

*Vitamin D Expert Panel Meeting
October 11 - 12, 2001
Atlanta, Georgia*

Final Report

Kelley S. Scanlon, PhD, RD, editor

Background

On October 11 and 12, 2001, scientists, health practitioners, and policy makers from the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), academic and professional institutions, and government agencies met in Atlanta, Georgia to discuss vitamin D supplementation of infants. CDC convened the meeting to examine scientific issues and policy implications regarding vitamin D supplementation and to identify current research needs. Experts presented information on the incidence of rickets in the United States; the role of sunlight in preventing vitamin D deficiency and in the occurrence of skin cancer; and the risks and benefits of vitamin D supplementation, including its impact on breastfeeding; alternatives to supplementing infants with vitamin D; and development of a communication strategy to promote a new policy on vitamin D. Following is a summary of the presentations given at the meeting and the panel discussions that followed each presentation. The statements in this document reflect the views of the expert panel members and guests and should not be interpreted as CDC policy.

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Welcome

Dr. Kelley Scanlon, CDC, called the meeting to order at 8:15 and welcomed the participants. The participants introduced themselves.

An overview of questions about vitamin D supplementation of infants: the need to share information and the global implications of a policy - *Dr. William Dietz, Director of the Division of Nutrition and Physical Activity (DNPA), CDC*

Dr. Dietz expressed CDC's concern about the number of reported cases of rickets in the United States, especially in children with darkly pigmented skin. He noted that, although science is important, sometimes policy must move before data are available. This meeting was convened to examine and share scientific knowledge in the field, discuss policy implications, and determine a research agenda. This meeting will address the following questions: how does the science fit into public health policy; what is subclinical rickets; what are the implications of untreated cases; is it reasonable or necessary to conduct population-based screening; should vitamin D supplementation be recommended; if supplementation is recommended, should it be recommended universally or targeted to at-risk populations; what are the benefits and drawbacks of recommending supplementation; what is the message to the general population about breastfeeding if supplementation is recommended; and what should the research agenda include?

The incidence of rickets in the United States - *Dr. Laurence Grummer-Strawn, Chief, Maternal and Child Nutrition Branch, DNPA, CDC*

There are no national data on the incidence of rickets in the United States. Therefore, data must be drawn from other sources to estimate incidence. We examined Georgia hospital records dated January 1997 through June 1999, the National Hospital Discharge Survey (NHDS) data for 1990 through 1998, and Pediatric Research in Office Settings (PROS) network pilot data of rickets cases reported between January 1999 and June 2000. We also conducted a preliminary review of rickets cases published in the literature between 1966 and 2001.

Georgia hospital records indicated that nine per million children in Georgia were hospitalized with rickets between January 1997 and June 1999. Laboratory data on cases were reviewed to determine whether nutritional deficiency caused rickets. Our review revealed that five per million Georgia children were hospitalized with rickets due to vitamin D deficiency during the study period. All the children were African Americans 8 to 21 months old (CDC 2001).

NHDS data revealed that nine per million children in the United States were hospitalized with rickets between 1990 and 1998. The ICD-9-CM codes used on the NHDS do not distinguish nutritional deficiencies from other causes of rickets. Also, the rarity of rickets as a diagnosis in

the NHDS results in an unstable estimate and therefore should be interpreted with caution. Seventy-five percent of rickets cases detected through NHDS data occurred in African American children, 20% in Caucasias American children, and 5% in Asian American children. All cases occurred in children less than 4 years old; 50% were infants less than 12 months old (K. S. Scanlon and L. Grummer-Stawn, unpublished data, 2001).

The PROS pilot survey detected 23 to 32 ambulatory cases of rickets due to vitamin D deficiency per million children served between January 1999 and June 2000. All were African American children. Age data were incomplete. A limitation of the pilot survey of pediatric practices was a low response rate (26%) (K. S. Scanlon and L. Grummer-Stawn, unpublished data, 2001).

A preliminary review of published reports between 1966 and 2001 revealed 13 reports of 122 cases of rickets due to vitamin D deficiency in 12 U.S. states (P. Weisberg, K. S. Scanlon, M. E. Cogswell, and R. Li, unpublished data, 2001). The racial/ethnic distribution of cases was as follows: 87% African American, 3% Caucasias American, 1% Asian American, and 9% other or unknown. The children with rickets ranged from 4 to 58 months of age at diagnosis.

Discussion of Dr. Grummer-Stawn's presentation by expert panel members and guests

Dr. Grummer-Stawn said case reports were distributed throughout the United States. All cases of rickets from the Georgia and PROS data occurred in full-term infants. All cases also occurred in breastfed children. Vitamin D status of the mother was usually unknown. According to the published literature, some mothers were Muslim and were covered all the time, as were their children. Other mothers reported their children did not receive sunlight exposure because of a lack of sidewalks in their neighborhoods or because the neighborhood was too dangerous for children to walk or play outdoors.

Additional contributory factors include the following:

- Vitamin D status of a woman during pregnancy directly affects the vitamin D status of her infants at birth.
- Low milk consumption by African Americans because of confirmed or perceived lactose intolerance may affect vitamin D status.
- African Americans may have chronic vitamin D deficiency. Parathyroid hormone (PTH) concentrations are elevated when serum 25-hydroxyvitamin D [25(OH)D] is decreased. (Vitamin D deficiency results in hypocalcemia, which in turn raises PTH concentration. PTH stimulates bone resorption to mobilize bone calcium to maintain plasma calcium concentrations). Fasting phosphorus concentration may be low or normal in vitamin D deficiency and therefore is not a good indicator.

- It was the opinion of experts at the meeting that we should be concerned about secondary hyperparathyroidism in adults when serum 25(OH)D is ≤ 37.5 nmol/L (15 ng/mL). Studies in older white populations have shown that PTH concentration rises when 25(OH)D concentration falls below 37.5 nmol/L (15 ng/mL), providing support for this cutoff in determining vitamin D adequacy in adults (Gloth et al. 1995, Lips et al. 1988, Thomas et al. 1998, Webb et al. 1990). Some studies suggest that the increase in PTH may start at an even higher 25(OH)D concentration (Chapuy et al. 1997, Malabanan et al. 1998). There is currently no study in children to determine the serum 25(OH)D concentration at which PTH increases. As a result, there is no definitive cutoff value to determine vitamin D deficiency in children; however, a serum 25(OH)D < 27.5 nmol/L (11 ng/mL) is considered to be consistent with vitamin D deficiency in infants, neonates, and young children and is used as an indicator for establishing the vitamin D reference value (IOM 1997, Specker et al. 1992).
- Rickets was a common childhood disease in the United States until vitamin D was added to milk.
- North Carolina reported 30 cases of rickets in a recent publication (Kreiter et al. 2000). Since then, 16 additional cases have been diagnosed at the same two medical centers; four were Muslim children.
- An ongoing study in England may provide an opportunity for studying determinants of vitamin D deficiency in children. An upcoming longitudinal study in the United States may also provide this opportunity.

Sunlight exposure to protect against rickets in infancy: the impact of sunscreens and indirect sunlight - Dr. Bonny Specker, South Dakota State University

Dr. Specker reviewed five studies.

Study I (Lichtenstein et al. 1986)

This study looked at 192 term infants < 18 months of age ($128 < 6$ months of age; $64 > 6$ months of age). Infant serum 25(OH)D was lower in winter than in summer and lower in breastfed than in formula-fed babies. In this study, no racial differences were noted in 25(OH)D concentrations.

Paradoxically, serum 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] concentrations were higher in winter than in summer and higher in black than white infants. Seasonal differences were greater in breastfed infants. Higher serum $1,25(\text{OH})_2\text{D}$ concentrations in black infants may be due to lower serum phosphorus concentrations observed in black than in white infants and toddlers in this population. The higher serum $1,25(\text{OH})_2\text{D}$ and lower serum phosphorus concentrations in black than in white infants and toddlers, despite similar vitamin D status, suggests racial differences in calcium and vitamin D metabolism.

Studies II and III (Specker et al. 1985a, Specker et al. 1985b)

The sources of vitamin D in breastfed infants are placental transfer, human milk, and sun exposure.

In the first study (Specker et al. 1985a), mothers recorded sunshine exposure and clothing coverage of their breastfed infants < 6 months of age for 1 week before blood was drawn. They also kept 3-day diet diaries of their own food and vitamin intake. Breast milk and blood samples from both mother and infant were taken on exam day.

