore, such diets were not associated with the development of osteoporosis.

**ADAPTATION TO LOW-CALCIUM DIET**

The necessity for vitamin D when there is enhanced calcium absorption has been known for more than 50 years, but the discovery in the past 15 years of the functional metabolism of vitamin D has partly revealed the mechanism by which this adaptation takes place. Nicolaysen postulated that there existed an endogenous factor that stimulated calcium absorption when calcium supply was inadequate (24). It is now clear that Nicolaysen’s factor is mainly, if not entirely, the metabolite 1,25-dihydroxyvitamin D \([1,25(\text{OH})_2\text{D}]\). When there is an increased requirement for calcium, the synthesis of 1,25(\text{OH})_2\text{D} in the kidney is increased (25). This metabolite passes into the circulation and is taken up by many cell types in which it associates with specific, high-affinity binding proteins ("receptors"). This protein complex with 1,25(\text{OH})_2\text{D} is then thought to mediate the vitamin D effect by inducing new protein synthesis in the manner of the standard steroid hormones.

The action of 1,25(\text{OH})_2\text{D} in the cells of the intestinal mucosa is to increase the capacity for active transport of calcium. Hence, the central concept in the mechanism of adaptation is an endocrine loop. During growth, pregnancy, and lactation, when there is an increased demand for calcium, 1,25(\text{OH})_2\text{D} synthesis is also increased, and the intestinal absorption capacity for calcium rises. As the demand for calcium declines, the synthesis of 1,25(\text{OH})_2\text{D} also declines.
If growth suddenly ceases because of insufficient supply of protein or energy, the absorptive capacity for calcium declines abruptly (26,27). This would be predicted by the theory of an endocrine loop, and it is assumed (but has not been demonstrated) that in undernutrition the synthesis of 1,25(OH)₂D is suppressed although the synthesis of other metabolites, 25-hydroxyvitamin D [25(OH)D] and 24,25-dihydroxyvitamin D [24,25(OH)₂D] are apparently unaffected (28).

There is, however, a problem with this interpretation of the adaptation being mediated entirely by 1,25(OH)₂D according to the prevailing need for calcium. It has been shown that in growing children the synthesis of 1,25(OH)₂D is not just regulated according to the demands of calcium homeostasis. The concentration of 1,25(OH)₂D in the plasma of children has been found to be directly related to the concentration of its precursor, 25(OH)D (29). Hence, not only does variation in calcium status control the synthesis of 1,25(OH)₂D, it is also determined by the vagaries of vitamin D status [25(OH)D level in plasma]. The absolute level of 1,25(OH)₂D cannot then be linked directly to the degree of response in the target cells.

From this it follows that homeostatic regulation of calcium absorption may depend on some other factor acting in concert with 1,25(OH)₂D in the intestine. Such a factor (or factors) might modify the number of receptors for 1,25(OH)₂D (30) or might modulate the activity of proteins induced by 1,25(OH)₂D in the mucosal cells. However, because in other circumstances the production of 1,25(OH)₂D has been clearly shown to be related to growth (31,32), it must nevertheless be the major influence in the adaptation to a low-calcium diet.

Of course, in vitamin D deficiency the ability to absorb calcium is greatly impaired, and the rate of bone growth is markedly reduced (33). However, as vitamin D functions in such a wide variety of cells, the effect of its absence must compromise growth in a multiplicity of ways other than merely interfering with the utilization of dietary calcium for the growth of bone.

**AVAILABILITY OF DIETARY CALCIUM**

The proportion of dietary calcium that is actually retained is seldom more than 50% and usually, in adults, is no more than 30% (34). There are two explanations for any variation in the limited amount of calcium that is absorbed. As described above, the adaptive increase in absorptive capacity can improve the availability of calcium. The other modifying factor is variable interaction of calcium with other dietary components in the lumen of the gut.

