21 Nutritional Supplements and Upper Respiratory Tract Illnesses in Young Children in the United States

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KEY POINTS

- In the United States, children have lower blood levels than adults of eicosapentaenoic acid (EPA), an important ω-3 fatty acid that helps decrease inflammation; vitamin A, the "anti-infective" vitamin; and selenium (Se), a trace metal that is an intrinsic part of glutathione peroxidase, an important free-radical scavenging enzyme.
- EPA, vitamin A, and Se are important in controlling inflammation and can be supplied by oral nutritional supplements.
- Cod liver oil contains EPA (and other important ω-3 fatty acids), and vitamin A as well as vitamin D.
- Fish oil contains ω-3 fatty acids (including EPA) but no vitamins.
- Our clinical research demonstrates that daily supplementation with a flavored cod liver oil (which meets European purity standards) and a children's multivitamin-mineral with trace metals, including Se, can decrease morbidity from upper respiratory tract illnesses, otitis media, and sinusitis in young children living in the United States.
- These supplements can be used by practitioners on an individual basis, when clinically indicated; the supplements can be purchased in the United States without a prescription.
- Socioeconomically disadvantaged children are at risk for micronutrient deficiencies. However, their families may not be able to afford to purchase these supplements, which are not available through Medicaid, The Special Supplemental Nutrition Program for Women, Infants and Children, or the Food Stamp Program.
- If our results are confirmed in larger studies, a system change will be needed to provide these supplements to nutritionally vulnerable, socioeconomically disadvantaged children living in the United States.

1. INTRODUCTION

Upper respiratory tract illnesses, otitis media (OM), and sinusitis are common and costly disorders among young children living in the United States. Inflammation is a

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key element in the pathophysiology of these disorders. This chapter discusses the role of essential fatty acids, vitamins, and trace metals in the pathophysiology of inflammation; reviews our clinical research on the use of a lemon-flavored cod liver oil (which meets European purity standards) and a children's chewable multivitamin-mineral with Se for the prevention and adjunctive treatment of these disorders; reviews the history of cod liver oil, including its importance in the discovery of vitamin D and the anti-infective properties of vitamin A; and discusses the current clinical use of these supplements. If additional research confirms the utility of these supplements in improving the health of young children, the problem of access to these supplements by socioeconomically disadvantaged children in the United States will need to be addressed.

2. BACKGROUND

2.1. Upper Respiratory Tract Illnesses, Otitis Media, and Sinusitis in Children in the United States

Children under age 5 yr had an average of 20.7 million ambulatory care visits per year for upper respiratory conditions in the United States from 1993 to 1995, with another 14.5 million visits per year for OM during the same time period *(1)*. In addition to their cost, unnecessary health care visits for the treatment of colds generate a significant number of inappropriate antibiotic prescriptions *(2,3)*, although the situation is now improving *(4,5)*. Bacterial antibiotic resistance is considered to be a major public health problem in the United States, and an interagency federal action plan has identified the decrease of unnecessary antibiotic prescriptions as critical to combating antimicrobial resistance *(6)*.

In 1996, Gates *(7)* estimated that the total annual cost of treating OM with effusion in the United States was $5 billion, including both direct and indirect costs. This estimate included the cost of surgical placement of tympanostomy tubes (ventilation tubes placed in the tympanic membrane of the ear), a procedure that is commonly performed for the treatment of this disorder *(8)*. Frequent OM with effusion in early childhood may be associated with later speech and language problems, although causative relationships have not been definitively established *(9,10)*.

Sinusitis also is a common and costly condition *(11)*; in 1996, overall health care expenditures for sinusitis in the United States were estimated to be $5.8 billion, of which $1.8 billion was for children age 12 yr or younger. The primary treatment of sinusitis in children is medical management. Adenoidectomy may be helpful *(12)*, although endoscopic sinus surgery is reserved for chronic, refractory cases *(13,14)*. Chronic sinusitis has a major negative impact on the quality of life of children whose disease is sufficiently severe to require endoscopic sinus surgery *(15)*.

2.2. Viruses and Vaccines

Viral illnesses usually are brief and self-limited conditions. However, viral infections produce inflammation, enhance nasopharyngeal bacterial colonization and adherence, alter the host's immune defenses, and are associated with bacterial complications, including acute OM *(16)*, sinusitis, and pneumonia *(17,18)*. Acute OM occurs in about 20% of children with viral upper respiratory infections *(17)*. Although viral vaccines are in development, the use of vaccines to prevent upper respiratory tract infections is hampered by the large number of different viruses causing these

infections *(17)*. The US Advisory Committee on Immunization Practices voted to recommend influenza vaccination for children ages 6 to 23 mo for the coming influenza season of 2004 to 2005; the impact of this recommendation remains to be seen *(19)*. Despite the fact that *Streptococcus pneumoniae* is the most common cause of bacterial acute OM, the heptavalent pneumococcal polysaccharide conjugate vaccine only produced a 6% reduction in the overall number of episodes of acute OM from any cause *(20)*.

2.3. Free Radicals, Trace Metals, and Inflammation

Free radicals are molecules, or molecular fragments, with one or more unpaired electrons in their outer orbit; they are highly reactive chemical entities that can initiate oxidative stress and damage lipid membranes by a process known as lipid peroxidation. Free radicals are important in the pathophysiology of inflammation; they can also damage proteins and DNA, and have been linked to numerous disease states *(21)*. The body's free-radical scavenging capacity is determined by the levels of free radical scavenging enzymes, as well as their related trace metals and vitamins; this system protects membranes from peroxidation *(21)*. The trace metals Se, zinc, copper, and manganese are critical for the function of these enzymes; oral supplements of trace metals can increase the activity of the free radical scavenging enzymes.

Glutathione peroxidase (GSH-Px) is one of the key enzymes in the protective free-radical scavenging system, and Se is a structural component of the active center of GSH-Px *(22)*. GSH-Px activity decreases during Se depletion and increases during Se repletion *(22–24)*. Superoxide dismutase (SOD) is another important free-radical scavenging enzyme. Two SOD isoenzymes have been identified in mammalian cells. An isoenzyme containing copper and zinc has been found in the cytosol; the SOD isoenzyme found in the mitochondria contains manganese. These isoenzymes are dependent on their respective trace metals for their activity *(24)*. Vitamins, especially vitamins A and C and the B vitamins, are important cofactors in this system. Other free-radical scavenging enzymes include glutathione reductase, glutathione transferase, and catalase, discussed in refs. *24* and *25*.

2.4. Essential Fatty Acids

Fatty acids containing more than one double bond are classified as polyunsaturated fatty acids (PUFAs). There are two series of PUFAs, the ω-3 and ω-6 fatty acids, named for the distance of the first double bond from the methyl end of the molecule *(26)*. The two essential fatty acids (EFAs) are linoleic acid, the parent compound of the ω-6 series, and α-linolenic acid, the parent compound of the ω-3 series. They are essential because humans, like all mammals, cannot make them and must obtain them from their diet. Once consumed, linoleic acid and α-linoneic acid may be elongated further and desaturated to form long-chain PUFAs *(26)*. The ω-3 and -6 series are not interconvertible in the human body; they are metabolically and functionally distinct, compete for the same enzymes, have opposing physiological functions, and their proper balance is important for homeostasis and normal development *(26)*.

EPA and docosahexaenoic acid (DHA) are two important ω-3 fatty acids. The brain and retina are rich in DHA *(27)*, which is necessary for normal visual and neural development (ref. *28*; *see* Chapter 26). EPA is an important precursor of anti-inflammatory eicosanoids, whereas the ω-6 fatty acids (especially arachidonic acid [AA]) are precursors

of inflammatory eicosanoids *(29)*. The level of ω-3 fatty acids and other PUFAs is largely determined by diet, unlike proteins, whose structure is genetically determined *(26,30)*.

Changes in dietary habits in the United States in the last 20 to 30 yr have markedly increased the amount of ω-6 EFA consumed (as in vegetable oils), whereas the amount of consumed ω-3 EFA (as in cod liver oil and fish oil) has decreased *(26,31,32)*. The optimal ratio of ω-6/ω-3 EFA in the diet is 3 to 4:1; in the United States, it is currently 10 to 20:1. This abnormal ratio has been linked with numerous disease states, especially those associated with inflammation. ω-3 fatty acid levels can be increased by eating more fatty fish and by consuming nutritional supplements such as cod liver oil, algal-derived long-chain fatty acids, or fish oils *(26,31,32)*.