Placental transfer (Specker et al. 1985a)

Maternal and infant serum 25(OH)D concentrations were correlated, especially in infants < 8 weeks of age. After 8 weeks, maternal 25(OH)D concentrations are not as important to the child's 25(OH)D concentrations as sunlight exposure [n = 61 mother-infant pairs (51 white and 10 black); n = 48 pairs with all data]. It was not clear from the study if the correlation between infant and maternal concentrations is the result of placental transfer, human milk transfer, or similar exposure to the sun.

Human milk (Specker et al. 1985b)

In a second study, maternal milk vitamin D correlated with maternal vitamin D intake, and maternal milk vitamin D correlated with maternal serum 25(OH)D. However, infant serum 25(OH)D did not correlate with maternal milk vitamin D. Breast milk vitamin D correlates with maternal vitamin D intake in black and white women; black mothers have lower vitamin D intake and lower milk vitamin D.

Sun exposure (Specker et al. 1985a)

In the first study, infant serum 25(OH)D concentration was correlated with exposure to sunshine independent of maternal 25(OH)D. An additional study investigating the role of sunscreen on vitamin D synthesis in breast fed infants received Institutional Review Board (IRB) approval, but doctors did not cooperate, because they thought it was unethical to expose children to sunlight without sunscreen.

To achieve a serum 25(OH)D concentration > 27.5 nmol/L (11 ng/mL) in the infant, Specker and colleagues (1985a) estimate that the infants of mothers with low serum 25(OH)D [< 87.5 nmol/L (35 ng/mL)] would need to be in the sunlight 10 to 30 minutes per week wearing only a diaper or 30 minutes to 2 hours per week fully clothed with no hat. Infants of mothers with a high serum 25(OH)D [> 87.5 nmol/L (35 ng/mL)] would require < 10 minutes per week wearing only a diaper or 30 minutes per week fully clothed with no hat. Adopting conservative estimates, the authors suggest that infants would need to be outdoors for either 30 minutes per week (diaper only) or 2 hours per week (fully clothed, no hat). All the black infants in this study had no sunshine exposure and their mothers had low vitamin D status. Therefore, it was not possible to determine the amount of sunshine exposure needed to maintain adequate vitamin D for black

infants. A study by Brazerol and colleagues (1988) indicated that black adults increase serum 25(OH)D in response to UV exposure similar to white adults.

Study IV (Specker and Tsang 1987)

This study looked at the time an infant spends outside daily based on season of birth. All babies received more sun exposure in summer than in winter, regardless of the season when they were born. Seasonal changes in serum 25(OH)D parallel sun exposure.

Study V (Specker et al. 1992)

This study looked at vitamin D supplementation in infants fed human milk at two sites in northern China and two sites in southern China. Serum 25(OH)D concentrations increased with increasing vitamin D dose and were lower in infants in northern than in southern China. Among infants in northern China supplemented daily with 2.5 or 5 µg (100 IU or 200 IU) of vitamin D, 36% and 30%, respectively, had serum 25(OH)D concentrations below the lower limit of normal [27.5 nmol/L (11 ng/mL)]. These data suggest that these doses may be too low for infants in northern China. No cases of rickets were observed in the 280 infants who completed the 6 month study. Serum concentrations increased as vitamin D dose increased in infants from northern China, but there was no dose effect among infants in southern China.

Conclusions

Both maternal vitamin D status and sunlight exposure affect the vitamin D status of breastfed infants. Sunlight exposure appears to have the greatest impact. Maternal vitamin D status appears to be more important before infants are 8 weeks of age, possibly through placental transfer. The contribution of vitamin D from maternal milk is insignificant relative to the contribution from sunlight exposure.

Discussion of Dr. Specker's presentation by expert panel members and guests

The difficulty in measuring sun exposure with a dosimeter was noted because dosimeter readings do not take into account the amount of skin exposed to sunlight. It was also pointed out that ozone absorbs UVB rays used in the synthesis of vitamin D. Dr. Specker said cases of rickets appear to be increasing in Mexico City, perhaps as a result of the high concentration of ozone in the city. A study was planned, but a volcano erupted, and it was not possible to interpret the results.

Ultraviolet radiation exposure during childhood and subsequent risk of skin cancer - Dr. Mona Saraiya, Division of Cancer Prevention and Control, CDC

Sunlight exposure is necessary for vitamin D synthesis. A few studies identified UV light exposure as playing a positive role in treating seasonal affective disorder and breast and prostate cancer. UV exposure has been identified as a definite major risk factor in causing basal and squamous cell carcinoma, melanoma, and potentially cataracts and immunosuppression. The population attributable risk of UV exposure for melanoma is between 65% and 90%; for the nonmelanoma skin cancers (basal and squamous cell carcinoma), it is about 60%.

Skin cancer is the most common cancer in the United States. Both the incidence of and mortality from melanoma have increased since the early 1970s (from 6/100,000 in 1973 to 14/100,000 in 1998). In 1998, there were 51,400 new cases and 7800 deaths from melanoma in the United States. The incidence of melanoma is higher in whites than in blacks. Among blacks, incidence is less than 2/100,000 and mortality is less than 1/100,000. Family history, personal history, and the presence of large and/or numerous moles affect cancer risk. Sun exposure in childhood is an important risk factor for melanoma in adults, and sunburn is a risk marker.

Ambient exposure studies (studies that measure UV exposure based on latitude) show that when a person moves from an area of low sun exposure to one of high sun exposure, the risk of developing melanoma is increased if the person arrives earlier in life. Alternatively, the later in life the person arrives, the lower the risk of developing melanoma. Reverse migration studies show that, when moving from an area of high exposure to an area of low exposure, the duration of residence in the lower exposure area affects the risk of cancer later in life (Autier et al. 1997). These studies indicate that exposure early in life is more important than exposure later in life. Personal exposure studies show sunburns in childhood lead to a greater cancer risk, but the association is not strong (odds ratio = 1.91). However, the association is consistent, as this is a pooled odds ratio from 29 case control studies (Elwood and Jopson 1997).

Melanocytic nevi are potential mediators of melanoma. If these nevi develop during childhood, reach their maximum density on the skin at about 10 years of age, and are caused by sun exposure, they correlate with a high risk of melanoma.

The International Agency for Research on Cancer (IARC) has deemed solar UV radiation a carcinogen and artificial UV radiation a probable carcinogen. UV radiation damages DNA, and sunlight has both early and late effects on the development of melanoma. A study by Noonan et al. (2001) showed that transgenic mice given a sunburn-inducing dose of UV light at 3.5 days of age began to develop melanomas around 6 months of age. By the time they were 1 year old, half the mice had cancer. Six-week-old mice given the same dose of UV light did not develop tumors.

Sun-safe behaviors include minimizing UV exposure during peak periods, wearing sun-protective clothes, seeking shade, wearing sunscreen of SPF 15 that protects for both UVA and UVB rays, and avoiding artificial tanning devices.

Topical use of sunscreen reduces the risk of sunburns. When used mainly during unintentional sun exposure, sunscreens probably prevent squamous cell carcinoma of the skin. No conclusion can be drawn about the cancer-preventive activity of the topical use of sunscreens against basal cell carcinoma and cutaneous melanoma. The use of sunscreen may extend the duration of intentional sun exposure, which may increase the risk of cutaneous melanoma.

Most people do not use sunscreen properly; one quarter of a bottle per use is needed to get the SPF protection. Also, some sunscreens do not block UVA rays (IARC 2001).

Discussion of Dr. Saraiya's presentation by expert panel members and guests

There was debate about whether decreased sunlight exposure contributes to the development of other types of cancer, such as breast, colon, and prostate cancers. Dr. Saraiya responded that there is insufficient evidence; other members of the panel disagreed. One participant added that vitamin D and sunlight provide protection against tuberculosis. If a patient is vitamin D deficient, the infection may be more aggressive.

Other comments included the following:

- It was asked whether there was a dosage of sunlight exposure that would make vitamin D, but not encourage cancer. The opinion of one panel member was 25% of the minimal erythermal dose (MED) twice a week.
- Approximately 25 µg (1000 IU) of vitamin D can be synthesized when 6% of the body is exposed to one MED for 5 minutes two or three times per week (Holick 1999). This is based on the observation that a healthy individual whose whole body is exposed to one MED of simulated sunlight will have circulating vitamin D concentrations comparable to those from ingesting 250 µg to 625 µg (10,000 IU to 25,000 IU) of vitamin D.
- One expert added that blacks need up to ten times the sun exposure of whites to synthesize the same amount of vitamin D (Clemens et al. 1982). These results vary from those of Brazerol et al. (1988) discussed by Dr. Specker.
- Proper use of sunscreen reduces vitamin D synthesis by 97.3%.
- It was asked whether vitamin D can be synthesized from indirect sunlight. The response was that it depends on what reflects the light. Sun reflection from sand produces some synthesis of vitamin D. There is no vitamin D synthesis when an individual is in total shade. Indirect light reflected from asphalt does not produce vitamin D, whereas reflection from light cement may produce some vitamin D.
- It was asked whether infants are less efficient in synthesizing vitamin D than adults and the response was no.