In general, such interaction tends to decrease the availability of calcium. However, in the special case of milk and milk products, calcium absorption is promoted by the presence of other constituents. Lactose specifically enhances the uptake of Ca²⁺ across the brush border of mucosal cells (35,36). The mechanism by which this occurs is unknown, but there is some evidence to suggest that lactose diminishes the sodium content of the mucosa with a resulting hyperpolariza-
tion of the brush border membrane, favoring the entry of calcium. Casein also promotes calcium absorption, mediated by phosphopeptides produced during proteolytic digestion (37,38). These phosphopeptides form soluble complexes with Ca2+ and increase its availability for absorption in the ileum.

Apart from dairy products, dietary calcium comes mainly from fruit, vegetables, and cereal grains. Three components of plant foods are known to form complexes with calcium that decrease its availability. These are complexes with phytate (39), oxalate (40), and unavailable carbohydrate (dietary fiber) (41,42). In comparison with milk, plant foods have a lower content of calcium, much of which is unavailable for absorption by the small intestine.

Although an increased absorptive capacity of the small intestine can, in principle, provide more calcium for bone growth and development, if this calcium is complexed in an unavailable form, then the increased absorptive capacity will be ineffective in raising the calcium supply.

 Adaptation to a low-calcium diet is usually considered to be a capability of the small intestine only, yet the colon also has some capacity for absorbing calcium. Calcium deficiency in experimental rats and in humans with the short bowel syndrome leads to an increased absorption of calcium by the colon (43,44). As with the small intestine, this adaptation in the colon is mediated by 1,25(OH)2D (45). Because bacteria in the colon are able to break down any fiber and phytate that has resisted enzymatic digestion in the small intestine, the complexed calcium carried into the colon could then be available for absorption. If children on a persistently low calcium intake have an adaptive increase in calcium absorption by the colon, then the availability of calcium from cereal, vegetable, and fruit diets may be much higher than has hitherto been considered likely. Such a possibility has yet to be investigated.

INFLUENCE OF CALCIUM DEFICIENCY ON VITAMIN D STATUS

With the discovery of 25(OH)D, it has been possible to determine the adequacy of vitamin D supply. The concentration of 25(OH)D in plasma reflects the amount of vitamin D obtained from the environment (46). By comparing seasonal variation in the plasma levels of 25(OH)D to variation in both the oral intake of vitamin D and the exposure of skin to ultraviolet light, it is evident that in western Europe vitamin D status is determined mainly by solar irradiation. Dietary vitamin D at less than 5 μg per day has little significance in adults except when vitamin D reserves are very low (46).

It is therefore a paradox that those areas of the world where vitamin-D-deficiency rickets is more common, such as India (47), Egypt (48), Saudi Arabia (49), and Greece (50), are regions where the sun shines in abundance. Such observations raise the possibility of some other factor in these sunny countries that might reduce the efficiency of utilization of the vitamin D formed in skin.

Research in our laboratory has recently demonstrated in rats that deficiency of calcium enhances the hepatic destruction of vitamin D and, depending on the sup-
ply, leads sooner or later to vitamin D deficiency. With secondary hyperparathyroidism, the production of 1,25(OH)$_2$D is increased, and this metabolite acts in the liver, stimulating the metabolic inactivation of vitamin D.

Vitamin D deficiency is most often found in those countries where both the intake and the availability of dietary calcium are low. Of course, vitamin D deficiency causes a more acute response on bone development than does a prolonged low intake of calcium, and the effect of simple vitamin D deficiency is readily apparent. What might not be so obvious is any deleterious influence on growth of combined low status of vitamin D and calcium. In communities where calcium intake is low, the possibility of such a combined deficiency should be considered.

GENERAL CONCLUSIONS

From the experimental research summarized in this chapter, a number of problems can be identified concerning the influence of a low calcium intake on the growth of children.