2.5. Inflammation in Animal Models of Otitis Media and Sinusitis

Free radical-induced lipid peroxidation may play a role in the acute *(33–35)* and chronic inflammation *(36)* of a guinea pig model of acute, unilateral OM caused by infection with *S. pneumoniae.* Inflammatory mediators have been demonstrated in both experimental and human middle ear effusions; these mediators include leukotrienes and prostaglandins, which are metabolites of AA and are derived from phospholipids in cell membranes. Treatment with specific inhibitors of these mediators has prevented the development of OM in some animal models of OM *(37)*. Free radicals are significant components of the inflammatory response, which is part of the pathophysiology of pneumococcal infections *(38)* and the influenza A virus *(39)*; the latter are important causes of OM. Reactive oxygen species (ROS) *(40)* have also been implicated in sinusitis.

2.6. Nutritional Supplements and Infection

The association between respiratory virus infections and acute OM in children is well-established *(41,42)*. Oral supplementation with EFAs *(43)* and zinc *(44)* has been shown to decrease the incidence of respiratory infections in children. Trace elements (including zinc and Se) have been shown to have important effects on the regulation of immune responses *(45)*. Supplementation with ω-3 fatty acids has been reported to be beneficial in preventing infection in surgical patients *(46)*. The importance of ω-3 fatty acids and trace metals (including zinc and Se) is already recognized in the relatively new field of "immunonutrition" *(47–49)*. The clinical efficacy of antioxidants in the treatment of OM has been reported by two groups of Russian investigators *(50,51)*. Of interest is the work of Ginsburg *(52)*, who proposed that the main cause of tissue damage in infectious and inflammatory conditions is synergistic interactions among ROS, microbial hemolysins, enzymes, and cytokines.

2.7. Anti-Inflammatory Properties of Antibiotics

Antibiotics may have anti-inflammatory actions in additional to their antibacterial effects *(53,54)*. Macrolide antibiotics, effective in the treatment of adults with chronic rhinosinusitis *(55)*, have anti-inflammatory properties that contribute to this effect. However, the overuse of antibiotics is associated with the development of bacterial antibiotic resistance. In Finland, the prevalence of macrolide-resistant group A streptococci diminished after the heavy use of macrolide antibiotics decreased *(56)*. In this age of antibiotic resistance, it is preferable to use antibiotics for their antibacterial effects rather than as anti-inflammatory agents.

3. CLINICAL RESEARCH

3.1. Blood Levels of Fatty Acids, Trace Metals, and Vitamin A

In our first study *(57)*, we obtained blood samples from 44 children undergoing clinically indicated ambulatory surgery at The New York Eye & Ear Infirmary (NYEE). There were 39 subjects in the tympanostomy tube group (TT); these children were undergoing placement of tympanostomy tubes for frequent ear infections and/or persistent middle ear effusion, with or without concomitant adenoidectomy and/or tonsillectomy. Their mean (± standard deviation [SD]) age was 3.8 ± 1.8 yr; 72% were male; approximately half were Hispanic and half were white; approximately half were private patients; and almost half were taking vitamin supplements.

The comparison group (COMP) was composed of children undergoing eye-muscle surgery as well as those undergoing ear, nose, and throat procedures such as bronchoscopy or laryngoscopy that did not involve the ears, adenoids, or tonsils. These subjects were slightly older, with a mean age of 5.7 ± 1.8 yr, and there was a lower percentage (20%) of private patients.

No demographical information was available for the six adults in the adult control group (AC), supplied by Ann Moser of the Peroxisomal Disease Section of the Kennedy Krieger Institute Genetics Laboratory (Baltimore, Maryland). Data regarding red blood cell (RBC) fatty acids, trace metals, and vitamin A were available for subsets of these subjects.

3.1.1. Red Blood Cell Fatty Acids

The RBC fatty acid data are summarized in Table 1. The mean values for EPA were lower in both groups of NYEE children than in the ACs supplied by Kennedy Krieger. The mean RBC EPA values were: (a) TT = 0.31% ± 0.02% (standard error [SE]), (n = 16); (b) COMP = 0.31% ± 0.04% (SE), (n = 5); and (c) AC = 0.48% ± 0.4% (SE), (n = 6). These differences were statistically significant when analyzed by both parametric (ANOVA, $p < 0.002$; F[2,24] = 8.336) and nonparametric (Kruskal-Wallis ANOVA by Ranks, $p = 0.007$; H[2, n = 27] = 9.924) tests. No other significant differences in RBC fatty acids were noted among the three groups, although additional differences might become apparent with larger sample sizes.

In 1986, Japanese investigators reported lower plasma levels of ω-3 fatty acids in young normal and atopic children than in adults *(58)*. They ascribed these findings to dietary changes in Japan in the 30 yr prior to the study.

3.1.2. Trace Metals

Data for plasma Se, zinc, and copper for the children in the TT group are summarized in Table 2; data from the published literature for children *(59)* and adults *(25)* for these parameters is also included, as are International System Units. There was no statistically significant difference between the mean plasma Se for study subjects (TT = 110 ng/mL ± 16.3 SD; n = 39) and the published values for children. Both groups of children had lower Se levels than published values for adults ($p < 0.005$, ANOVA; F = 20.442; F[0.005] 3140 = 4.47) *(60)*. Statistical analyses were performed only for Se because only the variances for Se were homogeneous (Bartlett's test for homogeneity of variances *(60)*.

3.1.3. Vitamin A

The mean plasma vitamin A (retinol) level for the TT group was 39.1 µg/dL ± 10.8 (SD); (range: 23.6–72.1 µg/dL; n = 39). (Multiply conventional units by 0.0349 to convert

Table 1
Red Blood Cell Levels of Fatty Acids

Fatty acids	*Tympanosotomy tube group (NYEE children; n = 16)*	*Comparison group (NYEE children; n = 5)*	*Adult control group[a] (Kennedy Krieger; n = 6)*
ω-6 18:2 ω-6 (linoleic)	9.35 ± 0.28	9.46 ± 0.50	8.55 ± 0.45
20:3 ω-6 (dihomo-γ-linolenic)	1.57 ± 0.08	1.69 ± 0.15	1.70 ± 0.14
20:4 ω-6 (AA)	15.94 ± 0.36	15.44 ± 0.64	16.36 ± 0.59
ω-3 18:3 ω-3 (α-linolenic)	0.29 ± 0.06	0.23 ± 0.10	0.29 ± 0.09
20:5 ω-3 (EPA)	0.31 ± 0.02[b]	0.31 ± 0.04[b]	0.48 ± 0.04
22:6 ω-3 (DHA)	3.78 ± 0.33	3.65 ± 0.60	3.97 ± 0.54
Total ω-6	33.49 ± 0.40	33.38 ± 0.72	32.31 ± 0.66
Total ω-3	6.35 ± 0.36	6.10 ± 0.65	6.79 ± 0.60
Total ω-9	13.56 ± 0.26	13.44 ± 0.47	13.76 ± 0.43

Data are mean percentage of total fatty acids ± SE.

[a]Adult Control data supplied by Ann Moser of Peroxisomal Diseases Section of Kennedy Krieger Institute Genetics Laboratory (Baltimore, Maryland).

[b]Values for NYEE groups are less than those for adult control group; $p = 0.007$, Kruskal-Wallis analysis of variance by ranks.

NYEE, New York Eye and Ear Infirmary; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

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to international units *[61]*). Ballew *(62)* defined an inadequate vitamin A level as less than 20 µg/dL and a suboptimal vitamin A level as less than 30 µg/dL. The upper limit of the pediatric reference range for vitamin A is 80 µg/dL *(61)*. Therefore, overall, the values for our subjects were within the reference range. Russell *(63)* stated that a vitamin A level of 40 µg/dL predicted normal dark adaptation 95% of the time; 69% (27/39) of our subjects had vitamin A levels less than or equal to 40 µg/dL, although parents denied symptoms of night blindness for all children. Our finding is consistent with Ballew's *(62)* report that the 75th percentile for serum retinol levels in children ages 4 to 8 yr was 39.0 µg/dL. In addition, 15% (6/39) of our sample had suboptimal levels (<30 µg/dL), although none were inadequate *(62)*. In this suboptimal group, five of six children were not taking vitamin supplements, five of six children were Hispanic, five of six children were general service patients, and four of six children were female (all of whom were Hispanic). The overrepresentation of Hispanic children in the subgroup of children with suboptimal vitamin A levels was also consistent with previous reports *(62)*.

On a group basis, there was no statistically significant difference in the mean vitamin A levels between the subgroup of children whose families reported that they were taking vitamin supplements (39.7 µg/dL ± 11.6 SD; $n = 17$) and the subgroup of children whose families reported that they were not taking vitamin supplements (38.7 µg/dL ± 10.4 SD; $n = 22$). Our subjects took a variety of prescription and over-the-counter vitamin preparations; no children were receiving or had taken cod liver oil; only one child in the fatty acid subgroup had a history of fish oil ingestion. Of the eight different children's vitamin preparations examined, all contained vitamin A palmitate, vitamin A acetate, and/or β-carotene.