Supplementing breastfed infants with vitamin D: a historical perspective and current discussions on age, dosage, preparation, and targeting - Dr. Frank Greer, Meriter Hospital, Wisconsin

History of vitamin D supplementation of infants

In the first half of the 20th century, vitamin D deficiency was a big problem, with many cases of rickets reported in the United States. Eventually, cow's milk was fortified with vitamin D and nutritional rickets became almost extinct. In 1963, the AAP Committee on Nutrition recommended that all infants receive 10 µg (400 IU) of vitamin D per day starting in the first 2 weeks of life (AAP 1963). More than 10 µg (400 IU) does not improve the effect of rickets prevention. The committee did not comment on the vitamin D levels in human milk but did comment on the increase in vitamin D deficiency in African Americans and that sunlight exposure cannot be relied on to improve vitamin D status.

The 1974 Textbook of Infant Nutrition (Fomon 1974) estimated the daily requirement of vitamin D for infants to be 2.5 to 5 µg (100 to 200 IU), citing the 1963 AAP recommendation. The 1963 AAP recommendation actually recommended twice the estimated requirement, or 10 µg (400 IU) of vitamin D daily. Fomon also recommended ignoring the contribution of sunlight during the first weeks of life. Fomon's text noted that human milk contains 0.55 µg (22 IU) of vitamin D per liter.

A 1978 breastfeeding statement from the AAP Committee on Nutrition in Pediatrics (AAP 1978) recommended vitamin D as a possible supplement for breastfed infants. In 1982, the committee's statement said that arguments could be made for supplementing breastfed infants with both fluoride and vitamin D during the first 6 months of life, but there was disagreement about whether all breastfed infants needed such supplementation (AAP 1982).

The 1998 Pediatric Nutrition Handbook, 4th edition (AAP 1998), as in earlier editions, recommends 10 µg (400 IU) of vitamin D per day for breastfed infants in the chapter on vitamins. However, the chapter on breastfeeding states that only dark-skinned infants need vitamin D supplementation. The 5th edition (currently in production) will provide a consistent recommendation throughout the text.

In 1997, the National Academy of Sciences Food and Nutrition Board recommended 5 µg (200 IU) per day as the adequate intake (AI) of vitamin D for all infants (IOM 1997).

In the 1997 breastfeeding policy statement from the work group on breastfeeding, AAP states that vitamin D and iron may need to be given to selected infants before they are 6 months of age,

if the mothers are vitamin D deficient or if the infants are not exposed to adequate sunlight (AAP 1997). Those who have low iron stores or anemia would need iron.

Current discussions on vitamin D supplementation of infants

AAP has decided to develop a policy statement on vitamin D supplementation for the following reasons: the results of the North Carolina study (Kreiter et al. 2000) on nutritional rickets in breastfed African American infants; the Healthy People 2010 goal of having 75% of infants breastfed for the first 6 months of life (U.S. Department of Health and Human Services 2000); the uncertainty about how much sun exposure is required for each infant as well as how air pollution and latitude affect sun exposure; the growing concern about UV exposure in childhood and its relationship to skin cancer in later years; the uncertainty about the amount of sunlight exposure needed for people with darker skin pigmentation; and the fact that vitamin D is not a nutrient but a precursor of steroid hormones that is not naturally present in any infant food, including human milk, in quantities that will meet individual needs.

Considerations for vitamin D supplementation include the following: 1) prevention of rickets in all infants, including those with chronic diseases that may decrease vitamin D absorption; 2) a minimum dosage of 5 µg (200 IU) a day to meet the AI recommended by the National Academy of Sciences and Food and Nutrition Board (IOM 1997); 3) no ethnic or minority group should be singled out for supplementation, given the increasing difficulty in defining those groups; 4) supplementation should be started at birth and continued until vitamin D is adequately derived from food; 5) infants who are fed formula exclusively do not need supplementation; 6) vitamin D supplementation must not cause any harm; 7) supplementation should not interfere with breastfeeding; 8) vitamin D supplements should be safe to have in the home; 9) the ideal preparation should contain vitamin D only; 10) to maximize compliance, vitamin D supplementation should become part of the daily routine; 11) the vitamin D status of the pregnant/lactating mother should be taken into consideration by providers in the population; and 12) supplementation should be cost-effective, including treating overdoses and missed cases that need further care.

Discussion of Dr. Greer's presentation by expert panel members and guests

There was much discussion of whether the recommendation to supplement infants with vitamin D should target infants with dark skin. The major arguments on both sides are as follows:

Not targeting

- Defining dark skinned is difficult.

- Dark-skinned populations are not the only ones at risk. Any breastfed infant is at risk if not exposed to sunlight. Therefore, the recommendation must be applicable for all groups.
- Muslim infants who are covered are at risk, regardless of race.

For targeting

- The parents of African American infants, for example, need to know about their infants' increased risk of vitamin D deficiency and need for supplementation, and so do the physicians who care for those infants.
- It appears paternalistic to say "if it is good for one group, it is good for all".
- Because most minorities are treated by nonminority doctors, the recommendation may be missed if African Americans are not singled out in the policy.
- Because race is a sensitive issue, we sometimes make poor recommendations.

Panel members concluded the discussion in agreeing that supplementation should be universal, but education efforts should be targeted to infants at highest risk.

Other comments included the following:

- If supplementation at birth is recommended, it could interfere with breastfeeding.
- Formula manufacturers will use the recommendation to market formula. The packaging of an infant supplement of vitamin D from Canada was displayed to show how it was used to advertise formula.
- In Bulgaria, it is recommended that infants be supplemented with 20 µg (800 IU) of vitamin D per day.
- In Romania, it is recommended that infants be supplemented with 10 µg (400 IU) of vitamin D per day.
- In Canada, it is recommended that breast fed infants be supplemented with 10 µg (400

IU) of vitamin D per day and 20 µg (800 IU) per day in the winter. Canada has had this recommendation for 10 years.

Risks associated with vitamin D supplementation during infancy - *Dr. Ali Calikoglu, University of North Carolina at Chapel Hill*

Vitamin D supplementation during infancy may cause hypervitaminosis D as well as an excess of other vitamins and minerals when vitamin D is given in a multivitamin form. Hypervitaminosis D is rarely fatal but it can cause significant morbidity due to the complications of hypercalcemia and hypercalciuria. Complications include general symptoms, such as muscle weakness and fatigue; central nervous system symptoms; gastrointestinal problems; cardiac rhythm abnormalities; urinary system complications such as kidney stones and nephrocalcinosis; and soft tissue calcifications.

The risks associated with vitamin D supplementation depend on the following factors: the type of vitamin D given, the dosage and duration of supplementation, and the vitamin preparation.

Type

Vitamins D₂ and D₃ are similar in terms of toxicity, although vitamin D₂ has poorer stability and purity. Supplementation is mainly with D₂ in the United States and D₃ in Europe. The half-lives of vitamins D₂ and D₃ are 20 days to months. The half-life of 25(OH)D is about 15 days. Hypercalcemia secondary to hypervitaminosis D can last as long as 18 months. In contrast, hypercalcemia secondary to high doses of 1,25(OH)₂D, which cannot be stored in the body and has a short half-life, is brief.

Dose, scheduling, and duration

High doses of vitamin D can cause hypercalcemia, hypercalciuria and their consequences.

Intermittent high-dose studies

Markestad et al. (1987), Germany - 43 infants were given 15 mg (600,000 IU) of ergocalciferol. Two weeks later, all had high 25(OH)D levels, and 14 infants had hypercalcemia. Hypercalciuria was not assessed.

Zeghoud et al. (1994), France - 15 mg (600,000 IU) of ergocalciferol was given to 30 infants. Two weeks after ingestion, all but two had high 25(OH)D levels. Six months after the first dose, 50% of all infants still had high 25(OH)D levels. In the other arms of the study, 58% of the infants who received 5 mg (200,000 IU) of ergocalciferol and 23% of infants who received 2.5

mg (100,000 IU) of ergocalciferol had high 25(OH)D levels 2 weeks after ingestion. There was no hypercalcemia; hypercalciuria was not assessed.