The recommended dietary allowance for calcium ranges between 500 and 1,200 mg/day. If milk is not included in the diet, it is difficult to see how such levels could be achieved without food fortification. Because many populations receive considerably less than the recommended intake of calcium, it is necessary to determine whether these apparently low supplies have deleterious consequences. More information is needed on whether adaptation by children to calcium intakes significantly below those recommended is able to compensate for the shortfall. Although balance data on well-fed individuals on a Western diet do indicate the amount of dietary calcium that is retained, such information may not be applicable to malnourished children. Certainly, when young children are recovering from malnutrition, the amount of dietary calcium that is retained may be as high as 87% (51).

Studies in the rat indicate that, provided the diet is not severely deficient in calcium, growth takes precedence over bone formation. There is no information about whether children with a low supply of calcium also have normal stature but bone undermineralization.

If children are receiving inadequate amounts of energy or protein, does a superimposed dietary deficiency of calcium further promote their failure to thrive?

The relationship between calcium supply and long-term growth has not been studied in experimental animals. To decide whether calcium deficiency is a cause of stunting requires that this possibility be specifically investigated in children.

REFERENCES


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**DISCUSSION**

**Dr. Rappaport:** You didn’t mention a problem that might be of interest to discuss: How do we evaluate clinically the calcium status of malnourished children? What is supposed to be a reliable index of the calcium status in various conditions of severe or less severe undernutrition? You did not mention urinary calcium.

**Dr. Fraser:** That is a very good point. The evaluation of calcium status is a particularly tricky thing; it has usually been done by inference, that if the calcium supply is low, then calcium status must be low, and it is well known that calcium supply is low in a large number of populations. Probably the most effective way of measuring calcium status is by measuring the mineralization of bone; the only really efficient way of doing this is by taking the bone and ashing it, which of course is not a practical prospect in population studies. There is, however, the technique of single-photon absorptiometry of bone, which I think
might be of great significance. This is a process by which one can measure the attenuation of a photon beam going through bone and, by computation, calculate from this attenuation the amount of mineral that is actually in the bone. This can be done very easily with little interference with the subject. We have been doing this type of work, looking at the mineralization of the radius in children in Gambia and in Great Britain, but the data have not been analyzed yet. Looking at the raw figures, it seems that there is very little difference between the mineralization of the bones in children in Gambia, on a very low calcium intake, and that of the bones of children in Cambridge. The conclusion from this would have to be either that children were growing more slowly in Gambia, which does not appear to be the case (provided that other nutrients have been supplied in reasonable amounts), or they are absorbing calcium in their diet much more efficiently than one would have predicted from what we know of calcium balance of children in affluent societies.

Dr. Waterlow: Is it not the case that Pettifor, in South Africa, has described vitamin D deficiency consequent to low calcium intake?

Dr. Fraser: Yes, this is true. The studies that he did (1) were with young children who, to his surprise, had clear signs of rickets in the face of adequate 25-hydroxyvitamin D levels. It is probably true that if the supply of substrate for bone formation is greatly diminished, then the clinical effect or the radiological appearance of the bone is very similar to that produced by frank vitamin D deficiency. Except in children during times of rapid growth, frank calcium deficiency probably doesn't produce exactly the same effects on bone as vitamin D deficiency.

Dr. Waterlow: You discussed plasma phosphorus levels in animals on a low-calcium diet, and I couldn't quite grasp what was happening to the phosphates. Could you elaborate on that?

Dr. Fraser: The plasma phosphate in those animals was elevated. This is somewhat surprising because in the face of hyperparathyroidism, which would enhance the excretion of phosphorus by the kidney, one could imagine that the plasma phosphorus, if anything, would be low. But these animals were on an extremely low calcium diet, and they were still growing; in fact, their growth rate was only marginally less than that of the controls. Their bone mineralization was greatly reduced, and I think the plasma phosphorus had been elevated merely because the bone mineral had been so rapidly resorbed that the rate of delivery of phosphorus to the plasma was greater than the rate of excretion of phosphorus by the kidney.

