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COMMENTARY

Cod Liver Oil, the Ratio of Vitamins A and D, Frequent Respiratory Tract Infections, and Vitamin D Deficiency in Young Children in the United States

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We would like to take this opportunity to respond to the Commentary by Cannell and his distinguished colleagues[1] (herein referred to as the "Commentary"). We agree that extensive basic research and adult clinical research performed in the past few decades have demonstrated that the levels of vitamin D required for optimal health are much higher than those needed to prevent rickets in children or osteomalacia in adults; it is also clear that vitamin D deficiency and insufficiency, newly defined for optimal health, are widespread.[2] However, as discussed below, we take a different view on several issues criticized by Cannell et al[1] in their Commentary.

COD LIVER OIL

Cod liver oil, available without a prescription for hundreds of years, is a valuable source of vitamins A and D, as well as long-chain omega-3 fatty acids,[3] all of which may be important in the prevention of respiratory tract illnesses in children (see below, Frequent Respiratory Tract Infections in Young Children). In many populations around the world, cod liver oil continues to be a valuable source of these important nutrients. The across-the-board dismissal of cod liver oil as a supplement advocated by the Commentary ignores this reality. Since the advent of synthetic vitamins in the 1950s, cod liver oil has gone out of favor in the United States, and a valuable source of omega-3 fatty acids has thereby been lost. Only 2% (2 of 94) of children entering Linday's randomized sites supplementation study had a history of cod liver oil use on study entry.[4]

One teaspoon of cod liver oil historically contained 400 International Units (IU) of vitamin D, and it was used for the prevention and treatment of rickets.[5] However, manufacturing processes for the production and purification of cod liver oil have changed substantially over the years.[6] Historically, cod liver oil was "cold-pressed,"[7] meaning that the oil was obtained by pressure alone.[6] Modern manufacturing methods remove both impurities and vitamins (particularly vitamin D); vitamins A and D may or may not be added back to various degrees.

Cod liver oil is not currently regulated or standardized in the United States, and the concentration of both vitamins D and A can vary with the manufacturer, as well as over time. Indeed, as noted in the Commentary,[1] some modern cod liver oils contain very little vitamin D. One such formulation is Nordic Naturals' Arctic Cod Liver Oil, which contains only 1 to 20 IU of vitamin D per teaspoon.[8] On the other hand, the same company's Arctic-D Cod Liver Oil currently contains 1,000 IU of vitamin D per teaspoon,[9] whereas in 2005 the formulation bearing the same name contained only 400 IU of vitamin D per teaspoon.

In their previous work, Linday et al[4,10,11] used Carlson Laboratories' lemon-flavored cod liver oil. Whereas the concentration of vitamin D in this product has remained constant over time at 400 IU per teaspoon, the concentration of vitamin A has steadily decreased. The cod liver oil formulation used in their first supplementation study contained 2,000 to 2,500 IU of vitamin A per teaspoon[10]; that used in their subsequent research contained only 1,000 to 1,250 IU of vitamin A per teaspoon[4,11]; and the current product contains only 700 to 1,200 IU of vitamin A per teaspoon.[12]

For children, a formulation that contains 400 IU of vitamin D per teaspoon is consistent with the current recommendations of the American Academy of Pediatrics (AAP).[5] Use of higher doses of vitamin D should

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be discussed with the child's qualified health-care practitioner. Further considerations, particularly important for children, are the taste and purity of the product; information on purity must be obtained from the manufacturer. The toxic limits for contaminants are based on the size (weight) of the consumer. Whereas most cod liver oils and fish oils are sufficiently pure for older children and adults (because of their larger size), only a few products are sufficiently pure for infants and young children.[13]

Cod liver oil contains vitamins A and D, as well as long-chain omega-3 fatty acids, and has been a traditional source of maintenance doses of these 3 constituents. However, it is not appropriate to use a combination product, whether a pharmaceutical product or cod liver oil, to provide high doses of a single constituent. Thus, if high doses of any single constituent of cod liver oil are needed, an appropriate individual product should be used. For example, cod liver oil should not be used as the source of the high doses of omega-3 fatty acids needed for the treatment of bipolar disorder[14] or hypercholesterolemia.[15]

