Nutrition and Chronic Disease

The first victories of human clinical nutrition were the conquests of the classic deficiency diseases (eg, beriberi and pellagra). Each nutrient was associated with a specific disease, the approximate mechanism of its action was elucidated, and programs of supplementation or fortification that led to control or virtual elimination of the disease were implemented, more or less in that order. Most of this occurred more than half a century ago, and with those gains to its credit, nutrition has virtually disappeared from the radar screens of many, perhaps most, medical specialties. Except for alleged negative effects (eg, fat, salt, cholesterol), what more did nutrition have to offer human medicine?

In essentially every instance, the index disease for each of the classic micronutrients had a short latency; otherwise the connection between cause (deficient intake) and effect (deficiency disease) could not have been discerned. Deficiency conditions that have long latencies are not precluded, and expanded understanding of cell biology suggests that they may, perhaps must, exist. Nevertheless, they have proved difficult to recognize, as have deficiency states that develop through mechanisms different from those understood to mediate the index disease.

Today, at the beginning of its second century as a science, clinical nutrition faces 2 major and very different problems: (1) the need to develop investigative approaches to define the role nutritional deficiency plays in a broad array of chronic diseases and (2) the fact that American medicine tends either to ignore1 or to dismiss2 nutritional evidence relating to the diseases it treats.

In the current issue of Mayo Clinic Proceedings, Holick3 summarizes a massive body of data indicating that vitamin D, in addition to its classic role in the calcium economy, is involved in many other systems and diseases. It is now known, for example, that more than 200 human genes contain vitamin D response elements,4 only a fraction of which are directly involved in operation of the calcium economy or in bone biology. We now know that vitamin D is intimately involved in regulating gene expression for such basic cell biologic processes as proliferation, differentiation, and apoptosis, in addition to various aspects of both primary and acquired immunity. The ubiquity of vitamin D involvement suggests that deficiency of the nutrient could be expressed in myriad ways distinct from rickets and osteomalacia. Defining optimal vitamin D status in this context will prove challenging because most chronic diseases typically share 2 characteristics that make investigation difficult: long latency and multifactorial causation.

The challenge is not only to determine whether changing vitamin D status will alter development or severity of any of the conditions concerned but also to figure out how to show efficacy in a context of long latency, a problem not readily attacked by randomized controlled trials. There are also the lesser problems of determining how much vitamin D is needed to optimize a given system and how most effectively to improve vitamin D status for whole populations. At stake are far-reaching consequences for nutritional policy. Current micronutrient intake recommendations are pegged to preventing only the index disease. That will have to change. For vitamin D, current recommendations are sufficient to prevent only rickets. We already know that that is not enough to prevent the portion of the osteoporosis burden caused by low vitamin D status.

Vitamin D is actually a sort of poster child for a broad array of essential nutrients, many of which are now known to function in diverse systems and, for some of their effects, to exhibit latencies varying from days to years (the latter of course not recognizable in the early days of nutritional science). Calcium is a good example because both its multiple system involvement and mechanisms of some of its manifold actions are now reasonably well worked out.

Inadequate calcium intake depletes or limits skeletal mass, which functions as the body’s calcium nutrient reserve, thereby causing or aggravating osteoporosis.5 Of course, low calcium intake is not the only cause of osteoporosis; nevertheless, osteoporosis is the index disease for calcium, just as rickets (which also has other causes) is the index disease for vitamin D. Gradually we have come to recognize that calcium has nonskeletal health effects as well, many with shorter latencies. For example, unabsorbed calcium in the gut lumen (which averages about 90% of intake) complexes and neutralizes certain potentially harmful byproducts of digestion, such as oxalic acid, free fatty acids, and bile acids. The effect is purely chemical and is immediate; however, optimal complexation requires a high calcium intake.

Reducing absorption of food oxalate decreases kidney stone risk in those susceptible,6 a benefit that has zero latency. Complexation of fatty acids serves at least 2 useful functions: (1) it reduces absorbed energy7,8 and thereby helps with weight control, and (2) it reduces cancer promotion by uncomplexed free fatty acids.9,10 For these intralu-
minal effects, the energy balance and stone-protective effects of high calcium intakes have zero latency, while the antipromoter effect, like osteoporosis, has a latency of many years.

Folate provides yet another instance of a nutrient acting in multiple systems through mechanisms distinct from that responsible for the index disease (macrocytic anemia), eg, embryonic neural tube development and adult oncogenesis. Folate facilitates 1-carbon transfers for an array of biochemical systems ranging from thymine synthesis, needed in all rapidly growing tissues, to DNA methylation, involved in regulation of gene expression.

Additionally, folate shares with calcium and vitamin D the feature that, for some of the manifestations of deficiency, the pathogenesis can be indirect. For example, low folate levels lead to decreases in methylation of homocysteine. Serum homocysteine levels rise, and the compound binds irreversibly to disulfide bonds in extracellular elastic proteins. In this way, folate deficiency is postulated to lead to age-related deterioration in connective tissues, an outcome with a long latency.