Dr. Valyasevi: Could you comment on the situation that exists in rural northeast Thailand, where there is endemic bladder stone disease. The oral phosphate intake in that area is extremely low, as well as the urinary excretion, about 1/10 of what is measured in children from Bangkok. Calcium intake is low too, 200 to 250 mg/day in preschool children, but phosphate intake is even less than that. We did a survey of about 200 preschool children living in the village. Of these, we found four or five cases of radiological rickets; serum alkaline phosphatase was high in general. To prevent bladder stone disease, we gave a supplement of phosphate, about 60 mg of phosphorus per kilogram per day, roughly 600 mg per day. If we give this supplement on a long-term basis, will it have any kind of undesirable effect on bone mineralization? In such cases, with an extremely low intake, how do adaptation mechanisms operate?

Dr. Fraser: The situation in man may be different from that in experimental animals. In rats, when you increase the amount of phosphorus in the diet, it has a negative effect on the absorption and availability of calcium, but in man this doesn't seem to be quite so important; the phosphorus content of the diet probably has to go up considerably more in man
to cause an impairment of calcium absorption. On the other hand, if the calcium supply is very low, this will probably enhance the availability of phosphorus when the phosphorus supply is also limited. So it may well be that in children who have got both a low calcium supply and not a very high phosphorus intake, their phosphorus availability could be enhanced because of the low calcium in the diet. If the rickets, which you say is present in this community, is really because of a low vitamin D status and not any other cause, that could be related to the low calcium supply. The easiest way of treating this would be merely to enhance the availability of calcium without supplying extra vitamin D. Because these children are presumably also vitamin D deficient, the way to correct this is of course to insure that they get exposed to sunlight.

A particular puzzle has been to explain why vitamin D deficiency seems to occur in regions where there is plenty of sunlight. We know that most vitamin D comes from the effect of sunlight on vitamin D formation in skin. The two things can be taken together: sufficient sunlight and sufficient calcium. If you are on a low-calcium diet, you have a greater requirement for vitamin D, and if you are not exposed to adequate sunlight, either for cultural or any other reason, then this will put you at more risk of vitamin D deficiency. Thus, you can reduce the requirement for vitamin D by increasing the calcium supply, but nevertheless vitamin D still has to be provided, so the two things should go together.

Dr. Waterlow: I have learned three things in the last few days. First, that stunting is very common in northeast Thailand; secondly, that phosphate deficiency is very common in northeast Thailand; and thirdly, and I quote from you, phosphate deficiency is probably more important in affecting the growth of bone than calcium deficiency. Is it reasonable to put these things together and to suggest that phosphate deficiency might be a cause of stunting?

Dr. Fraser: In theory, phosphate deficiency is a cause of stunting. If it were possible for you to do the unethical experiments of putting children on a phosphorus-deficient diet, I would be very surprised if it did not produce growth failure because it does so in every domestic and experimental animal. Phosphorus deficiency in cattle and sheep, for instance, is a cause of profound growth failure. What I don’t know, though, is what level of deficiency would produce this effect in children; what is the cut-off point at which growth retardation would occur?

Dr. Guesry: May I first make a short comment: you focused in your chapter quite exclusively on absorption. I think we have also to consider fixation of minerals in bone. Low-birth-weight infants, when the phosphorus supply is insufficient, may absorb 50% of their calcium intake, but they don’t fix it in the bone, and calcium is excreted in the urine. With the addition of phosphorus, hypercalciuria is reduced, and bone mineralization starts. All international bodies, such as the Committee of Nutrition of the American Academy of Pediatrics or the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN), when they make recommendations for calcium intake, recommend at the same time that the calcium/phosphorus ratio should be between 1.2 and 1.8 or 2. You did not mention that ratio except that in rats when phosphorus intake increases, it has the same effect as providing a low-calcium diet. Could you comment and expand on the importance of phosphorus in the diet for calcium absorption?