Table 2
Plasma Levels of Selenium, Zinc, and Copper

		Tympanostomy tube group (57) (NYEE Children; n = 39)	*Children (59) (n = 83)*	*Adult Long Island Jewish Controls (25) (n = 12)*	*Adult West Coast Controls (25) (n = 14)*
Selenium	(ng/mL)	110 ± 16[a]	106 ± 18[a]	129 ± 22	142 ± 18
	(μmol/L)	1.40 ± 0.21	1.35 ± 0.23	1.64 ± 0.27	1.81 ± 0.23
Zinc	(μg/mL)	0.9 ± 0.1	1.0 ± 0.2	1.3 ± 0.2	1.8 ± 0.5
	(μmol/L)	13.9 ± 2.0	15.3 ± 3.1	19.9 ± 3.1	27.5 ± 7.6
Copper	(μg/mL)	1.3 ± 0.2	1.2 ± 0.3	1.1 ± 0.2	1.3 ± 0.5
	(μmol/L)	20.7 ± 3.3	18.8 ± 4.7	17.3 ± 3.1	20.4 ± 7.8

Data are mean ± SD.
[a]Children less than adults ($p < 0.005$, analysis of variance).
(Reprinted with permission from ref. *57*.)

3.1.4. Summary of Blood-Level Data and Choice of Nutritional Supplements

The blood-level data *(57)* revealed that (a) study children had lower levels of RBC EPA than adult controls; (b) 69% of study children had plasma vitamin A (retinol) levels in the lower reference range, with 15% in the suboptimal range; and (c) study subjects, like other children, had lower levels of plasma Se than adults.

Therefore, for our clinical studies, we chose cod liver oil as a source of both vitamin A and EPA and used it in conjunction with a marketed children's chewable multivitamin/mineral preparation containing Se. We specifically chose cod liver oil as a source of vitamin A on the basis of our blood-level data, which revealed no significant difference in the vitamin A levels between the subgroups of children who were taking vitamin supplements and those who were not. Although we could have used fish oil as the source of EPA, fish oil does not contain vitamin A or D. The detailed contents of these supplements are shown in Table 3. The vitamin A content of cod liver oil used in our initial pilot study on OM was 2000 to 2500 IU/teaspoon (5 mL); in the subsequent two studies, the vitamin A content was decreased to 1000 to 1250 IU/5 mL.

3.2. Pilot Clinical Research on Otitis Media

To explore the clinical utility of these supplements, we then performed an open-label secondary prevention study, in which each child served as his or her own control *(64)*. We studied one OM season, from September 1, 2000 to March 31, 2001 *(57)*. All children were patients of the Soho Pediatrics Group, a private group practice in lower Manhattan, New York. Children were required to have had at least one episode of OM from September 1 to November 30, 2000 (the early portion of OM season under consideration). Children with a known allergy to fish were excluded.

Eight children were enrolled, ranging in age from 0.8 to 4.4 yr; seven were Caucasian, half were female, and all families were English-speaking. After enrollment, subjects received 1 teaspoon of lemon-flavored Norwegian cod liver oil and one-half of a tablet of Carlson's Scooter Rabbit chewable multivitamin-mineral (MVM) tablet per day (*see* Table 3). Mothers were instructed to crush the MVM

Table 3
Contents of Supplements

Carlson's lemon-flavored cod liver oil (1 teaspoon; 5 mL):	
ω-3 essential fatty acids:	
DHA	500–550 mg
EPA	460–500 mg
α-Linolenic acid	45–50 mg
Vitamins:	
Vitamin A	1000–1250 IU: randomized pediatric sites *(83)* 1000–1250 IU: Sinusitis Pilot Study *(81)* 2000–2500 IU: Otitis Media Pilot Study *(57)*
Vitamin D	400–500 IU
Vitamin E	1 IU
One-half of a tablet of Carlson's Scooter Rabbit chewable vitamins and minerals[a]:	
Vitamins:	
Vitamin A (palmitate)	2500 IU
Vitamin D_3	200 IU
Vitamin E	30 IU
Vitamin K	20 µg
Vitamin C	60 mg
Thiamin (B_1)	0.75 mg
Riboflavin (B_2)	0.85 mg
Niacin	2.5 mg
Vitamin B_6 (pyridoxine)	1.0 mg
Folate (folic acid)	100 µg
Vitamin B_{12} (cyanocobalamin)	3 µg
Biotin	15 µg
Pantothenic acid	5 mg
Minerals:	
Calcium	25 mg
Iron	4.5 mg
Phosphorus	11 mg
Iodine	37.5 µg
Magnesium	12.5 mg
Zinc	3.75 mg
Selenium	17.5 µg
Copper	0.5 mg
Manganese	0.88 mg
Chromium	30 µg
Molybdenum	19 µg
Potassium	1.25 mg
Lemon bioflavenoids	5 mg (daily value not established)

[a]Equivalent to one tablet of Carlson's new Mini Scooter Rabbit chewable vitamins and minerals. (From ref. *57*.)

tablet, measure the cod liver oil, and mix both in a small amount of food (such as applesauce, yogurt, or rice cereal) to administer the supplements to their children. Parents were informed verbally and in writing that supplements were to be given only in the amounts required by the study and that study supplements were to be kept out of reach of children.

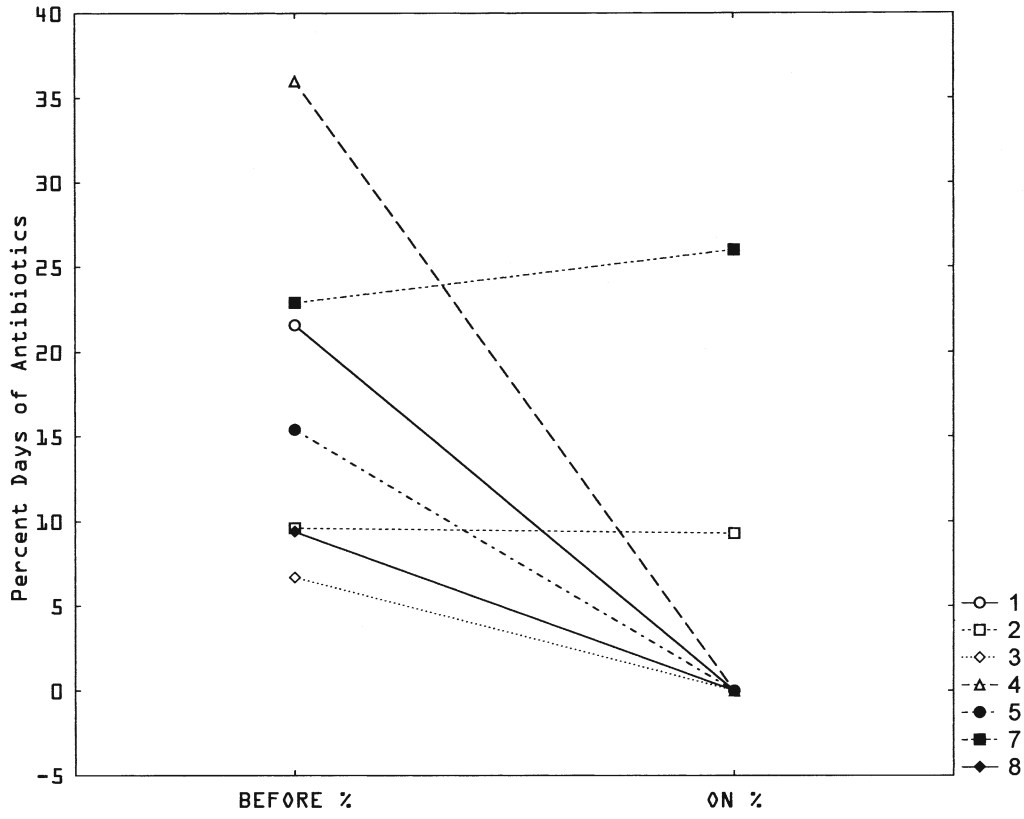

Fig. 1. Otitis Media Pilot Study: percent days of antibiotics. Subjects received antibiotics for OM for 12.3 ± 13.4 (SD) fewer days during supplementation (ON%) than before (BEFORE%); ($p < 0.05$, Wilcoxon Matched Pairs Test). (Reprinted with permission from ref. *57*.)

Of the eight children who entered the study, one could not tolerate the taste of cod liver oil. The remaining seven children received antibiotics for OM for 12.3 ± 13.4 ($p < 0.05$; mean ± SD) fewer days during supplementation than before supplementation during the OM season under study (*see* Fig. 1). Five of seven subjects had no additional episodes of OM during supplementation, although it had no apparent effect on established serous middle ear effusions in two children. However, because our study lacked a randomized, parallel control group, we could not exclude the possibility that the decreased antibiotic usage we found might have occurred without the use of study supplements.