Reinhold Vieth, a co-author of the Commentary,[1] stated, "Basically, if you're taking your teaspoon full of cod liver oil, it's fine...but higher levels are not associated with health."[16] The fact that cod liver oil is not currently standardized or regulated in the United States results in variability in the concentrations of vitamin D and vitamin A in different preparations of this product. It is therefore essential that a well-informed and knowledgeable consumer *read the label* before purchasing any given formulation of cod liver oil.

RATIO OF VITAMIN A TO VITAMIN D

In the responses to the Commentary from the on-line supplement[17,18] and nutrition newsletter[19] communities, the issue of the proper ratio of vitamin A to vitamin D emerged as a major concern. Whereas the proper ratio is not well established in humans, excellent information is available on this topic for developing poultry, species in which bone growth and calcium metabolism have been closely studied.[20,21] The most recent recommendations for growing turkeys are 5,000 IU of vitamin A and 1,100 IU of vitamin D_3 per kilogram per day, yielding a vitamin A/D ratio of 4.4.[21] For immature Leghorn-type chickens laying white eggs, the recommendations are 1,500 IU of vitamin A and 200 to 300 IU of vitamin D_3 per kilogram per day, yielding ratios of 5 to 7.5.[21]

In their first supplementation study, Linday et al[10] used a total of 4,500 to 5,000 IU of vitamin A and 600 to 700 IU of vitamin D per day, yielding vitamin A/D ratios of 7.1 to 7.5. In their subsequent supplementation studies, these researchers used a basic dose of 3,500 to 3,750 IU of vitamin A and 600 to 700 IU of vitamin D per day, yielding ratios of 5.4 to 5.8.[4,11] Thus, the ratios of vitamin A to D utilized by Linday et al[4,10,11] in their studies with growing children are consistent with those recommended for growing poultry.

The Commentary[1] cites the work of Rohde et al[22,23] to support the statement that "Retinoic acid antagonizes the action of vitamin D and its active metabolite."[1(p866)] However, very high doses of vitamin A were used in that work. It is therefore enlightening to calculate the vitamin A/D ratios utilized by Rohde et al[22,23] in their rat studies and compare them to the above ratios. The following conversion factors were used in this calculation: 1 μg of vitamin D_3 = 40 IU; 1 μg of vitamin A = 3.3 IU.[24] In their original rat study, Rohde et al[22] reported toxicity at a vitamin A/D ratio of 54,702 (based on International Units). In their later work, Rohde and DeLuca[23] noted that vitamin A interfered with vitamin D at ratios of 5,676 and 11,353 (also based on International Units). We therefore conclude that it is not appropriate to apply the results of these two rat studies by Rohde et al[22,23] to those of Linday et al.[4,10,11]

PREVIOUS WORK OF LINDAY AND COLLEAGUES

Randomized Sites Supplementation Study. The Commentary states that the earlier work of Linday et al on the prevention of upper respiratory tract infections was "less than robust,"[1(p866)] and that the intervention "slightly reduced ($p = 0.04$) the mean number of upper respiratory tract visits."[1(p864)] These comments suggest that the authors of the Commentary are confusing probability with clinical significance, and a clarification is therefore in order. A p value is the probability that a finding will occur by chance alone.[25] In the medical literature, the traditional p value of less than 0.05 means that there is less than a 5% chance that the finding occurred by chance alone, and a p value of 0.04 is therefore statistically significant. However, probability is not the same as clinical effect or effect size.[25,26] During the supplementation period, pediatric visits for upper respiratory tract disorders in the supplementation group of Linday et al[4] decreased by one third to one half (see their Table 2); this is a clinically meaningful effect that warrants repetition in further studies.