Ronnefarth et al. (2000), Germany - A retrospective survey of children with nephrocalcinosis was conducted. Thirteen of 152 patients with nephrocalcinosis received bolus vitamin D prophylaxis in infancy [15 mg (600,000 IU) of ergocalciferol every 3 months].

Intermittent high-dose vitamin D treatment is effective. However, high doses [15 mg (600,000 IU) and 5 mg (200,000 IU)] carry significant risk for hypervitaminosis D. 2.5 mg (100,000 IU) appears to be relatively safe.

Single high-dose study

Oliveri et al. (1996) - 79 healthy children (5 to 11 years of age) received 3.75 mg (150,000 IU) of ergocalciferol at the beginning of autumn. The dose was sufficient to maintain normal 25(OH)D levels, however, the winter increment of PTH was not inhibited. There was no hypercalcemia and no hypercalciuria.

Low-dose daily vitamin D

No data are available demonstrating that 10 µg (400 IU) or less of vitamin D daily is harmful. The current myth that hypervitaminosis D can occur with 50 µg (2000 IU) or less of daily vitamin D supplementation is based on very limited data and clinical observations.

I. Experience in childhood

Jeans and Sterns (1938) - Vitamin D in doses ranging from 45 to 90 µg (1800–3600 IU) was given to nine healthy infants for 9 to 12 months. Their linear growth decelerated after 6 months of normal growth and recovered after the doses of vitamin D were reduced. This observation led to the conclusion that vitamin D doses > 45 µg (1800 IU) can suppress growth. However, this study was small and poorly designed. There was only one child per dose, no control group, and no statistical analysis.

British experience - In the 1950s, milk and cereals were enriched with vitamin D [45 to 50 µg (1800 to 2000 IU)] in the United Kingdom. An epidemic of hypercalcemia was observed in the following years. The number of children with hypercalcemia declined when the vitamin D enrichment was lowered to 10 to 15 µg (400 to 600 IU). This observation led to the conclusion that even a modest amount of vitamin D can cause vitamin D intoxication. Of the thousands of children who ingested 100 µg (4000 IU) or more of vitamin D per day, a few hundred developed hypervitaminosis (Bransby et al. 1964). Most of the affected children had distinct phenotypic features, therefore, their hypersensitivity to vitamin D might be attributed to other causes, such as Williams syndrome.

Fomon et al. (1966) - Three groups of infants were given daily vitamin D₂ doses of 7.5, 8.75 to 13.75, or 34.5 to 54.25 µg (300, 350 to 550 or 1380 to 2170 IU). The groups had no differences in length, weight, or serum calcium concentrations. Neither 25(OH)D concentration nor hypercalciuria was assessed.

Pittard et al. (1991) - Sixteen low-birth-weight (LBW) or full-term infants were randomly assigned to receive either 10 µg (400 IU) or 20 µg (800 IU) of vitamin D daily from birth to 16 weeks of age. These doses were sufficient to maintain normal calcium, phosphorus, PTH, and 25(OH)D concentrations. No hypercalcemia was observed, and hypercalciuria was not assessed.

II. Experience in adults

The AI of vitamin D for adults is 5 µg (200 IU) until 50 years of age, 10 µg (400 IU) for ages 50 to 70, and 15 µg (600 IU) over age 70 (IOM 1997). There are no data to support the myth that a toxic dose of vitamin D can be as low as five times the AI.

Vieth et al. (2001) - 61 healthy adults were randomly assigned to receive either 25 µg (1000 IU) or 100 µg (4000 IU) of vitamin D₃ for 2 to 5 months. The maximum plateau serum 25(OH)D concentrations were 100 and 125 nmol/L (40 and 50 ng/mL), respectively. Serum calcium and urinary calcium excretion did not change from baseline at either dosage. The conclusion was that 100 µg (4000 IU) of vitamin D₃ daily caused no harm in adults.

Preparation

Multivitamin solutions for infants contain several vitamins plus iron. The amounts of the various vitamins vary greatly, thus increasing the probability of vitamin toxicity.

Vitamin A toxicity includes skin lesions, alopecia, pseudotumor cerebri, hepatotoxicity, and death. Adverse effects have been observed at 25,000 IU daily. There is no evidence that vitamin A supplements < 10,000 IU daily are harmful.

Vitamin C toxicity includes oxalate kidney stones, excessive iron absorption, and gastrointestinal distress. Adverse effects are observed at 1 to 1.5 g daily. There is no evidence that vitamin C supplements < 250 mg daily are harmful.

Vitamin E has no apparent toxicity after 100 to 800 IU daily for 3 years.

Thiamin, riboflavin, niacin, vitamin B₆, and vitamin B₁₂ have no toxicity.

Conclusion

Vitamin D supplementation at 10 µg (400 IU) or less daily appears to be safe for infants. Studies are needed to determine the lowest dose of vitamin D supplementation for infants that is both safe and effective.

Discussion of Dr. Calikoglu's presentation by expert panel members and guests

It was noted that vitamin A in as low a dose as 10,000 IU in pregnant women may be teratogenic.

Recommending vitamin D supplements for U. S. breastfed infants: does vitamin D interfere with the physiologic aspects of breastfeeding? - *Dr. Ruth Lawrence, University of Rochester Medical Center*

This question is not answered in the medical literature. The many articles on vitamin D and vitamin D supplementation do not address the impact on the breastfeeding infant or the breastfeeding mother. It is a matter of risk/benefit ratio. What is the risk to the infant's physiologic state of taking the vitamin D supplement, and what is the psychologic impact on the mother's ability to continue breastfeeding versus the benefits of giving vitamin D across the board to babies who do not have a deficiency.

If we look first at the infant, there are no physiologic changes examined or reported in the literature, but the following questions we need to pose: (1) Is there a change in the pH of the gut with vitamin D supplementation? (2) Keeping in mind that a change in gut flora may change the pH and precipitate a cascade of events, do gut flora change? (3) If there is a change in gut flora, would it affect the infection rate for this infant? (4) Would oral vitamin D change the absorption of calcium and phosphorus from milk?

Although we have no data on vitamin D, we have some experience with iron supplementation. For example, iron binds with lactoferrin, which is a prime infection protection constituent of human milk. An overload of iron inactivates lactoferrin and leaves excess iron in the gut. *Escherichia coli* depends on iron for growth. Lactoferrin therefore suppresses the growth of *Escherichia coli* in the gut in the breastfed infants. Increased growth of *Escherichia coli* suppresses *Lactobacillus*, which is the normal flora of newborn and young infants. This consequence has the potential for increasing the number of infections, particularly infections that result in diarrhea and malabsorption.

We know also that iron is better absorbed from human milk than from formula. This work was done in adult volunteers who were provided tagged iron either in human milk or in formula. Does human milk enhance absorption of vitamin D?

Would there be an effect on growth of infants who are given vitamin D when they are not vitamin D deficient? Domellof et al. (2001) studied iron absorption of Swedish infants and noted that linear growth was impaired in healthy infants who did not need the iron, especially in the first 6 months. Whether a similar response occurs with vitamin D is not known.

The need to evaluate pH, intestinal flora, infection rate, and linear growth in infants supplemented when they are not deficient remains crucial. It is interesting to note as well that Coutoudis et al. (1999) showed that partially breastfed infants (mixed feed of formula and breast milk) of HIV-positive mothers had a greater incidence of HIV infection than exclusively breastfed infants of HIV-positive mothers.

The persistent issue of compliance needs to be addressed as well because other studies have shown that 75% of mothers are noncompliant with iron supplements.

Another risk to the infant receiving a supplement is aspiration. Breastfed babies often do not tolerate non-breast milk added to their diet in the early weeks. Years ago, when cod liver oil was given, many cases of lipoid pneumonia resulted. The risk of excessive vitamin D that is associated with hyperostosis needs to be investigated. Hyperostosis was a common disease in the 1950s and 1960s not only in England but also in this country where vitamin D supplementation of many foods was made available. Hyperostosis was diagnosed on physical exam, confirmed by x-ray, and associated with hyperpyrexia and loss of hair.

