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COMMENTARY

Cod Liver Oil, Vitamin A Toxicity, Frequent Respiratory Infections, and the Vitamin D Deficiency Epidemic

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In the previous issue of the *Annals*, Linday et al¹ reported a case series of 16 children who underwent tympanostomy tube placement, of whom they found that 80% had 25-hydroxyvitamin D [25(OH)D] levels of less than 30 ng/mL (reference range, 30 to 100 ng/mL in most American laboratories). Although interesting, especially in light of recent recommendations that the lower level of adequate 25(OH)D levels may be as high as 50 ng/mL²⁻⁴ (levels none of their children achieved), the implications of the work of Linday et al¹ are best appreciated when one reviews their 2 previous publications^{5,6} in this journal and puts their important work in a larger historical context.

In 2004, Linday et al,⁵ using a medical record control group, reported that 600 to 700 IU of vitamin D and 3,500 IU of vitamin A, given as cod liver oil and a multivitamin, slightly reduced ($p = 0.04$) the mean number of upper respiratory tract visits over time when given to 47 young children. However, the total number of visits for upper respiratory tract infections was slightly higher in the treatment group (68 versus 61). In an earlier pilot study, they found that a similar regimen reduced antibiotic use by 12% in 8 children.⁶ However, all but 1 of the treated children had an upper respiratory tract infection during the study period. In contrast, 2 larger, controlled studies in the 1930s found more robust results: the first found that cod liver oil given to 185 adults for 4 months reduced the incidence of colds by 50%,⁷ and the second study found that cod liver oil given to 1,561 adults reduced the incidence of respiratory infections by 30%.⁸ We suggest that the much higher vitamin D content in 1930s cod liver oil may explain the different results.

Vitamin D alone, whether from ultraviolet lamps, the sun, or from supplements, reduces the incidence of respiratory infections. In 1926, Smiley, who first discovered the strong inverse association between sun exposure and upper respiratory tract infections, also first theorized that such seasonality was caused by “disordered vitamin metabolism in the human. . . directly due to a lack of solar radiation during the dark months of winter.”^{9(p626)} This explains why Dutch children with the least sun exposure were twice as likely to develop a cough, and 3 times as likely to have a runny nose, as the children with the most sun exposure.¹⁰

Furthermore, sub-erythral courses of vitamin D–producing ultraviolet radiation administered twice a week for 3 years to 410 teenage Russian athletes, compared to 446 non-irradiated athletes, resulted in 50% fewer respiratory viral infections and 300% fewer days of absences.¹¹ Wayse et al¹² compared 80 non-rachitic children with lower respiratory tract infections to healthy controls and found that the children with the lowest 25(OH)D levels were 11 times more likely to become infected. Sixty thousand international units (IU) of vitamin D per week administered for 6 weeks to 27 children with frequent respiratory infections resulted in a complete disappearance of such infections for the following 6 months.¹³

More recently, some of us presented extensive epidemiological evidence that the seasonality of vitamin D deficiency may explain the seasonality of influenza epidemics.^{14,15} We concluded that physiological doses of vitamin D would reduce the incidence of influenza, but theorized as well — on the basis of vita-

min D's mechanism of action — that pharmacologic doses might effectively treat cases of influenza. Aloia and Li-Ng¹⁶ then published the most rigorous evidence to date supporting the prevention theory. In a post hoc analysis of their original 3-year randomized controlled interventional trial, they discovered that 104 African American women given vitamin D were 3 times less likely to report cold and flu symptoms than were 104 placebo control subjects ($p < 0.002$). A low dose (800 IU/d) abolished the seasonality of reported colds and flu, and even a sub-physiological dose of 2,000 IU/d (40% of treated women still had serum 25(OH)D levels of less than 32 ng/mL after 1 year) virtually eradicated all reports of upper respiratory tract infections (see Figure¹⁶).