Blood Levels of 25-Hydroxyvitamin D. In their study of plasma 25-hydroxyvitamin D [25(OH)D] levels in 16 young children undergoing placement of tympanostomy tubes, Linday et al[27] reported that there was no statistically significant difference in 25(OH)D levels when analyzed by vitamin use (as reported by the subjects' parents[10]). This is a legitimate statement; however, a finding of "no difference" with a small sample may be an artifact of the small sample size. Valid, generalized conclusions of "no difference" require a large sample size to have sufficient statistical power.[25,26] In the above-referenced study,[27] the sample size needed to perform a study large enough to support the general conclusion that vitamin supplementation has no effect on plasma 25(OH)D levels, with the traditional statistical power of 0.8, would be 360 subjects (180 in each group),[26] not the 16 subjects (8 in each group) reported by Linday et al.[27]

The Commentary notes that "children taking a multivitamin with vitamin D actually had slightly lower mean 25(OH)D levels than did children not taking multivitamins."[1(p868)] The latter statement is correct; the mean plasma 25(OH)D level in the no-vitamin group was 2.5 ng/mL (6.2 nmol/L) higher than that for the vitamin group.[27] However, although the above Commentary statement is correct, it is not meaningful, since a valid inference cannot be drawn from data that are not statistically significant. Given the context of the above-referenced statement, the authors appear to be implying that the combined use of vitamins A and D in a supplement leads to lower 25(OH)D levels than would be achieved with the same dose of vitamin D given alone. This is not a fact, but a hypothesis that needs to be tested in a study with a sufficient sample size to support a valid negative result, as discussed above. In addition, the original specimens of Linday et al[10,27] were collected from February through April as part of a different study that did not include vitamin D; thus, no data were collected regarding family holiday trips to sunny areas, which might have influenced the plasma 25(OH)D levels.

VITAMIN A TOXICITY AND YOUNG CHILDREN IN THE UNITED STATES

It is unlikely that infants and children in the United States are suffering from subclinical vitamin A toxicity,[19] since young infants and children in the United States have lower levels and stores of vitamin A than adults.[28-30] Severe vitamin A deficiency to the degree seen in equatorial countries is not present in the United States. However, US children with a poor diet may be at risk of vitamin A insufficiency, and this is particularly true of low-income children.[31] Cannell et al[1] are correct that none of the children from whom Linday et al[10] obtained serum retinol levels were deficient (less than 20 μg/dL). However, 15% (6 of 39) had suboptimal levels (less than 30 μg/dL); most of these children were Hispanic general service patients not taking vitamins.

The Commentary states, "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."[1(p867)] Although this may be true for adults, young children are "notorious for not eating fruits and vegetables,"[29(p380)] and those "fruits and vegetables high in vitamin A are frequently not the child's favorite foods."[29 (p380)] Thus, toddlers and preschool-age children, especially children with poor health care living at or below the poverty level, are at risk for subclinical vitamin A deficiency in the United States.[29] Moreover, there is a growing literature showing a wide interindividual variation, and relative inefficiency, in the metabolism of carotenoids; in contrast, vitamin A absorption has not been shown to have widespread interindividual variation.[32]

The Commentary[1] is correct that Hess et al,[33] studying the diet and supplementation of infants and children institutionalized at the Home for Hebrew Infants in New York City in the 1930s, found that the addition of thousands of units of vitamin A to their basic diet did not protect these infants and children from additional infections. However, it should be noted that by 3 months of age, their baseline diet already contained about 1,500 IU/d of vitamin A from milk[34]; the importance of the infant diet was emphasized in this institution, where "orange juice is prescribed at the age of 6 weeks, cereal at 4 months, vegetables at 6 months, desserts at 8 months, eggs at 10 months and meat at 1 year."[35(p1338)] Furthermore, it is unclear how the results of this pioneering study of institutionalized infants and children from more than 70 years ago should be applied to children living under the socioeconomic and nutritional conditions in the United States at the present time.