Dr. Fraser: The importance of the calcium/phosphorus ratio goes a bit beyond the mere absorption of calcium from the diet. Again, the studies don’t seem to have been done as thoroughly in man as they have in experimental and domestic animals. In most mammals and in birds, the calcium/phosphorus ratio is very important in optimizing the efficiency of utilization of both nutrients, and the variation of the ratio outside a fairly narrow range
produces reduction in growth and possible bone abnormalities. Such studies haven't been done in man except in the case of premature children, so it would be difficult to predict exactly what is likely to happen in older children in the absence of this information. From the studies that have been done in experimental and domestic animals, it appears that if there is a large deviation from a narrow range, either with excessive phosphorus or with excessive calcium, then the absorption of the other nutrient will be impaired. An excess of phosphorus, for example, will tend to diminish the plasma calcium concentration, increase the excretion of calcium, and reduce the availability of calcium for its physiological functions in most cell types and certainly for the mineralization of bone. Thus, if there is an excess of phosphorus, one would predict that this would cause an impairment of the utilization of calcium. This does seem to apply, as you mentioned, in premature children. I would think that calcium deficiency is much less a problem than phosphorus deficiency in maintaining the growth of bone in that condition. The other circumstance, a high calcium supply, is very unlikely to occur. It can really occur only by excessive supplementation of calcium. I didn’t, in fact, consider the possibility of phosphorus deficiency as being very significant in populations of children, but Dr. Michael Golden raised the possibility that phosphorus deficiency might be more common than has been reported. It doesn’t seem to have been looked at very thoroughly even though the effect on growth is much more severe than any effect that calcium deficiency might have.

Dr. M. Golden: We find very low plasma phosphorus levels in Jamaican malnourished children, and they have very low urinary phosphorus excretion. At one stage we gave them magnesium supplements in the form of magnesium chloride, which we now know represents a massive acid load, and in the face of the massive acid load, there was no increase in phosphorus excretion. I take this to indicate that we have a low phosphorus status in our malnourished children. We have also been looking at stool silicon to try to get a measure of pica. Although we say that calcium intake is very low throughout much of the Third World, I think this is true if we just look only at the dietary calcium intake. Many children practice pica and significant geophagia, which I think has been underestimated to a great extent. What effect would geophagia by children in limestone areas potentially have on their phosphorus status? Would this really potentiate phosphorus deficiency? Much of the phosphorus in the diet may well be unavailable if it is present as phytate phosphorus.

Dr. Fraser: If I were to assume that the human child was the same as a young experimental animal, an increase in calcium would reduce the availability of phosphorus. However, it just doesn’t seem to apply in adult humans, so whether or not this interaction occurs during growth I don’t know. I could perhaps interpret your low plasma phosphorus and low urinary excretion of phosphorus in another way. Plasma phosphorus, unlike plasma calcium, is very susceptible to changes in the phosphorus flux, and if these children have stopped growing, then the amount of phosphorus that is coming from bone and from the diet may be very small, and so under the conditions of suppressed growth, I think plasma phosphorus could very well fall. Naturally then, urinary phosphorus would fall also; so I think that, apart from indicating phosphorus deficiency, which it could do, one would have to see whether or not growth itself was affected.

Dr. Martorell: You said that our notions about calcium requirements are really based on what we know from industrialized nations, and you were wondering to what extent these notions apply to developing countries. Bone loss, osteoporosis, for example, is a problem of great public importance in the United States and other Western nations where calcium intakes are high. The recommendations are such that, to meet them, people would have to drink a lot of milk or even take calcium supplements. In other regions of the world, bone
deminerlization and osteoporosis are much rarer, and yet populations exist on much lower calcium intakes. What are the physiological factors that can explain this? Nutrient interactions? Exercise? Genetic factors?