Although Lindsay et al¹ mention vitamin D's antimicrobial mechanism of action, a more detailed explanation would remind readers that the pathology of respiratory infections involves a complex interaction among the microbe, adaptive immunity, and innate immunity. Whereas adaptive immunity requires prior exposure to an antigen, innate immunity is that branch of host defense that is “hard-wired” to respond rapidly to antigens by using effectors that are genetically coded for activation before they ever encounter that antigen. Of the effectors, the best studied are the antimicrobial peptides (AMPs).¹⁷

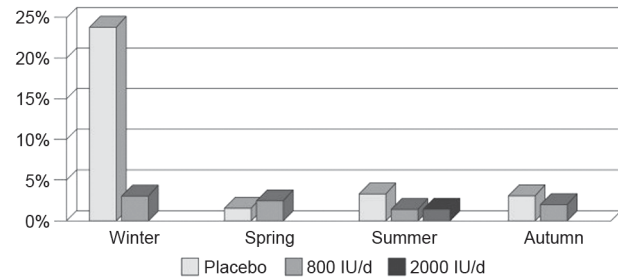
These endogenous antimicrobials exhibit broad-spectrum microbicidal activity against bacteria, fungi, and viruses. In general, they rapidly damage the lipoprotein membranes of microbial targets, including enveloped viruses such as influenza. Both the epithelium, in which they form a protective shield in mucus, and professional phagocytes, in which they provide microbicidal activity within the phagolysosome, produce AMPs. The innate immune system not only provides direct antimicrobial defense for these “front lines,” but it also signals and primes the adaptive immune system to produce antigen-specific T lymphocytes and immunoglobulins. In addition, AMPs — such as the potent antimicrobial cathelicidin — trigger tissue repair through activation of epithelial growth and angiogenesis.¹⁸

Antimicrobial peptides protect mucosal epithelial surfaces by creating a hostile antimicrobial barricade. The epithelia secrete them constitutively into the thin layer of fluid that lies above the apical surface of the epithelium but below the viscous mucous layer. To effectively access the epithelium, a microbe must first infiltrate the mucous barrier and then survive assault by the AMPs present in this fluid. Should microbes breach this constitutive cordon, their binding to the epithelium rapidly mobilizes the expression of high concentrations of specific inducible AMPs such as human β -defensin 2 and cathelicidin, which provide a “backup” antimicrobial shield.

Vitamin D's pivotal role in innate immunity has become evident only recently.¹⁹ First White's group at McGill University,²⁰ then 2 independent groups at the University of California–Los Angeles,^{21,22} showed that activated vitamin D [$1,25(\text{OH})_2\text{D}$] dramatically up-regulates genetic expression of AMPs in immune cells. (For details of the mechanism of action, see White's²³ review.) Both epithelial cells and macrophages increase expression of the antimicrobial cathelicidin upon exposure to microbes — an expression that is dependent upon the presence of vitamin D. Pathogenic microbes, much like the commensals that inhabit the upper airway, stimulate the production of a hydroxylase that converts 25(OH)D to $1,25(\text{OH})_2\text{D}$, a seco-steroid hormone. In turn, this activates a suite of genes involved in defense.

In the macrophage, the presence of vitamin D also suppresses the pro-inflammatory cytokines interferon γ , tumor necrosis factor α , and interleukin-12 and down-regulates the cellular expression of several pathogen-associated molecular pattern (PAMP) receptors. In the epidermis, vitamin D induces additional PAMP receptors, enabling keratinocytes to recognize and respond to microbes.²⁴ Thus, vitamin D both enhances the local capacity of the epithelium to rapidly produce endogenous antibiotics and, at the same time, dampens certain arms of adaptive immunity, especially those responsible for the signs and symptoms of acute inflammation.