3.3. Effect of these Supplements on Upper Respiratory Pediatric Visits by Young, Inner-City, Latino Children: Randomized Pediatric Sites

Based on our prior research (discussed in ref. *57*) and the historical studies on cod liver oil and upper respiratory illnesses *(65)*, we hypothesized that use of the study supplements by young children would decrease their doctor visits for upper respiratory illnesses during the late fall, winter, and early spring. We studied the effect of daily use of these supplements on the number of pediatric visits by young, inner-city, Latino children from late autumn 2002 to early spring 2003 *(83)*.

We did not have a matched placebo for liquid cod liver oil. Although adults and older children can swallow capsules, infants and toddlers cannot. Furthermore, if capsules were cut open to administer the contents, the distinctive odor and taste of cod liver oil would immediately become apparent *(57)*.

The absence of a matching placebo for liquid cod liver oil precluded our performing a classical double-blind, placebo-controlled study. Lack of a placebo coupled with the fact that cod liver oil can be purchased without a prescription by interested parties *(57,66)* led us to choose a study design in which we randomized pediatric sites, rather than individual patients. This type of design has been used in the worldwide studies of vitamin A supplementation, which are discussed in Subheading Section 5.3, that have included randomization by ward, household, village, or district *(67)*. It was also used in a food-consumption study to avoid changes in food habits resulting from knowledge of the other treatment *(68)*. Randomized site design is commonly used in behavioral and educational studies where no placebo is possible *(69–72)*; a recent study of herd immunity and the pediatric heptavalent pneumococcal vaccine also used a randomized site design *(73)*. To minimize the influence of the study on the behavior of the participating families *(69)*, we used a "no-contact" control group *(74,75)*, which has also been used in behavioral and educational studies.

The study was performed at Pediatrics 2000, a multisite, private, pediatric group practice in New York City. Two of the offices with similar demographics (low-income Latino families), located 1.1 miles apart in upper Manhattan, were randomized to a supplementation site and a medical records control site. Study participants were children ages 6 mo to 5 yr of either gender and any race, religion, or nationality who were patients enrolled at the two offices where the study was being performed. Study participants were required to be in New York City from enrollment through April 2003 (with the exception of brief vacations), and to have some type of medical insurance. Patients who routinely received additional health care at other practices or medical centers were excluded; children with known fish allergy, a chronic, life-threatening condition (such as HIV/AIDS or cancer), feeding disorders, and epilepsy were also excluded. Study materials were available in both English and Spanish. Per practice routine, two professional coders reviewed all charts from both sites, coded the visits, and entered the data into a computer with NDC Medisoft™ Network Professional 7.02 software *(76)*.

Participants in the medical records control group were enrolled from October 21 to November 10, 2002; those in the supplementation group were enrolled from November 11 to December 12, 2002. We were unable to randomize enrollment at the two sites because the lemon-flavored cod liver oil used in the study (which was manufactured in Norway) had been reformulated with less vitamin A *(77)* and was delayed in the US Customs Office. The study follow-up/supplementation period ended on May 1, 2003.

A total of 94 children (47 at each site) were enrolled in the study. The mean age of the supplementation group was 2.03 yr (±1.04 SD), and the mean age of the control group was 2.08 yr (±1.10 SD). There were no statistically significant differences in the demographical characteristics of the study participants in the two groups: most were Latino children from low-income families (as indicated by health insurance), and their mothers were predominantly unmarried immigrants from the Dominican Republic whose first language was Spanish.

Children of at least 1 yr of age received 1 teaspoon of Carlson's lemon-flavored cod liver oil per day and one-half tablet of Carlson's Scooter Rabbit chewable MVM, the same doses used in our previous research administered in the same manner *(57)*.

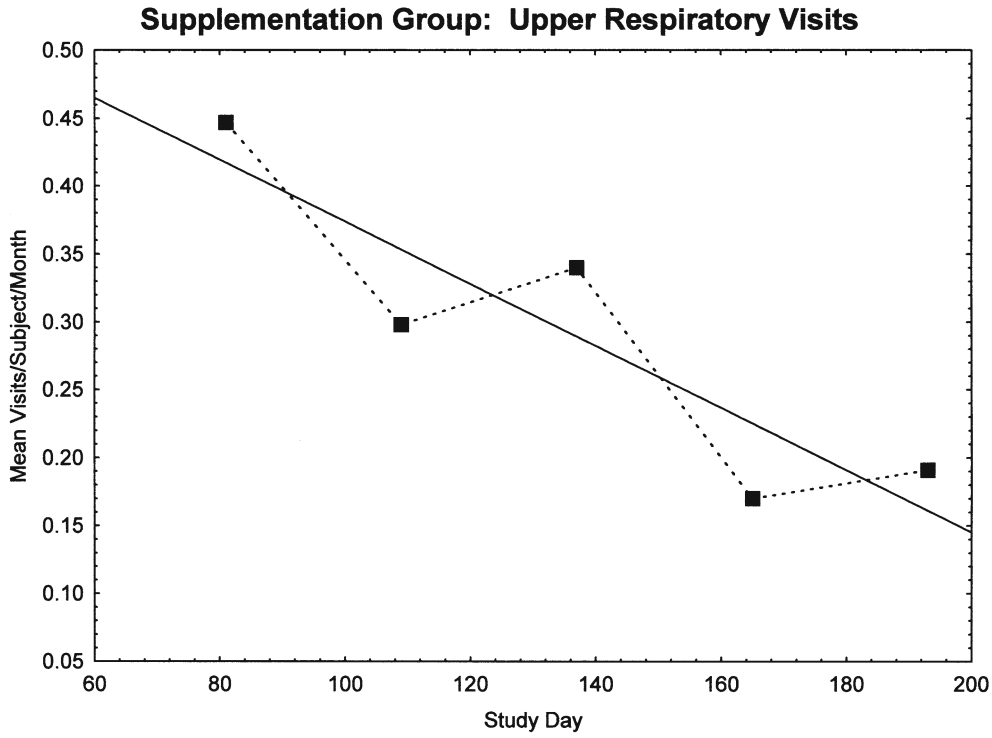

Fig. 2. Randomized pediatric sites: the supplementation group had a statistically significant decrease in the mean number of upper respiratory visits over the course of the follow-up/supplementation period ($p = 0.042$; $r = 0.893$; $r^2 = 0.797$; $y = 0.602 - 0.002x$). (Reprinted with permission from ref. *83*.)

However, the vitamin A content of the cod liver oil was approximately half that used in our first pilot study of OM (see Table 3). Thus, the full dose of supplements provided a total of 3750 IU of vitamin A and 700 IU of vitamin D per day. However, in the current study, the starting dose of supplements was halved for children ages 6 mo to 1 yr .Visits were classified as upper respiratory visits, other illness visits, or visits not analyzed on the basis of the ICD-9 visit code *(78)*. The primary outcome measure was upper respiratory visits during the follow-up/supplementation period; other illness visits during the same time period were considered as secondary outcome measures.

As shown in Figs. 2 and 3 and Table 4, the supplementation group had a statistically significant decrease in the mean number of upper respiratory visits over the course of the follow-up/supplementation period ($p = 0.042$; $r = 0.893$; $r^2 = 0.797$; $y = 0.602 - 0.002x$), whereas the medical records control group had no change in this parameter ($p = 0.999$; $r = 0.0006$; $r^2 = 0.0000$; $y = 0.259 + 1.43 \times 10^{-6}x$). There was no statistically significant change in the mean number of other illness visits for either study group during the same time period. Although there was a significant difference in the pattern of decreasing upper respiratory visits over time in the supplementation group, there was no difference in the total number of visits made by the two groups. Data were analyzed on an intention-to-treat basis.