Dr. Fraser: I think that nutritionists in affluent societies have got calcium requirements completely wrong. They base their estimates of calcium requirements on two assumptions. One is that dietary calcium is very poorly absorbed: only 20 to 30% as measured by balance studies. That is true in the types of studies that are done. They also make the assumption that it is very important to supply lots of calcium in early life in order to protect against osteoporosis in later life, and this is an act of faith because there have been no studies that have actually demonstrated protection. The reasoning is that in cases of osteoporosis negative calcium balance occurs, i.e., a greater loss of mineral from bone than is actually introduced into bone during bone turnover. Thus, osteoporosis is regarded as a calcium balance problem, as a disease produced by inadequate supply of calcium. The whole concept is based on a nutritional approach, but it is possible to interpret osteoporosis in quite different ways. The point that you raised about exercise and the effect of mechanical stress on bone is probably of great importance, and it has not been considered widely in osteoporosis. The other possibility is that osteoporosis is really a change in the function of bone cells. If the bone cells are not actually incorporating mineral into bone at that time of life as effectively as they were in early life, then there isn’t the same requirement for calcium and phosphorus obtained from the diet. Thus, the balance studies might merely reflect what those bone cells are doing. I suspect that if one were to reevaluate calcium requirements, one could quite easily look at what is happening in countries where calcium intakes are very low and see these people surviving perfectly well on low calcium intakes, with a very low incidence of osteoporosis. It would be necessary to reevaluate both problems: (a) whether or not calcium requirements need to be as high as the recommendations suggest when it is perhaps possible to increase the availability of calcium by adaptive mechanisms; and (b) whether or not the calcium supply at any stage in life is directly related to bone loss in the elderly.

Dr. Kraisid: Short-term studies in adults have shown that increased protein intakes tend to result in increased excretion of calcium in urine (2,3). Recently we have done a study in young children on the effects of different protein intakes on calcium and phosphorus excretion. Giving either a relatively low but adequate protein intake or double that amount had no effect, not like in adults. People in developing countries do not drink milk as they grow older; their calcium intake is low, and at the same time their protein intake is relatively low, adequate, or marginal. On the contrary, in industrialized countries protein intake usually is high, 1.5 to 1.6 times the recommended levels. This might cause some metabolic changes such as increased mobilization of calcium and phosphorus and increased excretion of calcium. Could this in the long run be an explanation for osteoporosis?

Dr. Fraser: I don’t know if that is true, but it is an interesting area worth further investigation. The effect of a high-protein diet on calcium excretion is clear cut both in humans and in experimental animals—if you increase protein intake, calcium excretion by the kidney is increased also—but it is not well explained. There are various theoretical reasons why this may occur, but as far as I know, none has actually been proven. It is an interesting idea to think that a long-term intake of a high-protein diet, and perhaps the perpetuation of increased excretion of calcium by the kidney, may have some effect on the turnover of bone and the ability of bone to maintain its strength throughout total life-span. I think that those are points that should be considered and are much more interesting in fact than just the nutritional aspects of supplying adequate calcium and phosphorus in early life. This seems to be an obsession with people who have been working on osteoporosis, in that they
have been unwilling to consider other possibilities even though they have been unable to
solve the problem from the studies and the approaches that they have taken.

Dr. Barbara Golden: Undernourished children tend to get small bowel overgrowth, so
they may radically alter their calcium availability through fermentation. Have there been
studies done to show the differences in calcium availability in patients with small bowel
overgrowth, and does it alter phosphate availability?