The work of Liu et al²² is of particular interest. Plasma levels of vitamin 25(OH)D in African Americans, known to be about one half those of light-skinned individuals, are inadequate to fully stimulate the vitamin D–



Incidence of reported cold and influenza symptoms according to season. Subjects ($n = 104$) in placebo group (light shading) reported cold and flu symptoms year-round, with most symptoms in winter. While on 800 IU/d (intermediate shading), 104 test subjects were as likely to get sick in summer as in winter. Only 1 of 104 test subjects had cold and/or influenza symptoms during final year of trial, when they took 2,000 IU/d of vitamin D (dark shading). (Modified with permission.¹⁶)

dependent antimicrobial circuits that are operative within the innate immune system. However, the addition of 25(OH)D restores the dependent circuits and the expression of cathelicidin. High concentrations of melanin in dark-skinned individuals shield the keratinocytes from the ultraviolet radiation required to generate vitamin D in skin.²⁵ Therefore, relative — but easily correctable — deficiencies in innate immunity probably exist in many children during the dark days of winter, with dark-skinned children at highest risk. Black children continue to have twice the rate of mortality from pneumonia of white children, despite modern antibiotics.²⁶

Furthermore, during any season, for any skin type, and at any latitude, a percentage of the population is vitamin D-deficient, although the percentage is highest in the winter and in dark-skinned individuals, and increases the further poleward the population. For example, seasonal variation of vitamin D levels even occurs in equatorial Hong Kong,²⁷ and widespread vitamin D deficiency occurs at such latitudes,²⁸ probably because of sun avoidance,²⁹ rainy seasons,³⁰ and air pollution.³¹ A study of Hong Kong infants showed that about half had 25(OH)D levels of less than 20 ng/mL in the winter.³² None of the infants had levels higher than 40 ng/mL, even in the summer. Thus, a substantial percentage of all children will have impaired innate immunity at any given time, although the impairment is greatest during the dark days of the cold and flu season.

Our main concern with the previous work of Lindsay et al^{5,6} is the cod liver oil. They gave their children approximately 3,500 to 5,000 IU/d of preformed retinol, although none of their children had low serum retinol levels. However, they only administered 700 IU/d of vitamin D. (International units of vitamin D and vitamin A are not comparable.) We believe, first, that the ratio of the vitamins should be reversed and, second, that the dose of each vitamin should be lowered. Detrimental amounts of vitamin A may explain why their earlier work on prevention of upper respiratory tract infection was less than robust.

Although activated vitamin D and vitamin A signal through common cofactors, they compete for each other's function. Retinoic acid antagonizes the action of vitamin D and its active metabolite.^{33,34} In humans, even the vitamin A in a single serving of liver impairs vitamin D's rapid intestinal calcium response.³⁵ In a dietary intake study, Oh et al³⁶ found that a high retinol intake completely thwarted vitamin D's otherwise protective effect on distal colorectal adenoma, and they found a clear relationship between vitamin D and vitamin A intakes, as the women in the highest quintile of vitamin D intake ingested around 10,000 IU/d of retinol.

Furthermore, the consumption of preformed retinol — even in amounts consumed by many Americans in both multivitamins and cod liver oil — may cause bone toxicity in individuals with inadequate vitamin D status.³⁷ Women in the highest quintile of total vitamin A intake have a 1.5-times elevated risk of hip fracture.³⁸ Indeed, a recent Cochrane Review found that vitamin A supplements increased the total mortality rate by 16%,³⁹ perhaps through antagonism of vitamin D. Another recent Cochrane Review concluded that although vitamin A significantly reduced the incidence of acute lower respiratory tract infections in children with low intake of retinol, as occurs in the Third World, it appears to increase the risk and/or worsen the clinical course in normal children.⁴⁰ As early as 1933, Alfred Hess, who discovered that sunlight both prevented and cured rickets — writing in *JAMA* — warned about vitamin A consumption, concluding, "...as to a requirement of thousands of units of vitamin A daily, the unquestionable answer is that this constitutes therapeutic absurdity, which, happily, will prove to be only a passing fad."⁴¹(p662)

Unfortunately, Hess's⁴¹ prophecy of the fad's passing proved premature. Americans continue to consume multivitamins and/or cod liver oil containing disproportionately small amounts of vitamin D but detrimental quantities of vitamin A. Until quite recently, when most manufacturers willingly changed their product composition, nearly all multivitamins had small amounts of vitamin D (200 to 400 IU) but high amounts of preformed retinol (5,000 IU). This pales in comparison to a tablespoon of modern cod liver oil, most of which contains sub-physiological amounts of vitamin D (400 to 1,200 IU) but supra-physiological amounts of completely preformed retinol (4,000 to 10,000 IU or, in some cases, 30,000 IU).