As reported by their parents, 70% of our subjects completed a 5- to 6-mo course of lemon-flavored cod liver oil. By comparison, only 47% of families reported compliance

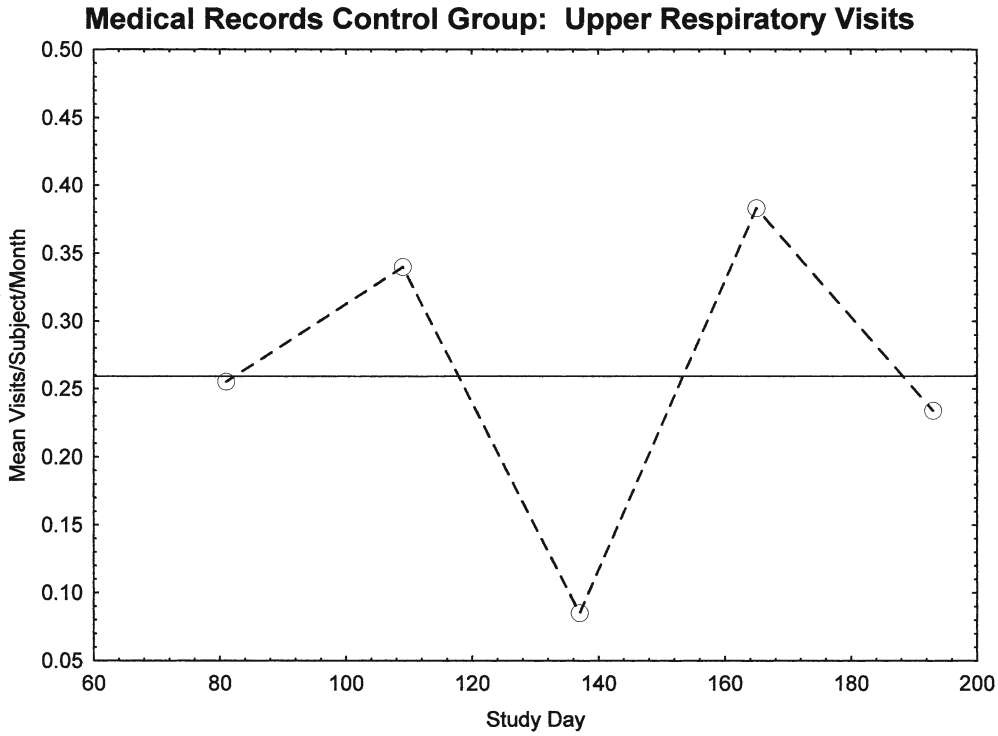

Fig. 3. Randomized pediatric sites: the medical records control group had no change in the mean number of upper respiratory visits over the course of the follow-up/supplementation period ($p = 0.999$; $r = 0.0006$; $r^2 = 0.0000$; $y = 0.259 + 1.43 \times 10^{-6}x$). (Reprinted with permission from ref. *83*.)

with antibiotic prophylaxis for OM in a study of Latino children who attended an otolaryngology clinic *(79)*. Our favorable compliance rates may partly result from the fact that young children in the Dominican Republic are often given cod liver oil or similar supplements, although families rarely continue this practice after moving to the United States.

3.4. Adjunctive Therapy for Children With Chronic/Recurrent Sinusitis: Pilot Research

Inflammation and edema of the sinonasal mucosa are important in the pathophysiology of sinusitis. Based on our previous research and the similarities between OM and sinusitis *(80)*, we hypothesized that these nutritional supplements would also be effective adjunctive therapy for the treatment of children with chronic and/or recurrent sinusitis. Therefore, we performed a 4-mo, open-label, dose-titration study in which each patient served as his or her own control *(64,81)*.

Study participants were private pediatric otolaryngology outpatients of Jay N. Dolitsky, MD, who resided in the New York Metropolitan area and had a clinical diagnosis of chronic and/or recurrent sinusitis as well as symptoms of at least 3 mo of duration that were refractory to treatment with antibiotics. Subjects were between ages 2 and 18 yr, of either gender and any race, religion, or nationality. Children with known allergy to fish; chronic, life-threatening condition (such as HIV/AIDS or cancer); feeding disorder;

Table 4
Randomized Pediatric Sites: Upper Respiratory Visits and Other Illness Visits During the Follow-Up/Supplementation Period

		Upper respiratory visits				*Other illness visits*			
		Supplementation group (n = 47)		*Medical records control group (n = 47)*		*Supplementation group (n = 47)*		*Medical records control group (n = 47)*	
Dates	*Study days*	*No. of visits*	*Mean visits/subject*	*No. of visits*	*Mean visits/subject*	*No. of visits*	*Mean visits/subject*	*No. of visits*	*Mean visits/subject*
12/13/2002 to 1/9/2003	54–81	21	0.45	12	0.26	3	0.06	0	0
1/10/2003 to 2/6/2003	82–109	14	0.30	16	0.34	6	0.13	3	0.06
2/7/2003 to 3/6/2003	110–137	16	0.34	4	0.09	6	0.13	2	0.04
3/7/2003 to 4/3/2003	138–165	8	0.17	18	0.38	2	0.04	3	0.06
4/4/2003 to 5/1/2003	166–193	9	0.19[a]	11	0.23[b]	1	0.02[c]	2	0.04[d]

[a] $p = 0.042$; $r = 0.893$; $r^2 = 0.797$; $y = 0.602 - 0.002x$
[b] $p = 0.999$; $r = 0.0006$; $r^2 = 0.0000$; $y = 0.259 + 1.43 \times 10^{-6}x$
[c] $p = 0.337$; $r = -0.550$; $r^2 = 0.303$; $y = 0.160 - 0.61 \times 10^{-3}x$
[d] $p = 0.369$; $r = 0.520$; $r^2 = 0.271$; $y = 0.72 \times 10^{-3} + 0.31 \times 10^{-3}x$
(Reprinted with permission from ref. *83*.)

seizure disorder; known cystic fibrosis; aspirin-intolerant asthma; and family plans to move outside the metropolitan area during the course of the study were excluded. Subjects were enrolled from late January to early March 2003 and received supplements for 4 mo from the time of enrollment. Primary endpoints were the number of doctor visits for acute respiratory illnesses and the child's sinus symptoms, which were quantified using a pediatric sinusitis symptom questionnaire *(82)*.

The starting dose of supplements in the current study was the same as in our previous research *(57)*: 1 teaspoon (5 mL) of Carlson's lemon-flavored cod liver oil and one-half of a tablet of Carlson's Scooter Rabbit chewable multivitamin-mineral per day (providing a total of 3750 IU of vitamin A and 700 IU of vitamin D per day). The vitamin A content of the cod liver oil was lower than in our first pilot study of OM *(57)* but was the same as that used in our study of Latino children (*83*; *see* Table 3). Supplement doses could be doubled to an intermediate dose (providing 7500 IU of vitamin A and 1400 IU of vitamin D per day) within 2 to 3 wk . If higher doses were needed, cod liver oil was discontinued and fish oil was administered instead (fish oil does not contain vitamin A or D). The maximum dose of fish oil was 3 g/d, and the maximum dose of multivitamin-minerals was four half-tablets per day (providing 10,000 IU of vitamin A and 800 IU of vitamin D per day). The titrated doses of vitamins A and D were higher than those used in our previous study *(57)* but were well-below the lowest daily toxic doses of these vitamins *(61)* (19,860 IU/d for vitamin A and 2800 IU/d for vitamin D). The US Food and Drug Administration (FDA) considers fish oil at dosages up to 3 g per day as safe for adults and children *(84)*.

Our four subjects were Caucasian males, ranging in age from 4.2 to 9.8 yr, with chronic/recurrent sinusitis for at least 3 yr prior to entry in the study. Three subjects had a positive response; one subject dropped out for administrative reasons. The responders had decreased sinus symptoms, fewer episodes of acute sinusitis, and fewer doctor visits for acute illnesses at 4, 6, and 8 wk after beginning study supplements. Their parents reported that they had begun to recover from upper respiratory illnesses without complications, which was unusual for these children, as was improvement in springtime; their improvement had previously been limited to the summer months or periods of home-schooling.

Our findings are consistent with prior work by other clinical investigators. In a study of upper respiratory tract infections in young children, Wald and colleagues *(85)* noted that an inflamed respiratory mucosa may not completely recover between episodes of infection. Parsons *(86)* hypothesized that inflammation and edema of the sinonasal mucosa was the primary event in sinusitis, with bacterial infection as a secondary phenomenon.

Chronic/recurrent sinusitis is a debilitating disorder that may require treatment with intravenous antibiotics and/or endoscopic surgery. Use of these supplements as adjunctive therapy for children with chronic/recurrent sinusitis is an inexpensive, noninvasive intervention that clinicians can use for selected patients, pending the outcomes of definitive, large, well-controlled studies.

3.5. Safety

In the 1930s, during the pre-antibiotic era, lipoid aspiration pneumonia was reported with cod liver oil, mineral oil, and egg yolk, which were used at that time to treat sick and debilitated infants *(87)*. In 1950, Caffey *(88)* reported vitamin A toxicity in children who were mistakenly treated with high-dose, long-term vitamin A administered in highly concentrated fish liver oil preparations that were available at that

time. However, none of Caffey's patients had received cod liver oil, and the highly concentrated fish liver oil preparations they received are no longer available in the United States.

In our clinical studies, parents were instructed to crush the half-tablet of MVM, measure the cod liver oil, and mix both with a small amount of food (such as applesauce, yogurt, or rice cereal) before administering the supplements to their child. Additionally, parents were informed both verbally and in writing that supplements were to be given only in the amounts required by the study and that study supplements were to be kept out of reach of children. The principal investigator spoke Spanish, and all parental study materials were available in both Spanish and English. To date, we have not encountered problems with aspiration or overdose in our studies.