Vitamin A supplementation has reduced child mortality worldwide; however, it has been known for some time that although large doses of vitamin A may be protective in undernourished children, they may be ineffective or even detrimental in healthy children; this is known as the "vitamin A paradox."[36] In the United States, the American Academy of Pediatrics only recommends high-dose vitamin A treatment for the prevention of complications of measles[24]; high-dose vitamin A therapy is not used to treat respiratory tract infections in chil-

dren in the United States. In addition, Penniston and Tanumihardjo's[37] published concern about possible subclinical vitamin A toxicity was in regard to developing countries in which undernourished women and children are given intermittent large doses of vitamin A.

Childhood cod liver oil consumption has recently been linked to decreased forearm bone mineral density in perimenopausal and postmenopausal Norwegian women.[38] However, as those authors note, the vitamin A content of Norwegian cod liver oil had been reduced by 75% by 2002 because of reports of detrimental effects of excessive vitamin A intake on bone (see also the above section Cod Liver Oil). Moreover, even this finding is debated; new research from the United States Women's Health Initiative Observational Study reported no association between vitamin A or retinol intake by postmenopausal women and the risk of hip or total fractures, and only a modest increase in total fracture risk in women in the low–vitamin D intake group with the highest vitamin A and retinol intakes.[39]

FREQUENT RESPIRATORY TRACT INFECTIONS IN YOUNG CHILDREN

The subject of vitamin D and infections is highly relevant to the health of young children and is likely to be the most fruitful area of research in this age group to provide the functional outcomes sought by those who write the pediatric guidelines.[40] This topic was the subject of a recent review article,[41] and it is an area of active research.[42-44]

However, there are numerous potential modifiers of the effect of vitamin D on immunity, including age, baseline vitamin D status, general nutritional status (including the status of other vitamins, lipids, and micronutrients), the cause of respiratory infections (viral versus bacterial), and the anatomic site of the infection (lower versus upper respiratory tract). For example, Roth et al[45] did not find an association between vitamin D status and the risk of hospitalization for acute bronchiolitis in young Canadian children with relatively replete vitamin D status. In another Canadian study, neonatal vitamin A deficiency appeared to be a significant risk factor for acute otitis media and lower respiratory tract infections in preschool Inuit children in Quebec, Canada.[46] Vitamin A has long been known to have important effects on immunity.[47,48] Additionally, long-chain omega-3 fatty acids, another important component of cod liver, have also been shown to have independent positive effects on immunity in Thai schoolchildren.[49]

Regarding susceptibility to infection, an interrelationship between vitamin A and other nutrients, including vitamin D, iron, and zinc, has been previously reported.[50,51] A recent report of a 9-month-old child with seizures and pneumonia revealed that he had vitamin D deficiency rickets, iron deficiency anemia, and severe protein-calorie malnutrition and was also vitamin A–deficient (serum vitamin A level of 7 μg/mL; the laboratory reference range was 11.3 to 64.7 g/mL).[52] In a recent review of nutrition and the global burden of acute lower respiratory tract infection in childhood, Roth et al[53] concluded that implementation and evaluation of multicomponent nutritional interventions in developing countries should be a high priority, both to reduce the mortality associated with these disorders and to decrease the overall disease burden. Noting problems in nutritional research with the current use of the pharmaceutical model, in which a randomized control trial is performed with a single nutrient, Heaney[54] suggested the use of a global index as the primary design end point for most studies of nutrient effects.

PREVALENCE OF VITAMIN D INSUFFICIENCY IN YOUNG CHILDREN IN THE UNITED STATES

The Commentary states, "The diagnosis of vitamin D deficiency in children rests solely on the practitioner's willingness to obtain a serum 25(OH)D level."[1(p867)] This unfortunate statement is not correct, and it is a gross oversimplification of a complex issue. Obtaining blood specimens from infants and young children can be difficult; 25(OH)D assays are expensive, and reimbursement is problematic; there are multiple different methods for the measurement of 25(OH)D, and standardization of the results obtained by the various methods is a work in progress.[55,56] In a pediatric review, winter season, higher body mass index, and black race/ethnicity were associated with lower blood 25(OH)D concentrations, as was older age (beyond the newborn period).[57] However, there was a significant variation in the assays employed and in the cutoff values used to define deficiency; estimates of the prevalence of hypovitaminosis D therefore ranged from 1% to 78%.