As Lindsay et al¹ point out, clinical lore holds that vitamin A is an "anti-infective." We suggest that lore exists because of old cod liver oil studies and newer studies in developing countries in which endemic vitamin A deficiency leads to a variety of adverse health outcomes.^{42,43} Semba⁴⁴ reviewed the early literature on vitamin A, finding cod liver oil was a successful "anti-infective." For reasons that are not entirely clear, the cod liver oil of the time contained higher amounts of vitamin D than does modern cod liver oil, perhaps because modern deodorization removes the vitamin D, which processors then replace at lower doses. However, for unclear reasons, the amount of vitamin D in modern cod liver appears to be falling over time. For example, one manufacturer sells cod liver oil with only "naturally occurring vitamins A and D." It contains only 3 to 60 IU

of vitamin D per tablespoon, but between 3,000 and 6,000 IU of vitamin A.⁴⁵

A meta-analysis concluded that vitamin A, when given alone, slightly increased the incidence of respiratory tract infections.⁴⁶ If vitamin A increases the risk of respiratory infections by antagonizing the action of vitamin D, its high content in modern cod liver oils will mask the benefit of adequate vitamin D nutrition. As the prevalence of vitamin A deficiency in the United States — but not in the Third World — is much lower than the prevalence of subclinical vitamin A toxicity,⁴⁷ we cannot recommend cod liver oil or even multivitamins with preformed retinol (retinyl palmitate and retinyl acetate) for either adults or children. (We exclude fish body oil from our warning, as it contains no vitamin A — or vitamin D — but is a very important source of omega-3 fatty acids.)

In a recent assessment of serum retinyl esters in a group of obese Wisconsin adults, 4% had levels of more than 10% of total retinol, which usually indicates hypervitaminosis A.⁴⁸ A diet rich in carrots, sweet potatoes, cantaloupe, and other colorful fruits and vegetables will supply all the carotenoids the body needs to make retinol without the potential for hypervitaminosis A from preformed retinol, especially when preformed retinol exists in other foods in the United States.⁴⁹ Manufacturers should properly balance vitamin D with vitamin A in fortified foods and dietary supplements, although at this time it is unclear what that ratio should be.

We wish that our diets were as rich in vitamin D as they are in vitamin A. With the exception of infants on formula or toddlers drinking large amounts of milk or vitamin D-fortified juice, adequate amounts of vitamin D are virtually impossible to obtain from diet. Unlike vitamin A deficiency, vitamin D deficiency in childhood is now epidemic in Western populations, probably because of the advent of sun exposure protection in the 1980s. Recently, Gordon et al⁵⁰ at Boston Children's Hospital found that 40% of 365 healthy infants and toddlers had 25(OH)D levels of less than 30 ng/mL, and it appears from our extrapolation of their data that more than 85% had levels below 40 ng/mL. Thus, unlike the rare occurrence of vitamin A deficiency in the developed world, childhood vitamin D deficiency is the rule, not the exception.

As Holick's⁵¹ *New England Journal of Medicine* review stressed, the litany of vitamin D deficiency diseases is now legion. Evidence even suggests that vitamin D is involved in the triple current childhood epidemics of autism,⁵² asthma,⁵³ and autoimmune diabetes.⁵⁴ Not only do tenable mechanisms of action exist to explain vitamin D's role in all three, but epidemiological evidence suggesting a vitamin D connection to these devastating diseases is growing. For example, in May 2008, a group at the US National Institutes of Health discovered that boys with autism have unexplained decreased metacarpal bone cortical thickness.⁵⁵ Whatever the connections are, all 3 epidemics appear to have blossomed after wide dissemination of sun avoidance advice in the 1980s.^{52,56,57}

What should practicing health-care providers do? Certainly, we need more science and better public health measures, but what do we do while we are waiting? The conclusion of the 334 scientists from 23 countries at the recent 13th Vitamin D Workshop was that although the problem of insufficient vitamin D is widely recognized and reported, diet will not solve the problem.⁵⁸