3.6. Implications for Asthma

There is a clear association between viral respiratory infections and acute exacerbations of asthma in both children and adults *(17)*. There is also a link between sinusitis and asthma *(89,90)*, with rhinovirus infections linked to both sinusitis and exacerbations of asthma *(90)*. Additionally, Latino children have a high incidence of asthma *(91)*. In view of the results of our studies *(57,81,83)*, we believe that these supplements could be clinically useful for young children (particularly Latino children) with asthma, and we are currently beginning to organize research in this area.

3.7. Nutritional Supplements for Socioeconomically Disadvantaged Children in the United States

Similarly to other countries worldwide *(92)*, socioeconomically disadvantaged children in the United States are at risk for micronutrient deficiencies *(57,62,93)*. Although the supplements used in our research can be purchased in the United States without a prescription, their cost may pose an excessive financial burden to low-income families.

Cod liver oil does not have a National Drug Code number, it is not available through Medicaid in New York, and the children's vitamins we have located that are available through this system do not contain Se or other trace metals. Additionally, cod liver oil is not available through the United States Department of Agriculture (USDA) Special Supplemental Nutrition Program for Women, Infants and Children (WIC); our request for such availability can be found online at http://www.fns.usda.gov/wic/anprmcomments/ihp-06.pdf. Furthermore, purchase of vitamins with US food stamps is not permitted (see http://www.fns.usda.gov/fsp/faqs.htm#9). If our results are confirmed in larger studies, a system change will be required to provide these supplements to nutritionally vulnerable, socioeconomically disadvantaged children living in the United States.

4. HISTORICAL PERSPECTIVE

4.1. History of Cod Liver Oil

Egyptian and Greek physicians may have understood the value of liver (high in vitamin A) for the treatment of night blindness, an early ocular manifestation of vitamin A deficiency *(94,95)*. The use of fish oils in medicine was mentioned by Hippocrates, and Pliny discussed the use of dophin liver oil for the treatment of chronic skin eruptions *(96)*. However, these classical physicians did not appear to know about the use cod liver oil.

The coastal fishermen of northern Europe apparently used cod liver oil for many years for the treatment of aches and pains *(96,97)*. However, the first recorded use of cod liver oil by physicians was from the Manchester Infirmary in England during the 1780s *(96,97)*, where it was found to be very effective for "old pains" and "rheumatism," which were probably cases of osteomalacia (a bone disease of adults) *(96)*. The pattern of discovery was that the use of cod liver oil by fishing folk and peasants was accidentally observed by a physician, who then tried it and made it known to the medical profession *(96)*.

Guy *(96)* states that there was no further mention of cod liver oil in the English medical literature until its revival in 1841 by Bennett, who had observed its use in Germany. Bennett reported that in Holland, cod liver oil had obtained a wide reputation as a cure for rickets (a bone disease of children) "long before its remedial properties were acknowledged by physicians" (*see* ref. *97*, p. 67). In the 1820s, Schenk and Schuette published independent reports in the German literature regarding the value of cod liver oil for curing rickets *(97)*, and Schuette reported that he used cod liver oil successfully for 25 yr. Cod liver oil for the treatment of rickets was introduced in France by Trousseau in the 1830s *(97)*. The demand for cod liver oil was so great that all types of substitutes were used, and reports of failure, contamination, and substitutes for cod liver oil began to appear in the literature before the middle of the 19th century.

4.2. The Discovery of Vitamin A

Vitamin A was discovered as the result of a long, incremental process with contributions by numerous investigators *(95,98)*. At the end of the 19th century and the beginning of the 20th century, nutritional theories were tested under well-controlled laboratory conditions through the administration of experimental diets to animals, and specific factors necessary for their growth and survival began to be identified. During this time, Frederick Hopkins, at Cambridge University, proposed that there were "accessory factors" in foods that were necessary for life but that had not been previously identified; Casimir Funk named these factors "vital amines" or "vitamines" *(65)*.

In 1913, in the same issue of the *Journal of Biological Chemistry*, two groups independently reported the existence of a fat-soluble factor that was essential for the growth of rats *(65,99–101)*. McCollum and Davis of the University of Wisconsin *(99)* demonstrated that after a certain age, the growth of rats was dependent on an ether extract from eggs or butter. Using a different experimental diet, Osborne and Mendel *(100)*, of Yale University, found that there was an "essential accessory factor" in butter needed for the normal growth of rats. This fat-soluble growth factor, originally termed "fat-soluble A," soon became known as "vitamine A" *(65)*.

4.3. The Discovery of Vitamin D

The discovery of vitamin D was closely tied to work on the prevention and treatment of rickets. During the Industrial Revolution, rickets spread rapidly throughout Europe, particularly among the urban poor, who lived in the sunless alleys of factory towns and urban slums *(97)*.

In 1918, Mellanby *(102)*, an English physician and professor of pharmacology, reported the first animal model of rickets, which he developed in puppies. In a simple, two-page report to the Physiological Society, he noted that the daily administration of

foods such as butter, cod liver oil, or 500 cc of milk (among others) was effective in preventing rickets in his model, whereas casein and linseed oil were among the substances that were ineffective. Mellanby felt that rickets was a deficiency disease and stated that "the anti-rachitic accessory factor has characters related to the growth accessory factor [vitamin A], although it is not identical with the latter …" (ref. *102*, p. xi). However, Mellanby was not able to distinguish these two factors; this was accomplished by McCollum and his new collaborators at Johns Hopkins University.

In the 1920s, McCollum and his colleagues developed a rat model of rickets that could also be cured with cod liver oil. They were then faced with the same question that perplexed Mellanby: Was the anti-rachitic factor vitamin A, or was it another substance with a similar distribution as fat-soluble vitamin A (103)? It was known that the vitamin A-deficient animals in these studies often developed ocular abnormalities, including dryness of the eyes, corneal ulceration, and blindness, similar to xeropthalmia in humans *(65)*. Additionally, Hopkins demonstrated that oxidation destroyed fat-soluble A *(103)*. Using these facts, in 1922, McCollum and his colleagues *(104)* reported that when cod liver oil was oxidized for 12 or 20 h, it could no longer cure xerophthalmia, although it could prevent rickets. Therefore, they concluded that the anti-xerophthalmic and the anti-rachitic properties were a result of two distinct substances, and that the anti-rachitic factor, which specifically regulated bone metabolism, was the more heat-stable factor. Because this was the fourth vitamin to be discovered, McCollum's group named it vitamin D in 1925 *(97)*.

The fact that both exposure to sunlight and cod liver oil could prevent or cure rickets was perplexing and controversial *(105)*. Careful experiments by Chick and coworkers *(103)*, working in Vienna from 1919 to 1922, confirmed the value of both cod liver oil and sunlight in the prevention and treatment of rickets in young infants.

In 1919, Huldschinsky *(97)*, a pediatrician in Berlin, used light from a mercury-vapor quartz lamp (which includes ultraviolet [UV] wavelengths) to cure four cases of advanced rickets in children with up to 2 mo of treatment. When Huldschinsky exposed one arm of a rachitic child to the UV irradiation, he found that the rickets in the child's other arm was cured to the same degree as in the exposed arm. Therefore, he concluded that phototherapy was not a local effect and speculated that as a result of exposure to UV light, something was formed in the skin that was then carried to other sites, where it had its anti-rachitic effect *(105)*. In 1925, Hess and Weinstock *(97)* reached similar conclusions based on experimental work in animals. These theories were confirmed in 1936, when Windaus, working in Germany, demonstrated that skin contains the natural prehormone of vitamin D, which is converted to vitamin D_3 when the skin is exposed to UV irradiation (including light from a mercury-vapor lamp) *(97)*.

4.4. Rickets and Respiratory Diseases

Historical investigators were well-aware of an association between rickets and respiratory diseases. In their 1917 paper on rickets, Hess and Unger stated that "rickets is a predisposing cause of these respiratory diseases (pulmonary tuberculosis, pneumonia, and whooping cough)" (ref. *106*, p. 1583). In her 1927 paper on community control of rickets, Eliot stated that "susceptibility to upper respiratory infections, such as colds,

bronchitis and pneumonia, is greatly increased in infancy and early childhood by rickets" (ref. *107*, p. 114). Based on prior animal studies and clinical work by German investigators, Ellison discounted the contribution of vitamin D in the efficacy of cod liver oil for measles. Nonetheless, he acknowledged that "it is possible that some adjuvant effect was obtained from the co-operation of the two factors [vitamins A and D]" (ref. *108*, p. 710). In a 1936 study of vitamins A and D (individually or combined) for children hospitalized with measles, Mackay noted "there is much to indicate that resistance to infections is reduced in children suffering form an overt deficiency of either of these vitamins [vitamin A or D]" (ref. *109*, p. 127).