Similarly, for both calcium and vitamin D, low inputs evoke increases in parathyroid hormone (PTH) secretion, a physiologically appropriate response to reduced intake or absorption of calcium. However, long-term high PTH levels, in addition to mitigating the effect of reduced intestinal calcium input, have several collateral effects. One is an increase in bone remodeling. Remodeling is now recognized as a powerful fragility factor. This indirect effect of calcium deficiency is probably more responsible for the increased bony fragility of osteoporosis than is the simple decrease in bone mass, which is the more intuitively evident effect of low calcium input and which is enshrined in the name of the disease. Even with rickets, the classic deficiency disease for vitamin D, the pathology is produced not so much by malabsorption of calcium and phosphorus, which is the direct effect of vitamin D deficiency, but by hypophosphatemia caused by PTH’s lowering of the renal reabsorption of filtered phosphorus, an indirect effect of vitamin D deficiency.

For both vitamin D and calcium, such collateral damage extends well beyond the arena of the calcium economy. High calcitriol production in response to elevated PTH levels, in addition to promoting calcium absorption, opens calcium channels in a variety of tissues, increasing intracellular [Ca\(^{2+}\)] and thereby augmenting cell expression of such tissue-specific effects as arteriolar smooth muscle contraction. This is likely the mechanism behind the small, but important, blood pressure reduction produced by increased calcium intake, and as Holick notes in his review, the corresponding blood pressure lowering effect of increased vitamin D intake as well.

The rich complexity of these interactions makes it clear why a simplistic 1-nutrient-1-disease model of nutrition is woefully inadequate. At the same time, it forces us to confront the difficulty of designing investigative approaches that are sufficient to demonstrate and quantify benefit from altered nutrient input at a population level. Which end point should we choose? How large a nutrient input should we use? How will we separate its effects from those of other simultaneously acting causal factors?

Even the short latency disorders present challenges, partly because of substantial population heterogeneity and partly because of medicine’s seeming preference for pharmacological solutions to medical disease. The former is exemplified by the fact that redundancies in intracellular signaling systems and/or ability to defend intracellular [Ca\(^{2+}\)] against unstimulated inputs varies considerably from individual to individual, just as, for example, does salt sensitivity. The preference for pharmacological solutions is illustrated nicely by Holick’s description of efforts to develop noncalcemic analogues of calcitriol. Doing this may seem to follow naturally from the fact that calcitriol is the principal biologically active form of vitamin D. However, it also presumes that it is serum calcitriol that is responsible for the effects of the vitamin. That is true for vitamin D’s role in intestinal calcium absorption but appears not to be the case for the probably more important autocrine actions of vitamin D.

One of the most exciting of the discoveries described by Holick is the finding that many cell types—perhaps most epithelial and immune response cells—express the vitamin D 1α-hydroxylase (CYP27B). They are able to synthesize and degrade calcitriol intracellularly. As a consequence, rather than all tissues responding to, or being dependent on, the same circulating calcitriol level, each tissue can make what it currently needs for itself. All that is required is an adequate availability of the precursor, serum 25-hydroxyvitamin D (25[OH]D). The 1α-hydroxylase operates well below its \(k_{m}\), and hence intracellular calcitriol synthesis is critically dependent on substrate concentration. It follows that, for most vitamin D–related disorders, the best (and most physiological) solution may be simple elevation of serum 25(OH)D by ensuring adequate inputs of cholecalciferol, not expensive drugs.

However, there will be a few situations in which such an approach is not likely to be adequate, principally because of abnormalities of intracellular calcitriol metabolism (eg, loss of the 1α-hydroxylase or overexpression of the 24-hydroxylase). That may be the case for human myelodysplasia and has been demonstrated for at least 1 cancer model—a mouse mammary tumor that has lost the 1α-hydroxylase but reverts to a quasinormal phenotype on exposure to exogenous calcitriol.
The concentration of 25(OH)D in serum that is required to optimize all vitamin D–related functions remains uncertain, but there is a growing consensus that it is at least 32 ng/mL (80 nmol/L) and may be as high as 48 ng/mL (120 nmol/L). Both values are lower than those found in outdoor workers in the tropics and hence are still less than the primitive levels to which human physiology adapted over the course of evolution. Fortunately, contemporary evidence confirms that such levels are safe: no credible reports exist of vitamin D toxicity at serum 25(OH)D levels below 500 nmol/L (J. N. Hathcock, PhD, A. Shao, PhD, R. Vieth, PhD, R.P.H., unpublished data, January 2006).

From the standpoint of public health, it would logically be necessary to demonstrate efficacy of increased serum 25(OH)D for only one of the disorders that may be vitamin D dependent. Preventing that one outcome could automatically produce other possible benefits without having to demonstrate each of them, one by one. “Proof” (or lack thereof) would then come from change in public health statistics, as occurred for dental caries after water fluoridation or for pellagra and neural tube defects after fortification of cereal products with niacin and folate, respectively.

Virtually the entire populations of the industrialized nations have substantially lower vitamin D inputs than our ancestors in equatorial East Africa. The extent to which lower input is “deficient” is what is at issue and remains to be conclusively shown. But, imagine, if you will, a search for the cause of lung cancer in a population of cigarette smokers. Identifying differences between those who do and do not develop cancer tells us nothing about cause, only about individual susceptibility. Is that the situation we face with vitamin D and the multiplicity of chronic diseases in the industrialized nations?

The triumphs of nutrition are not all behind us. If only a small fraction of the disorders for which a plausible vitamin D hypothesis can be framed turn out to be due at least in part to inadequate vitamin D status, and if we act on that knowledge, the medicine of the future could look extremely different from that of today.

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4. Carlberg C. Current understanding of the function of the nuclear vitamin D receptor in response to its natural and synthetic ligands. Recent Results Cancer Res. 2003;164:29-42.