Dr. Fraser: You could have two processes that are acting against each other here. When
you have small bowel overgrowth, you probably have an increased splitting of organic cal-
cium complexes in the small intestine and theoretically an increased availability of that cal-
cium for absorption. However, because in small bowel overgrowth you might have lower
efficiency of the intestinal mucosa to absorb nutrients in general, and this seems to apply
to calcium in particular under other conditions of malabsorption, then perhaps the enhanced
availability of calcium is not an advantage because of the reduced absorption capacity. In
studies on rats we tried to do an experiment to reduce the availability of calcium by feeding
a high-cereal diet. If you do this in man, feeding a high intake of wheat bran, you can put
adults into negative calcium balance within a few days (4). A sudden increase in the
amount of cereal fiber in the diet has quite a marked effect on the availability of calcium.
If you do the same study in rats, there is no effect whatsoever; calcium balance is main-
tained in the face of very high levels of these calcium complexes (5). The big difference
between adult humans and rats is that rats are coprophagous and thus have a physiological
overgrowth of bacteria in their small intestine, and it may well be that they are able to
release this complex calcium whereas humans are unable to do this.

Dr. Mukherjee: Although protein-energy malnutrition is a deficiency disease, and al-
though these patients sometimes have very low calcium intakes and low vitamin D levels,
we do not see clinical signs of florid rickets in them, especially in severe cases like kwashi-
orkor and marasmus. I wonder if you could comment on this?

Dr. Fraser: I don't think that calcium deficiency alone or a marked reduction of the
availability or supply of calcium is going to produce rickets. It will only do so, if the exper-
iments in rats are relevant to humans, when the supply of vitamin D is also low. A clear
example of this is the Asian immigrants in the U.K., particularly those that came from East
Africa. When they were in East Africa, they had the same sort of diet that they were able
to maintain when they reached Britain, and they showed no signs of vitamin-D-deficiency
rickets. A few years after their arrival in Britain, vitamin-D-deficiency rickets became very
common. The big difference between those two locations was in the supply of vitamin D,
because in East Africa they had plenty of sunshine, there was an adequate amount of vita-
mín D, and there were no signs of rickets even though the low calcium availability or low
calcium supply would have increased their requirements. When they arrived in Britain, be-
cause of the poor weather conditions, vitamin D supply was markedly reduced, the in-
creased requirement for vitamin D was not being met, and they started showing signs of
rickets. It is quite possible in your children that one of the protective factors is that they
have enough sunshine to prevent the development of rickets. If their growth rate had been
reduced because of the nutritional impairment, then that also would reduce their require-
ment for vitamin D. An increased requirement for vitamin D is only going to show up
where there is rapid growth, inadequate calcium intake, and inadequate vitamin D status.

Dr. Milner: I don't understand why, when you have rats on a low calcium intake and
with increased 1,25-dihydroxyvitamin D levels, this should stimulate an increased degrada-
tion of 25-hydroxyvitamin D. Is this a physiological adaptation or a pathological process?
Teleologically, I would expect the body to wish to conserve the 25-hydroxy as a precursor
for 1,25-dihydroxy synthesis, which the body needs. Could you explain this?
Dr. Fraser: I agree entirely. I cannot understand or explain it. How I interpret it at the moment is that it is not a purposeful destruction of vitamin D by the liver. I think this is a coincidental effect that has little importance except when there is a prolonged calcium deficiency and an inadequate supply of vitamin D. What I suspect is happening is that vitamin D is not, as was previously thought, a molecule that is active in only a few cells, the target tissues of the intestine, bone, and kidney. It is now apparent that most cell types in the body respond to 1,25-dihydroxyvitamin D, probably by modifying their ability to handle calcium. When there is a high plasma concentration of 1,25(OH)₂D, and because its half-life is exceedingly short in comparison to the other vitamin D metabolites, the liver takes up more 1,25(OH)₂D, and this may modify the liver’s own ability to handle calcium. A secondary consequence of this may be an enhancement of the degradative pathways for vitamin D. One of the things that we hope to do in the near future is to study other degradative pathways and see whether they have also been stimulated, therefore indicating that this is a nonspecific effect, perhaps mediated by changes in cytoplasmic calcium affecting the degradative aspects of liver function.

Dr. Milner: As if it were a futile cycle?

Dr. Fraser: It would be a whole-body futile cycle, yes.

REFERENCES