Classic rickets, a bone disorder of growing infants and children, is primarily a sunshine deficiency disease that was historically treated with exposure to sun and/or ultraviolet light; it was also treated and prevented with cod liver oil.[58,59] In 1925, Eliot[60] published the results of the United States Children's Bureau demonstra-

tion project, begun in New Haven in 1923, which documented that rickets could be prevented with cod liver oil and regular sunlight exposure beginning within the first month of life.[59,60]

Once fortification of milk with vitamin D became common in the 1930s, rickets was eradicated as a significant public health problem in the countries using this practice, currently the United States and Canada.[58,61] In the 1930s, infants fed human milk were also provided with some form of vitamin D supplementation.[59] Recently, there has been a resurgence of rickets in the United States, particularly among dark-skinned infants who are exclusively breast-fed without vitamin D supplementation.[62] The recognition that vitamin D status higher than that needed to prevent bone disease may reduce the risk of type 1 diabetes mellitus, hypertension, and cancer has stimulated renewed interest in vitamin D in the pediatric age group.[57] Low levels of vitamin D in black adolescents have recently been linked to obesity.[63] Along with the relationship of vitamin D to infection, these areas are likely to be the most fruitful research topics to provide the functional pediatric outcomes for vitamin D sought by those who write the guidelines for the AAP.[40]

TREATMENT OF VITAMIN D INSUFFICIENCY IN YOUNG CHILDREN IN THE UNITED STATES

Vitamin D supplements are inexpensive, particularly in comparison to the cost of vitamin D assays. However, the doses needed to treat vitamin D deficiency and insufficiency in US infants and children are equal to, or higher than, the tolerable upper intake levels of vitamin D supplementation set by the Institute of Medicine (IOM).[64,65] It is therefore unlikely that pediatricians will be comfortable prescribing these doses to asymptomatic children, particularly without the guidance of reliable blood 25(OH)D levels. Furthermore, although sunshine is free, limited sun exposure is recommended, since overexposure to sunlight is carcinogenic[58,66]; hence, pediatricians are unlikely to be comfortable recommending increased sun exposure.

In 1997, the IOM set the Adequate Intake (AI) of vitamin D at 200 IU (5 μg) per day from the newborn period through 50 years of age.[64] The AAP initially decreased their long-standing recommendation to comply with that of the IOM.[67] However, in 2008, the AAP reverted to its previous recommendation of a vitamin D intake of at least 400 IU (10 μg) to prevent vitamin D deficiency in healthy infants, children, and adolescents.[5] The AAP also recommended a serum 25(OH)D level of at least 20 ng/mL (50 nmol/L), but provided no specific recommendations regarding routine monitoring of levels.[5] Updated IOM guidelines on vitamin D and calcium are expected in May 2010.[68]

The amount of vitamin D needed to correct deficiency or insufficiency depends on the baseline blood level of 25(OH)D. The data from adults demonstrate a greater response in subjects with lower initial blood 25(OH)D levels.[69-71] Supplementation studies in infants and children indicate that 25(OH)D levels plateau around 30 ng/mL (75 nmol/L)[72]; thus, further research will therefore be needed to clarify whether higher levels are indicated in these younger age groups.

Regarding the final paragraph of the Commentary, we note that both the critical recommendation that "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"[1(p868)] and the authors' concerned comments about the need for adequate 25(OH)D blood levels in children with chronic illnesses are not referenced to specific clinical trials, but rather, are based on the authors' expert opinion. Clearly, additional research on functional outcomes and the long-term effects of vitamin D in childhood are needed. Nonetheless, we believe that new guidelines from the IOM with recommendations of higher levels for the adequate intake and tolerable upper intake of vitamin D for children and adults will have health benefits for Americans of all ages, and we await the updated IOM guidelines with great interest.

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