Vitamin D supplementation may have a 2-fold effect on breastfeeding. (1) Does supplementation destroy the mother's confidence so she never starts or (2) does supplementation affect the duration of breastfeeding? Dennis and Faux (1999) studied the self-efficacy framework. They point out that perception of abilities is much more important than the mother's true abilities in choosing a behavior and performing and maintaining it. Therefore, if the mother perceives a deficiency in her breast milk because she has to supplement, it could theoretically interfere with her ability to breastfeed successfully. Other factors affect one's self-efficacy or confidence including previous experience, verbal persuasion, and performance accomplishments. Confidence has always been an important factor in successful breastfeeding. As Derrick Jelliffe said, "Breastfeeding is a confidence game". For a mother who has not breastfed previously, infant vitamin D supplements may make her worry about her ability to breastfeed, she may be less likely to breastfeed, or she may be afraid to breastfeed. Confidence can influence women's judgments about their ability to initiate, persist, and continue breastfeeding.

Survey at the University of Rochester

A brief survey was performed with forced-answer format recording age, parity, and previous breastfeeding experience to examine maternal perceptions about vitamin D supplementation of their breastfed infants. Young mothers who had just given birth to their first child thought perhaps something was wrong with their milk and would give the vitamin D. Multiparous mothers who had breastfed before were very confident with their breastfeeding, and most would not give the supplement. Several mothers said they would supplement if their doctor said to do so. When professionals were interviewed, they expressed the belief that vitamin D should be given only to babies who are deficient. A solution in Germany is to put an oral vitamin D preparation on the mother's nipple once a day before the baby breastfeeds. This technique avoids feeding the baby some other substance with an artificial device that is not mother's milk.

Conclusions

- If all breastfed infants are to receive vitamin D regardless of risk of deficiency, the change in the physiologic state of the infant should be evaluated, including change in flora in the gut and the change in infection rate.
- The duration of breastfeeding with or without vitamin D should also be examined, particularly targeting primiparas women.

Discussion of Dr. Lawrence's presentation by expert panel members and guests

Some participants thought supplementation from birth would interrupt breastfeeding and should not be introduced until the child has been breastfed for 6 months. Another participant countered that, in his experience with babies with breast milk jaundice, breastfeeding was interrupted from 1 to 5 days; then all mothers went back to breastfeeding at the end of that period. The biggest factor in resumption of breastfeeding seems to be how the doctor addresses the topic with the mother. A third participant commented that a hospital study in Canada showed no change in breastfeeding practices when supplementation was introduced in the hospital.

Others comments included the following:

- There is no evidence that 5 μg (200 IU) of vitamin D will change gut flora per se, but it has not been proven unequivocally.
- Some doctors and other health care professionals recommend no sunscreen for the first year of life, whereas the AAP says not for the first 6 months (AAP 1999).

- One participant suggested that it might be easier to recommend that parents take children outside in the sunlight for 30 minutes per week than to recommend giving the infant a vitamin D supplement. Concerns about sunlight exposure and skin cancer were repeated.

Vitamin D supplementation of breastfed infants in North Carolina: cost, compliance, effectiveness, and impact on breastfeeding - Ms. Gladys Mason, North Carolina Department of Health and Human Services

North Carolina had a growing number of documented cases of rickets secondary to vitamin D deficiency. Two medical centers reported 30 cases between 1990 and 1999, half the cases occurred between 1998 and the first half of 1999 (Kreiter et al. 2000). All cases were in breastfed African American children who had not been given vitamin D supplements. This increase in cases was attributed to the increase in breastfeeding among African American mothers, the decline in the number of physicians prescribing vitamin D for breastfed infants, and a decrease in exposure to sunlight. Data show that breastfeeding rates in North Carolina have risen among low-income women of all races. Between 1988 and 1999 breastfeeding rates among African Americans increased from 5.2% to 34.7%.

Major problems in providing vitamin D supplements were as follows: 1) uncertainty and lack of awareness of who is at risk for rickets; and 2) Medicaid and some insurance plans were not reimbursing for vitamin drops even though rickets is a diagnosed condition.

At the request of the North Carolina Pediatric Association, the Women's and Children's Section of the Division of Public Health implemented the Vitamin D Initiative, using Maternal Child Health block grant funding to provide free vitamin D supplements to all breastfed infants, regardless of income. Tri-Vi-Sol vitamin A, D and C drops were purchased through the Minnesota multistate contract at a cost of \$1.50 per month per child and shipped to the 87 local Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) agencies in December 1999. Local agencies were instructed to begin distribution as soon as they developed procedures and standing orders signed by their medical director. A 3-month supply of vitamin drops could be issued to each breastfed child beginning at 6 weeks of age, provided the child was not receiving any infant formula or vitamin D-fortified milk daily.

There was some initial resistance and confusion about issuing vitamin D supplements to breastfed infants. Breastfeeding has been widely promoted in North Carolina, but vitamin D supplementation has not. The American Academy of Pediatrics policy statement "Breastfeeding and the Use of Human Milk" has done little to endorse vitamin D supplementation, whereas it strongly supports breastfeeding for at least 12 months (AAP 1997). A survey completed by 400

North Carolina physicians looking at their prescribing habits showed that only 42% prescribe vitamin D to breastfed infants (unpublished data).

Physicians, nutritionists, lactation consultants and nurses challenged the rationale for issuing vitamin drops to all infants who receive breast milk as their milk source. It was necessary to clarify that nutritionists could legally issue vitamins. Lactation consultants were very concerned that vitamin D would be "one more reason to stop breastfeeding". Some mothers refused the vitamin drops, and parents who had children diagnosed with rickets were very upset because no one told them about the consequences of vitamin D deficiency. One lawsuit resulted from parents who were never told that rickets could occur in their child.

As part of the initiative, health professionals and parents were instructed about vitamin D deficiency rickets, the essential role of sunlight and vitamin D supplementation for bone growth, and the history and prevalence of rickets before supplementation began in the United States before 1925. Fact sheets were developed and continue to be available on the Nutrition Services web site (www.ncnutrition.com). Presentations were made at grand rounds and professional meetings. Health professionals continue to counsel parents of breastfed infants whenever the vitamin supplements are issued.

Concerns prevail about the formulation of over-the-counter vitamin drops that contain vitamin D. It is unclear why a vitamin D only preparation is not available in the United States. Tri-Vi-Sol vitamin A, C and D drops is an approved and affordable product that provides 1500 IU of vitamin A, 35 mg of vitamin C, and 10 μ g (400 IU) of vitamin D and is the product issued in North Carolina. Tri-Vi-Sol vitamin A, C and D drops were not found in local pharmacies that were surveyed, but several other formulations were available without prescription that included additional vitamins and minerals, such as iron, zinc, vitamin E, and B vitamins. A 5 g/mL (200 IU/mL) drop preparation is not currently available (the current recommendation according to IOM's dietary reference intake level for this age group (IOM 1997). Furthermore, the supplement packaging is associated with formula recognition, which violates the World Health Code. Another concern some nutritionists expressed is that vitamin A is palmitate rather than β -carotene.

The North Carolina Initiative had a slower start than anticipated. There are approximately 100,000 births per year in North Carolina. Over a 16-month period only 1500 infants received vitamin drops, whereas 2810 bottles were issued. Eight months after the initiative began, 96% of local agencies had standing orders and distribution procedures in place, and all were in place when the agencies were surveyed 15 months after the initiative began. Most of the vitamin drops were issued to WIC participants. Some doctors prefer to distribute the drops from their offices because of the inconvenience of sending parents to the WIC clinics. Fewer infants have been eligible for the vitamin drops than originally estimated because fewer than expected consume

breast milk as their sole milk source. There is growing concern that the definition of “eligible” for vitamin D supplementation is too conservative and probably needs to allow up to 16 ounces of infant formula per day in addition to breast milk.

After nearly 2 years of experience, the North Carolina WIC Program remains the only source of free vitamin D supplements for breastfed infants. However, this may not be the best delivery system because it does not provide seamless service. Only a few private non-WIC clinic patients receive the free vitamin drops even though physicians are aware of the initiative and many say they refer their patients to WIC. Private clinic patients do not readily come to WIC clinics. Local agency commitment to this initiative varies. Parental compliance has not been evaluated, but there is documentation of some refusal to accept the vitamin drops. Increasing knowledge among health professionals and parents about the essential role of vitamin D and vitamin D-deficiency rickets will continue to be important.

Discussion of Ms. Mason’s presentation by expert panel members and guests

There was a lengthy discussion of the economic implications and cost of the program. If the cost is compared with the cost of treatment and hospitalization of rickets cases, the program may not be cost-effective. A quick calculation of the hypothetical cost for the United States, using an estimated cost of Tri-Vi-Sol vitamins to the consumer (\$5.69 per child per month) and our rough estimates of incidence (5 hospitalized cases per million children and 25 ambulatory cases per million children), produced the following estimates: cost per hospital case averted \$4,794,614.28; cost per case averted \$958,922.86 (L. Grummer-Stawn, unpublished data, 2001). Even if the cost were reduced to \$1.50 per child per month, the cost per case averted would be \$252,614. However, the cost of untreated vitamin D deficiency is unknown. A cost-effectiveness analysis is difficult, because the real incidence is unknown.