4.5. Cod Liver Oil for Tuberculosis

Semba noted that cod liver oil, a rich source of vitamins A and D, was used as a treatment for tuberculosis for more than 100 yr *(110)*. In the 1840s, Charlotte Brontë, the author of *Jane Eyre*, suffered from tuberculosis, and her treatment included cod liver oil *(111)*. A 1917 textbook on tuberculosis, although recognizing that there was no specific treatment for tuberculosis at that time, stated that "one of the oldest and best established remedies for the treatment of tuberculosis is cod liver oil" (ref. *112*, p. 467); however, the mechanism of action of cod liver oil was unknown. The situation had changed little by 1946, when Goldberg's textbook stated that cod liver oil "has been used empirically for many centuries in the treatment of pulmonary tuberculosis without any definite knowledge of its action" (ref. *113*, p. C-81). However, the use of cod liver oil for tuberculosis faded as specific treatments were developed, and "cod liver oil" is not listed in the index of a modern textbook on tuberculosis *(114)*.

4.6. Historical Research on the Anti-Infective Properties of Vitamin A

Mellanby (*see* Section 4.3.) had a large colony of dogs that were maintained on experimental diets. In 1926, Mellanby reported, "at one period in the course of my experimental investigations on dogs, the work was greatly hampered by the development of an inflammatory condition of the lungs" (ref. *115*, p. 518), which was bronchopneumonia. On postmortem examination, the pneumonia was largely restricted to the vitamin A-deficient dogs, and he speculated that this might be relevant to respiratory illness in children *(65,115)*. In 1928, Green and Mellanby reported that a deficiency of vitamin A, but not vitamin D, caused increased infections in a rat model, leading them to call vitamin A an "anti-infective" agent; they speculated that this was related to the epithelial changes caused by vitamin A deficiency *(116)*.

In 1932, Ellison *(65,108)* reported the results of a study of concentrated cod liver oil for children who were hospitalized with measles. Ellison was aware of Mellanby's work on the anti-infective properties of vitamin A and also knew that vitamin A deficiency damaged epithelial cells in the respiratory tract *(117,118)*. Ellison specifically chose to study measles because it was "a disease which attacks epithelial defences and whose incidence is greatest in those members of the community who are most likely to be suffering from various grades of vitamin deficiency…the children of the poorest classes" (ref. *108*, p. 709). He studied 600 children under age 5 yr who were admitted to the Grove Hospital (London) with measles. The cases were randomized by ward to treatment with a highly concentrated cod liver oil preparation or a control treatment of standard treatment (no placebo was used). Treatment with cod liver oil reduced measles mortality

by approximately one-half, from 8.7% in the control group to 3.7% in the treated group *(65,108)*. Based on animal studies and German clinical work, Ellison attributed the efficacy of cod liver oil to vitamin A, although he did concede that some adjuvant effect could have been obtained from the cooperation of the two factors (*108*).

A subsequent study published in 1936 *(65,109)* reported that neither vitamins A and D together nor vitamin D alone had an effect on reducing the mortality rate from measles. However, the control mortality rate in this later study decreased to 2.6%, making it difficult to demonstrate an improvement.

By 1940, numerous studies had been conducted to evaluate the ability of vitamin A (usually given as cod liver oil) to decrease the incidence of respiratory infections. The results were mixed, with about half showing a positive impact and the rest demonstrating no effect *(65)*. However, cod liver oil did have a significant impact on decreasing industrial absenteeism *(65)*. In a 1935 study of cod liver oil for the prevention of the common cold in school children, the investigator was not able maintain a control group given no supplements because enthusiastic families purchased cod liver oil for their children outside of the study *(65,66)*; this finding is relevant to our current work.

With the introduction of sulfa antibiotics and penicillin in the 1930s to 1940s *(65)*, as well as the improvements in diet in industrialized countries in the late 1930s, interest in anti-infective therapy shifted to antibiotics and away from vitamin A *(98)*.

4.7. Fortification of Milk With Vitamin D and Synthetic Vitamin A

In the mid-1920s, UV radiation of food and a variety of other substances was demonstrated to produce anti-rachitic properties *(105)*. Steenbock patented the addition of provitamin D to foods followed by UV irradiation to produce anti-rachitic activity. In the 1930s, the addition of provitamin D_2 to milk followed by UV irradiation was widely practiced in the United States and Europe. Rickets was eradicated as a significant public health problem in the countries that used this vitamin D fortification process *(105)*.

In the late 1940s, Otto Isler and his collaborators in Basel reported the synthesis of all-*trans*-vitamin A from the inexpensive precursor β-ionone *(95)*. In the same time period, Arens and van Dorp *(94)* reported the synthesis of retinoic acid. Within a few years, the price of vitamin A fell 10-fold, and it became economically feasible to add vitamin A more generally to foods.

4.8. Cod Liver Oil in the United States

During the latter part of the 19th century, cod liver oil was rarely used in America, although the reason for this lack of use is not clear *(96,97)*. However, there was a resurgence in interest, and in 1917, Hess and Unger wrote, "For many years cod liver oil has been regarded as the sovereign remedy for rickets" (ref. *106*, p. 1583). They successfully prevented rickets with cod liver oil in susceptible African-American babies in a low-income neighborhood in New York City *(106,119)*. Hess urged officials to dispense cod liver oil at the baby health stations at cost, but they declined because it would be too expensive, and they thought that additional milk would be preferable to cod liver oil *(106)*.

Cod liver oil and sunlight were highly valued for the prevention of rickets, and nurses taught mothers of infants how to use these remedies for their infants *(107)*. From the 1920s to the 1940s, many children in the United States were given cod liver oil each day *(26,65)* with orange juice (which was know to prevent scurvy). However, older

preparations of cod liver oil had an unpleasant taste, the quality of different preparations was erratic *(119)*, and medical professionals became concerned about lipoid aspiration pneumonia *(87)* and vitamin A toxicity *(88)*. By the 1950s, cod liver oil had been largely replaced by synthetic vitamins in the United States; however, the latter do not contain ω-3 fatty acids, which have anti-inflammatory properties *(26)* and important effects on immune function *(47,120)*. In Norway, the Norwegian Nutrition Council continues to recommend supplementation with cod liver oil beginning at age 4 wk, because it provides ω-3 fatty acids in addition to vitamin D *(121)*.

5. THE MODERN ERA

5.1. Over-Fishing of the Oceans

Before Columbus made his first voyage to America, Basque fisherman were secretly fishing the massive stocks of cod and other groundfish off the New England coast *(122,123)*. Their salt cod was a staple in Mediterranean markets, and cod was a staple of the European diet for more than 400 yr *(122)*. Although fishermen exploited cod for centuries, the technological innovations of the 20th century led to the collapse of cod stocks in North America. Motorized boats dragged the ocean floor with massive trawl nets, destroying both cod fish and their habitat. Factory ships with refrigeration have almost erased the limit to the amount of cod that can be caught and sold internationally without spoiling *(123)*; increasingly powerful and accurate sonar produces detailed readouts of nooks where schools of fish may lurk; and shipping fleets can position themselves precisely through use of the satellites of the Global Positioning System *(124)*.

Despite growing regulations on allowable catches and fishing equipment, cod stocks have continued to decrease across the North Atlantic. In 1992, the Canadian government declared a temporary moratorium on cod fishing; the moratorium was extended in 1994. In 2003, with cod stocks showing no sign of recovery, the Canadian government banned all cod fishing off its Eastern provinces and identified some cod populations as endangered. The US government also imposed restrictions on cod fishing *(123)*. However, it is unclear whether North Atlantic cod stocks will recover.

5.2. Pollutants in the Ocean

The level of polychlorinated biphenyls (PCBs) and dioxins in fish and fish oils has become a concern as oceans have become progressively contaminated with industrial waste. This issue was addressed in the United Kingdom and Europe by purity standards *(125)*, which were revised and made more strict in 2002 *(126)*. In the same year, the UK Food Standards Agency reported that exposure to dioxins had decreased by 75% over the previous 20 yr and that the levels of dioxins and PCBs found in most of the samples in their most recent fish oil survey were lower than in previous surveys that were performed in 1994 and 1996 *(126)*. Mercury contamination of fish is also a concern, and the FDA advises that young children and women of childbearing age should avoid tilefish, swordfish, shark, and king mackerel because of their elevated levels of mercury *(127)*. However, an analysis of US fish oil supplements revealed no detectable mercury, with a limit of detection of 0.1 μg of mercury per gram *(128)*.

5.3. Modern Clinical Studies of Vitamin A Supplementation

After a 40-yr hiatus, interest in the anti-infective properties of vitamin A was rekindled in the 1980s by the observation of increased mortality in Indonesian children who

had vitamin A deficiency and xerophthalmia *(65,129)*. The first symptom of eye disease from vitamin A deficiency is night blindness; at this stage, Bitot's spots (superficial, foamy gray, triangular spots) may be present on the conjunctiva *(129,130)*. This is followed in later stages by xerophthalmia (dryness of the conjunctiva), keratomalacia (corneal ulceration), and blindness *(77)*.