The first thing to remember is that the current Adequate Intakes (AI) and Upper Intake Levels (UL) of vitamin D for children, set by the US Institute of Medicine's Food and Nutrition Board (FNB) in 1997, are intended for non-medically supervised intake and do not — and never did — apply to medically supervised treatment. Astonishingly, the FNB says that the AI for vitamin D is the same for the largest pregnant woman as for the smallest premature infant (200 IU/d) — frightening advice for pregnant women, in light of animal studies that showed that gestational vitamin D deficiency causes both neuronal injury and autistic-like gross morphological changes in the brains of offspring.⁵⁹ Furthermore, the FNB's ULs for a 1-year-old, 9-kg (20 lb) child and a 30-year-old, 135-kg (300 lb) adult are also the same — 2,000 IU/d — and are based on their selective focus on 1 flawed study; ample new data from well-conducted clinical trials support raising the UL to 10,000 IU.⁶⁰ The 1997 FNB recommendations offend the most basic principles of pharmacology and toxicology, leading us to conclude that the current official guidelines and limitations for vitamin D intakes are scientifically indefensible.

The diagnosis of vitamin D deficiency in children rests solely on the practitioner's willingness to obtain a serum 25(OH)D level. Sadly, some practitioners still obtain serum 1,25-dihydroxyvitamin D levels, which are often high, not low, in vitamin D deficiency. Just as disappointing, practitioners still advise mothers to "give a multivitamin if you're concerned," without recommending a particular product with an appropriate balance of vitamins A and D, thus delivering inadequate amounts of vitamin D and potentially adverse amounts of vi-

tamin A. (According to our review of the Table of Linday et al,¹ children taking a multivitamin with vitamin D actually had slightly lower mean 25(OH)D levels than did children not taking multivitamins.) Very recent evidence indicates that ideal levels may be above 50 ng/mL. The parent compound (cholecalciferol) does not begin to be routinely stored in fat and muscle tissue until the 25(OH)D levels reach 50 ng/mL.^{3,4} At lower levels, the initial 25-hydroxylation in the liver often follows first-order mass action kinetics, and the reaction is not saturable. That is, at levels below 50 ng/mL, much of the ingested or sun-derived vitamin D is immediately diverted to metabolic needs, indicating chronic substrate starvation. Only a tiny fraction of our children now achieve levels of 50 ng/mL.

Until we have better information on doses of vitamin D that will reliably provide adequate blood levels of 25(OH)D without toxicity, treatment of vitamin D deficiency in otherwise healthy children should be individualized according to the numerous factors that affect 25(OH)D levels, such as body weight, percent body fat, skin melanin, latitude, season of the year, and sun exposure.² The doses of sunshine or oral vitamin D₃ used in healthy children should be designed to maintain 25(OH)D levels above 50 ng/mL. As a rule, in the absence of significant sun exposure, we believe that most healthy children need about 1,000 IU of vitamin D₃ daily per 11 kg (25 lb) of body weight to obtain levels greater than 50 ng/mL. Some will need more, and others less. In our opinion, children with chronic illnesses such as autism, diabetes, and/or frequent infections should be supplemented with higher doses of sunshine or vitamin D₃, doses adequate to maintain their 25(OH)D levels in the mid-normal of the reference range (65 ng/mL) — and should be so supplemented year round. Otolaryngologists treating children are in a good position to both diagnose and treat vitamin D deficiency.

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Competing Interests: Dr Cannell heads the nonprofit educational group The Vitamin D Council and consults for DiaSorin Corporation, which makes vitamin D testing equipment. Dr Vieth is a consultant to the D Drops Company, a vitamin D supplement manufacturer. Dr Grant receives funding from the UV Foundation, the Vitamin D Society, and the European Sunlight Association. Dr Hollis consults for DiaSorin Corporation. Dr Hathcock is an employee of the Council for Responsible Nutrition, a trade association representing manufacturers of dietary supplement ingredients and products.