It was asked whether recommending sunlight is out of the question.

Alternatives to daily vitamin D supplementation: supplementation of pregnant and lactating women - *Dr. Bruce Hollis, Medical University of South Carolina*

UV radiation promotes vitamin D₃ synthesis in the skin. The UVB rays are absorbed by the skin and induce conversion of 7-dehydrocholesterol into previtamin D₃. After a few hours, vitamin D₃ is generated and is carried in the bloodstream to the liver and kidneys, where it is activated.

A study by Matsuoka, et al. (1989) determined that the increase in serum 25(OH)D in the blood occurs after whole body exposure to UVB radiances equal to or above 18 mJ/cm².

Sun exposure and racial differences in vitamin D

A study by Matsuoka, et al. (1991) exposed 31 subjects to the equivalent of less than 10 minutes of noontime sun. Because peak serum 25(OH)D₃ occurs 24 hours after acute UVB exposure, serum levels were measured 24 hours later and compared with baseline measures. Subjects represented four racial/ethnic groups: eight African Americans, eight Caucasian Americans, seven South Asians, and eight East Asians. Basal serum levels were similar in all groups. After UVB irradiation, significant racial differences were apparent. The post-UVB serum 25(OH)D concentrations in Caucasian Americans and East Asians were significantly higher than in African Americans and South Asians. Intragroup serum 25(OH)D increases were significant for all groups except African Americans.

Another study looked at the effects of oral vitamin D₂ supplementation in adult males. Subjects were given 2.5 mg (100,000 IU) of vitamin D₂ for 4 days. Unpublished data from this study revealed that serum 25(OH)D concentrations among Caucasian Americans increased from 65.0 nmol/L (26 ng/mL) to 167.5 nmol/L (67 ng/mL), and among African Americans, they increased from 20.0 nmol/L (8 ng/mL) to 75.0 nmol/L (30 ng/mL), which indicates a difference in the metabolic handling of vitamin D, aside from just skin pigmentation. Also, 24-hydroxylation (inactivation step) of 25(OH)D is more active in South Asians and African Americans than in Caucasian Americans (B. Hollis, personal communication, 2001).

Older data showed that serum 25(OH)D₃ concentrations tended to be much lower in African Americans than in Caucasian Americans. Examination of cord blood indicates that 25(OH)D is transferred across the placenta; the neonates' levels are half that of their mothers. In a study by Hollis and Pittard (1984), 25(OH)D₃ concentrations among African American mothers and neonates were 16.5 ± 8.0 nmol/L (6.6 ± 3.2 ng/mL) and 8.8 ± 3.0 nmol/L (3.5 ± 1.2 ng/mL), respectively, compared with concentrations of 29.5 ± 13.3 nmol/L (11.8 ± 5.3 ng/mL) and 15.5 ± 7.5 nmol/L (6.2 ± 3.0 ng/mL) among Caucasian American mothers and neonates.

Vitamin D in human milk

Vitamin D levels in human milk from healthy mothers who are not vitamin D deficient, range between 0.5 and 1.5 μ g (20 and 60 IU) (Greer et al. 1984). Vitamin D (the parent compound) translocates to human milk at a much greater rate than does 25(OH)D.

Several studies have shown that the vitamin D content of breast milk can be raised by supplementing the mothers' vitamin D levels, but sufficient vitamin D levels cannot be achieved in human milk without doses exceeding the current AIs for mothers. Maternal UVB exposure greatly alters the vitamin D content of human milk, but the concentrations quickly fall without further exposure.

A Finnish study by Ala-Houhala et al. (1986) looked at three groups of healthy, well nourished mothers:

Group 1: 17 mothers given 50 µg (2,000 IU) of vitamin D₃ a day, infants not supplemented.

Group 2 : 16 mothers given 25 µg (1,000 IU) of vitamin D₃ a day, infants not supplemented.

Group 3 : 16 mothers not supplemented, breastfed infants given 10 µg (400 IU) of vitamin D₂ a day.

At birth, serum concentrations of all three vitamin D metabolites were comparable in all groups. At 8 weeks, the 25(OH)D concentrations in infants in groups 1 and 3 were similar, but in group 2 they were significantly lower, with three infants at or below the risk limit for rickets. At 15 weeks, the infant 25(OH)D concentrations were significantly lower for group 2 than for groups 1 and 3. The study concluded the following: 1) breast milk does not have enough antirachitic activity by itself or when mothers are supplemented with 25 µg (1000 IU) of vitamin D per day; 2) vitamin D supplementation of 10 µg (400 IU) per day to breastfed infants is adequate to prevent rickets during winter in northern latitudes; 3) an adequate supply of vitamin D to breastfed infants is achieved only by increasing maternal supplementation to 50 µg (2000 IU) per day, the safety of which is unknown.

Dr. Hollis wants to study supplementation of lactating mothers with 100 µg (4000 IU) of vitamin D per day and to look across racial lines and in various climates. He estimates that this dose will increase milk vitamin D to 5 to 7.5 µg/L (200 to 300 IU/L). Dr. Hollis also commented that chronic exposure of the mother to the sun has been shown to increase her breast milk vitamin D to 2.5 to 3.75 µg/L (100 to 150 IU/L), but these studies are in white women.

Discussion of Dr. Hollis's presentation by expert panel members and guests

According to a study published in the *American Journal of Nutrition*, 2001, vitamin D does not reach toxic levels until supplementation exceeds 250 µg (10,000 IU) per day (Veith et al. 2001).

Alternatives to daily vitamin D supplementation: less frequent, high dose supplementation of infants - Dr. Mike Holick, Boston University School of Medicine

After the movie *Jurassic Park* became popular, many children wanted their own dinosaur. The closest they could come to one was an iguana. Unfortunately, these animals are vertebrates like humans and need a source of calcium and vitamin D. However, they were put in terrariums where they received no sunlight and were often fed lettuce, which contains little calcium and no vitamin D. They developed rickets and osteoporosis. With the addition of a sun lamp and an

adequate source of calcium and vitamin D, the iguanas were healthy.

Case study of rickets

A case study was cited in which a 13-month-old African American child, who was solely breastfed and did not receive vitamin D supplementation, experienced cramping of the hands and feet. The child was developing normally, had no known medical problems, and was up to date on immunizations. He was solely breastfed, received 3 to 10 ounces of juice per day, no whole milk, and limited dairy products. His serum calcium was 5.9 (normal 8 to 10.5); ionized calcium was 3.4 (normal 4.5 to 5.3). Magnesium and phosphorus were normal. His serum PTH and 1,25(OH)₂D concentrations were checked [but not his serum 25(OH)D, the best indicator of vitamin D status]. Hypocalcemia was initially treated with intravenous calcium. Treatment progressed to oral calcium carbonate and 25 µg (1000 IU) of vitamin D twice per day. The child was eventually treated with 125 µg (5000 IU) of vitamin D four times per day and recovered. Chronic low phosphorus, not calcium, causes bone disease in vitamin D deficiency.

Vitamin D: assessment, function, source, and deficiency

Vitamin D is hydroxylated to 25(OH)D in the liver and 25(OH)D is further hydroxylated to 1,25(OH)₂D in the kidney. Although 1,25(OH)₂D is the active form of vitamin D, it has a short half-life and is not a marker of vitamin D status. The appropriate test is a serum 25(OH)D assay. The normal range of serum 25(OH)D is the mean serum 25(OH)D ± 2 standard deviations from a sample of healthy individuals. The lower limit of the normal range is as low as 20 nmol/L (8 ng/mL) or as high as 37.5 nmol/L (15 ng/mL), depending on the geographic location (IOM 1997). In general, a serum 25(OH)D concentration below 27.5 nmol/L (11 ng/mL) is considered deficient for children (IOM 1997). For optimal calcium and bone metabolism, studies in adults suggest that serum 25(OH)D concentrations should be ≥37.5 nmol/L (15 ng/mL) (Gloth et al. 1995, Lips et al. 1988, Thomas et al. 1998, Webb et al. 1990), ≥50 nmol/L (20 ng/mL) (Malabanan et al. 1998), or even higher (Chapuy et al. 1997).

Vitamin D is essential for bone health. Vitamin D regulates intestinal absorption of dietary calcium; without vitamin D the absorption rate of calcium is only 10% to 15%. With vitamin D, the intestine absorbs 30% to 80% of dietary calcium. Thus, calcium supplements are most effective when there is an adequate supply of vitamin D.