Since the 1980s, numerous studies have been performed regarding the effect of vitamin A supplementation on the health of children in developing countries. For a complete review of this subject, the reader is referred to Chapter 23, as well as reviews *(110,131,132)*, and meta-analyses *(67,133,134)*. For the purpose of this chapter, the findings are summarized to provide a basis of comparison to the status of vitamin A in the developed world as well as to provide a perspective on the results of our research.

Vitamin A supplementation of children in developing countries decreased overall childhood mortality by about 30% *(67,132)*. Community-based studies of vitamin A supplementation have indicated that it may decrease the severity, but not the incidence, of diarrhea *(131)*. In children hospitalized with measles in the developing world, vitamin A supplementation decreased mortality by an average of 60% *(67,132,135)*; the decrease in mortality from measles-related pneumonia was particularly noteable *(67)*. The modern studies are consistent with the results of Ellison's historical study of cod liver oil for children who are hospitalized with measles (*see* Section 4.6.). The role of vitamin A supplementation in measles is also consistent with the fact that infectious diseases that induce the acute-phase response transiently depress serum retinol concentrations, that vitamin A deficiency impedes the normal regeneration of mucosal barriers damaged by infection, and that it also diminishes the immune function of white blood cells *(136,137)*.

However, several placebo-controlled trials have demonstrated that high-dose vitamin A supplementation is not effective in decreasing the severity of pneumonia in hospitalized children in developing countries and that large doses of vitamin A may be harmful when given to well-nourished children in these areas *(132,134)*. Additionally, vitamin A supplementation is not effective for children who are hospitalized with pneumonia caused by respiratory syncytial virus, which is a paramyxovirus similar to measles and an important cause of infantile bronchiolitis and pneumonia *(138,139)*. In a multicenter study performed in the United States, patients who received vitamin A actually had longer hospital stays than those who received placebo *(138)*.

Infection with HIV has become increasingly prevalent in many developing countries. Vitamin A supplementation of children younger than age 5 yr who are HIV-positive decreases AIDS-related deaths as well as total mortality and morbidity from diarrhea *(140)*. Small, frequent doses of vitamin A may be more protective than large, periodic doses. Additionally, adequate dietary vitamin A intake is associated with a significant decrease in mortality *(141)*, diarrheal and respiratory infections *(142)*, and stunting *(143)*. New strategies in vitamin A supplementation in developing countries include targeting at-risk populations, improving dietary sources of vitamin A, using horticultural approaches, fortifying food, and addressing multinutrient deficiencies *(140)*.

5.4. Nonclassical Functions of Vitamin D

Modern studies of vitamin D indicate that calcitriol (1,25 dihydroxyvitamin D), the active form of vitamin D, has important nonclassical effects beyond the regulation of calcium metabolism. These include the modulation of hormone and cytokine production and secretion as well as the regulation of proliferation and differentiation *(144)*. Calcitriol, a potent inhibitor of human T-lymphocyte proliferation *(145,146)*, and vitamin D analogs

have been shown to be effective in the prevention and treatment of some models of autoimmune disease in rodents—particularly autoimmune diabetes in mice *(144,147,148)*. In 1997, Muhe and colleagues *(110,149)* reported the importance of nutritional rickets in the development of pneumonia in developing countries. This is consistent with the work of historical authors discussed earlier, who were also aware of this association.

5.5. Discrepancies in Vitamin A Status in the Developed World

Vitamin A deficiency that is severe enough to cause blindness is uncommon in the developed world *(62)*. However, some segments of the US population, particularly socioeconomically disadvantaged children *(93)* as well as African- and Mexican-American children *(62)*, may have suboptimal levels of vitamin A. In 1932, Ellison recognized that children from low-income households were the most likely to have vitamin deficiencies (*see* Section 4.6.) *(108)*. Consistent with these reports, in our original study, five of six children with suboptimal levels of vitamin A were Hispanic general-service patients *(57)*. Additionally, young children in the United States—particularly those in the toddler and preschool age groups—may not have adequate dietary intakes of vitamin A *(150)*.

In developed countries, high intakes of vitamin A (but not β-carotene) by pregnant women have been associated with teratogenesis *(151)*, leading to recommendations that prenatal vitamins should contain no more than 8000 IU of preformed vitamin A *(152)*. Additionally, high intakes of vitamin A by postmenopausal women in the United States *(153)* and 49- to 51-yr-old men in Sweden *(154)* have been associated with a higher risk of hip fractures. As a result, vitamin A supplementation and fortification of food with vitamin A in Western countries has been questioned *(77)*. As discussed under Section 3.3., the amount of vitamin A in Norwegian cod liver oil has been reduced. Nonetheless, the Norwegian Nutrition Council continues to recommend supplementation with cod liver oil beginning at age 4 wk, because it provides ω-3 fatty acids in addition to vitamin D *(121)*.

5.6. Deficiencies of Multiple Micronutrients

Numerous investigators have stated that vitamin A deficiency rarely exists alone and that it is usually accompanied by variety of other nutritional deficiencies *(92,131,132,134,155–158)*. In a 1986 review, Mejía *(92)* noted that vitamin A deficiency primarily affects the world's most underprivileged populations, which, because of their limited socioeconomic condition, also lack a variety of other essential nutrients. He emphasized the importance of the interaction between nutrients and reviewed the established relationships of vitamin A status to protein, dietary fat, vitamin E, zinc, and iron *(92)*. Mejía also mentioned the more controversial links of vitamin A to iodine metabolism; vitamins C, K, and D; calcium, and copper. Realizing that the relationships might be direct or indirect, he emphasized the importance of considering these interactions when "treating or preventing vitamin A deficiency both at the clinical and at the population levels" (ref. *92*, p. 95). Olson *(155)* reported that deficiencies of various other nutrients, including protein, α-tocopherol (vitamin E), iron, and zinc, adversely affects the transportation, storage, and utilization of vitamin A. He also noted that the absorption of vitamin A and carotenoids is markedly reduced when diets contain very little fat (<5 g/d).

More recently, Villamor and Fawzi *(132)* stated that supplementation with vitamins and minerals in addition to vitamin A is likely to "reduce the burden of adverse health outcomes," because of the physiological interactions between nutrients and overlapping

micronutrient deficiencies, including iron and zinc. Semba *(98)* noted that antenatal supplementation with multivitamins reduced fetal deaths and low birthweight in pregnant women who were infected with HIV, but vitamin A alone had no significant effect. Semba *(110)* also discussed the role that other deficiencies of vitamin D *(149)* and zinc *(159)* may have in susceptibility to respiratory infections. We agree with Semba, who stated that "further studies are needed to address the use of vitamin A in multi-micronutrient supplements, as there is increasing evidence that other coexisting micronutrient deficiencies may limit the efficacy of vitamin A" (ref. *131*, p. 105).

6. SUMMARY AND RECOMMENDATIONS

Our work is consistent with the historical uses of cod liver oil, vitamin A as the "anti-infective" vitamin, the link between rickets and respiratory tract infections, the modern understanding of immunomodulatory effects of vitamin D, the importance of ω-3 fatty acids and trace metals in decreasing inflammation, the clinical observation that inflamed respiratory mucosa may not completely recover between episodes of infection, and the current concept of the importance of multiple micronutrient deficiencies.

We have demonstrated that use of flavored cod liver oil (which meets European purity standards) and a chewable children's multivitamin-mineral with trace metals, including Se, can decrease morbidity from upper respiratory tract illnesses, OM, and sinusitis in young children living in the United States. These supplements were particularly well-accepted by Latino families from the Caribbean, where use of cod liver oil is a cultural tradition. Currently, there is adequate information for practitioners to recommend the use of these supplements, when indicated, to their individual patients; information for practitioners and families is available online at http://www.drlinday.com. The supplements can be purchased in the United States without a prescription. Further research is needed to evaluate the effect of the supplements on antibiotic prescription for these illnesses and to explore their role as adjunctive therapy in asthma. Additionally, our findings need to be confirmed in larger studies to facilitate large-scale, policy decision making.

Use of these supplements has the potential to improve children's health and decrease the cost of their health care. However, cod liver oil does not have a National Drug Code number and is not available through Medicaid in New York, and the children's vitamins we have located that are available through this system do not contain Se or other trace metals. Also, cod liver oil is not available through the USDA WIC Program; our request for such availability can be found online at http://www.fns.usda.gov/wic/anprmcomments/ihp-06.pdf. Furthermore, purchase of vitamins with US food stamps is not permitted (*see* http://www.fns.usda.gov/fsp/faqs.htm#9).

Socioeconomically disadvantaged children living in the United States are at risk for micronutrient deficiencies. Although the supplements used in our research can be purchased in the United States without a prescription, their cost may pose an excessive financial burden to low-income families. If our results are confirmed in larger studies, a system change will be needed to provide these supplements to nutritionally vulnerable, socioeconomically disadvantaged children living in the United States.

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