Vitamin D is rare in foods. Ice cream, yogurt, and cheese do not have vitamin D. Vitamin D-fortified milk should have 10 µg (400 IU) of vitamin D per quart, but only about 29% of milk samples tested contain between 8 and 12 µg (320 and 480 IU) of vitamin D per quart (Holick et al. 1992). Approximately 21% of skim milk samples had undetectable vitamin D (Holick et al. 1992). Vitamin D is also available in fatty fish and fish liver oils. A rich source of vitamin D is salmon. If eaten two or three times per week, it provides all the vitamin D a healthy person needs.

UVB rays make vitamin D when skin is exposed to sunlight. However, little vitamin D is made in the winter months, particularly at higher latitudes. Sunscreen, if used correctly, reduces the UVB rays absorbed by the skin. SPF 8 reduces vitamin D production by 97.5%; SPF 15 reduces vitamin D production by 99%.

Exposure of an individual's whole body to one MED of sunlight is equivalent to ingesting about 250 µg (10,000 IU) of vitamin D (Holick 1999). Therefore, exposure to 1 MED of sunlight is 17 to 50 times the recommended AI for vitamin D from dietary sources [5 to 15 µg (200 to 600 IU)] (IOM 1997). Therefore, for an older woman to obtain the equivalent of 15 µg (600 IU) of vitamin D per day (AI for women > 70 years of age), she would need to expose 6% of her body surface to sunlight for 15 to 30 minutes two or three times a week. In Britain, UVB lamps have been used as ambient lighting in nursing homes, and residents have maintained their vitamin D concentrations all year long. There have been reductions in fractures and depression in these facilities as a result of the lights. The average Caucasian in Boston needs to expose hands, face, and arms to 5 to 15 minutes of sunlight two or three times per week in the summer, before applying sunscreen. The average African American may need up to ten times as much sunlight as Caucasians to produce the same amount of vitamin D (Clemens et al. 1982). Muslims who are covered from head to toe present a major problem in terms of vitamin D synthesis. Their vitamin D production is almost 0, and all will need vitamin D supplementation.

The industrial revolution increased air pollution. Tall buildings blocked sunlight, so people were not synthesizing vitamin D. As a result, rickets became a common disease. Cesarean section became a common method of delivery in Great Britain because women had malformed pelvises from rickets and were unable to deliver their babies vaginally.

In 1822, Sniadecki noted that "strong and obvious is the influence of sun on the cure of rickets and the frequent occurrence of the disease in densely populated towns where the streets are narrow and poorly lit." Sunlight, a source of vitamin D, was used to treat disease throughout the last century. In 1905, phototherapy was used to treat tuberculosis, and rickets was first cured with sunlight in 1921. By 1939, phototherapy was a popular treatment for many diseases, including lupus.

Vitamin D treatment of adults aged 49 to 83 years resulted in a 109% increase in serum 25(OH)D concentrations and a 22% decrease in PTH concentrations (Malabanan et al. 1998). The decline in PTH was 55% among study subjects with an initial serum 25(OH)D concentration between 25 and 37.25 nmol/L (10 and 14.9 ng/mL) and 35% among those with a serum 25(OH)D between 37.5 and 49.75 nmol/L (15 and 19.9 ng/mL). There was no decline in PTH among people with a serum 25(OH)D concentration between 50 and 62.5 nmol/L (20 and 25 ng/mL).

Twenty-five micrograms (1000 IU) of vitamin D daily for adults in winter reduced PTH levels by 33%.

In the elderly, vitamin D deficiency is treated with 1.25 mg (50,000 IU) per week for 8 weeks.

Vitamin D deficiency can lead to osteoporosis. Many cases of fibromyalgia are often caused by vitamin D deficiency. Up to 50% of women over 50 years of age are vitamin D deficient (Malabanan et al. 1998). In those over age 65, sunlight deprivation is the leading cause of vitamin D deficiency.

Vitamin D and cancer

There may be a relationship between vitamin D and cancer. As early as 1941, it was discovered that there were higher cancer rates at higher latitudes (Apperly 1941). Breast (Garland et al. 1990), colon (Garland et al. 1990), and prostate (Hanchette and Schwartz 1992) cancer rates are all higher in northern than in southern latitudes. $1,25(\text{OH})_2\text{D}$ is the active form of vitamin D. $1,25(\text{OH})_2\text{D}_3$ inhibits proliferation of benign and malignant prostate cancer cells (T.C. Chen, G.G. Schwartz, and M.F. Holick, unpublished data, 1998). But increased vitamin D intake or sunlight exposure does not increase $1,25(\text{OH})_2\text{D}$. It is possible that prostate cells make $1,25(\text{OH})_2\text{D}$ to maintain normal cell growth activity by increasing $1\alpha\text{-OHase}$ activity. Research by Schwartz et al, (1998) suggests that benign and malignant prostate cancer cells metabolize $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ to control cell growth.

Vitamin D supplementation of breastfed infants

Vitamin D deficiency does not need to be a consequence of breastfeeding. To have adequate levels of vitamin D in breast milk, mothers would need 100 μg (4000 IU) of vitamin D daily. However, the tolerable upper intake levels recommended for individuals 1 to 90 years old is 50 $\mu\text{g}/\text{day}$ (2000 IU/day). Neonates should not leave the hospital vitamin D deficient. It was the speaker's opinion that all neonates should receive a 25 to 125 μg (1000 to 5000 IU) single dose of vitamin D before leaving the hospital.

Discussion of Dr. Holick's presentation by expert panel members and guests

One participant suggested that mothers, rather than infants, receive vitamin D supplements. The response was that the literature does not support that suggestion. Because the amount of vitamin D passed to the child through breast milk is so small, mothers would have to take large doses of vitamin D to provide an adequate supply to the infant. The dose necessary to increase breast milk vitamin D sufficiency is above the current tolerable upper intake level recommended by the Institute of Medicine (IOM 1997).

There was concern that the AI of 5 µg (200 IU) was based on infants receiving sun exposure, when, in fact, sun is no longer being recommended for infants under 6 months of age. Also, this amount does not take into account skin pigmentation, latitude, and pollution.

Bolus administration of vitamin D at birth was recommended as a way to avoid vitamin D deficiency. The problems with this approach are that rickets is a rare event, and supplementing infants at that level amounts to an uncontrolled population-based experiment. Toxicity is also a concern. There is no surveillance system that would catch problems with this strategy.

Other comments include the following:

- A reasonable dose of sunlight, free of sunscreen, that promotes vitamin D synthesis but does not increase skin cancer risk needs to be calculated.
- Infants in Europe are supplemented with vitamin D, and diabetes rates are low. Vitamin D may protect against diabetes.

**Rickets in low-birth-weight infants: approaches to detecting subclinical disease -
*Dr. Stephanie Atkinson, McMaster University Medical Center***

Protecting infants against osteopenia/rickets in early life may reduce their risk of osteoporosis as adults (Cooper et al. 1997). Before 1990, 15% of infants with a birth weight between 1000 and 1500 g and 73% of infants with a birth weight below 800 g developed rickets (Koo et al. 1989). Multiple etiologic factors contribute to the development of osteopenia and rickets in LBW infants. Fetal accretion of bone may be negatively influenced by maternal smoking and thinness, and size at birth and duration of gestation are strong determinants of bone mineral content (BMC) later in life (Godfrey et al. 2001). Because 80% of the calcium and phosphorus deposited in the fetus occurs during the last trimester of pregnancy, infants born prematurely begin life with very hypomineralized bones compared with full-term infants. Although they are born with normal circulating concentrations of 25(OH)D, it is unlikely that stores of vitamin D or 25(OH)D in prematurely born infants are extensive because of their shortened gestation and lack of adipose tissue for storage.

In early postnatal life of premature infants, calcium and phosphorus deposition as it would have occurred in utero may not be achievable for the following reasons: 1) prolonged total parenteral nutrition or oral feeds with inadequate calcium/phosphorus/vitamin D; 2) lack of cutaneous de novo synthesis of vitamin D when hospitalized for weeks to months after birth and lack of exposure to the outdoors and sunlight for an extended period after discharge; and 3) administration of steroid and/or diuretic drugs that interfere with vitamin D or calcium

metabolism. A tapering course of dexamethasone is used clinically in early life in very LBW infants because it improves lung function and allows earlier weaning from the ventilator. However, the negative side effects of dexamethasone therapy include lower weight and length growth and lower bone mineral mass (Weiler et al. 1997).

Measurement of whole BMC content of various subpopulations of LBW infants determined that, by term-adjusted age (equivalent to 40 weeks of gestation), LBW infants lag behind term infants in BMC (Atkinson et al 2000). All infants studied received at least 10 µg (400 IU) of vitamin D per day (as a supplement of D.Vi. Sol, Mead Johnson, Canada) while in the hospital. Thus, the deficit in bone mineral accrued during early life is likely due to a deficiency of calcium and phosphorus intake rather than of vitamin D.

After premature infants reach their expected term age (and usually are no longer in the hospital), the recommended intakes for vitamin D, calcium, and phosphorus are the same as for term infants. No data yet support recommendations for special nutrient needs. There is emerging evidence that higher intakes of calcium and phosphorus, and at least 5 to 10 µg (200 to 400 IU) of vitamin D, may be necessary for LBW infants to attain catch-up of BMC quickly. In extremely LBW infants, a randomized intervention with a high protein and mineral formula for 4 months after hospital discharge increased whole body BMC by 3 months corrected age among infants receiving the high mineral and protein formula (Brunton et al 1998). Follow-up of this population of extremely LBW infants to 12 months corrected age demonstrated a lack of catch-up in BMC compared with term infants fed standard formula despite intakes of calcium and vitamin D that met or exceeded current recommendations [intake from food and supplements averaged 8 to 10 µg (320 to 400 IU)/day] (Brunton et al. 1997).

In a descriptive study, LBW infants who were fed primarily mother's milk (defined as receiving over 60% of enteral fluid intake as breast milk) had lower intakes of calcium and phosphorus up to 6 months and significantly lower BMC at 6 months than infants fed standard infant formula (Wauben et al. 1998). These findings were supported by a subsequent longitudinal follow-up to 12 months corrected age of a larger number of LBW infants (Randall-Simpson et al. 2000). LBW infants receiving 50% or more of fluid intake as breast milk to 6 months corrected age were initially lighter and shorter than were formula-fed infants. BMC was lower in breastfed than in formula-fed infants at 6 and 12 months of age, even when expressed as a function of body weight. Calcium and phosphorus intakes met or exceeded the current recommendations for term infants. From these studies, one could hypothesize that such LBW infants have higher mineral and vitamin D needs than currently recommended or another nutrient is limiting to bone mineral growth. This raises the question "are these infants vitamin D deficient?"

A challenge for clinicians caring for LBW infants is to determine what biochemical and functional measures can serve as sensitive and specific indicators of abnormal bone status,

especially before the onset of severe osteopenia or fulminant rickets. Biochemical markers for abnormal bone status include low serum 25(OH)D, low serum phosphorus (P), high serum PTH, high urinary calcium, and high alkaline phosphatase (ALP). However, there are problems in interpreting these markers. Although 25(OH)D is the best early measure, the lower limit of normal that reflects interruption of the process of bone mineralization is not known for the LBW infant population. Also, the assay kits are costly and the lab must be appropriately equipped to analyze the sample. In addition, serum P_i is affected by PTH level, increased PTH and ALP are not early indicators of hypomineralized bone, and increased urinary calcium suggests only increased bone turnover.

Several studies indicate that ALP is an insensitive marker of subclinical bone disease. In term infants, grouped by values for plasma 25(OH)D of < 15 nmol/L (6 ng/mL), 16 to 30 nmol/L (6.4 to 12 ng/mL) or > 30 nmol/L (12 ng/mL), ALP values were similar (101 to 107 U/L); thus, the enzyme was not a sensitive biochemical indicator of vitamin D deficiency, as noted in the group with the lowest 25(OH)D value (Zeghoud et al. 1997). Glass et al. (1982) found that only very high ALP was associated with overt rickets or fracture. Ryan et al. (1993) reported that plasma ALP explains only 4% to 6% of the variation in radial BMC, and Pittard et al. (1992) reported no association between ALP activity and change in BMC. In LBW infants, increased ALP may reflect slow linear growth (Lucas et al. 1989, James et al. 1985) and not an acute index of bone mineralization. Therefore, plasma ALP will not likely identify LBW infants at greatest risk of bone mineral deficits until those deficits can be detected radiologically as osteopenia or rickets.

Additional measures of abnormal bone status in very LBW infants include BMC by dual-energy x-ray absorptiometry (DXA)/ultrasound, radiology, and osteocalcin or cross-linked C-telopeptide of type 1 collagen. The problems associated with DXA/ultrasound, osteocalcin, and pyridinium cross-links of collagen include expense of the tests, the need for special software or labs, and lack of reference data for young infants. A limitation of radiology is its insensitivity to mild bone loss.

The first report of rickets in infants was published in 1651. Given the recent reports of this clinical entity, it appears that we have regressed with time. LBW infants are a population at high risk of osteopenia and rickets. Whereas osteopenia/rickets in early life may be primarily related to calcium/phosphorus deficiency, vitamin D deficiency may be an important factor in the restricted catch-up of bone mass in the first year or two, especially in LBW infants who are breastfed.

Dr. Atkinson concluded, "breast is best" just add vitamin D and, for preterm infants, supplemental calcium and phosphorus in addition to what is found in breast milk or standard infant formula may be warranted.

Discussion of Dr. Atkinson's presentation by expert panel members and guests

- It was stressed that not enough is known about preterm infants, and more research is needed.
- In Canada, D.Vi.Sol (Mead Johnson Canada) is sold in a vitamin D only formula that is not available in the United States.

Recommending vitamin D supplements for U.S. breastfed infants: issues in developing a communication strategy - *Dr. Claudia Parvanta, CDC*

There are several levels to pass through between formulating a scientific policy and translating it into “messages” going out to the public. Some of the larger steps include wording of the policy, formulation of intervention objectives, and development of a communication strategy to achieve some of these objectives. A systematic approach to health communication planning at CDC includes six steps: 1) problem definition and description, 2) problem analysis, 3) audience identification and profiling, 4) communication strategy and tactics, 5) evaluation, and 6) feedback. Formulation of the policy overlaps with steps 1 and 2 in this model.

Formulation of the policy

During the problem definition stage, questions such as “what is occurring in contrast to what should be occurring” need to be asked. Analytical epidemiology is used to understand who is most affected; to what extent or how severe; where or when the problem is occurring; and whether there are behavioral factors. Potential solutions need to be worked through with the intended users (sometimes called “target audiences”). The potential solutions are the basis of the new public health policy. An optimal public health policy, if implemented on a population level, will result in the vast majority of individuals being healthier. To avoid unintended consequences, it is important to consider whether anyone will be less healthy if they follow the recommendation exactly as intended. At this stage, interpretation or misinterpretation of the policy is not the issue, but literal adherence to a scientific recommendation is.

Wording the policy

AAP and other scientists working on wording a new vitamin D policy share a paradigm, or world view, and the words selected for the policy all mean the same thing to everyone in the room. However, while trying to formulate a policy that is scientifically valid, virtually every item in it is subject to a cultural interpretation as well - an interpretation using different paradigms than the ones intended by the framers. Hence, a scientific policy could be misunderstood on a number of levels, which could lead to unintended effects.

Some alternative interpretations to be mindful of include framing vitamin D deficiency as a “health disparity” experienced in a greater proportion by racial minority infants. There is considerable debate about the value of making such a distinction, and whether it would cause more harm than good to call this issue to the attention of minority mothers in contrast to the general population.

There is debate about the risks and benefits of sunlight exposure and whether any quantity can be safely recommended. There is concern that women who hear that infants fed formula do not need supplements will conclude that breast milk is inferior, or they might cut short their breastfeeding when they learn a supplement is necessary. Although these interpretations need to be considered in developing the policy, they all stem from a scientific paradigm and can be easily accounted for in the policy itself.

There is still the possibility of what are called “incommensurate” interpretations. This occurs when people with diametrically opposed world views attempt to interpret the same information. An important example is the global health community’s regard for exclusive breastfeeding as a *sine qua non* for child survival. There is the possibility that a U.S. policy to supplement breastfed infants will be judged through fears that it will further erode exclusive breastfeeding in developing countries. In addition, there is an enormous cost to mounting supplement programs in developing countries. Therefore, supporters of international breastfeeding efforts are hopeful that wording of the policy will prevent wide-scale international emulation.

Formulation of intervention objectives

Intervention objectives may aim to affect any or all of the following: policies; products; delivery mechanisms; and beliefs, attitudes, and practices. There are many recipients of belief, attitude, and practice messages, including health care providers, managed care payers, and women (currently breastfeeding, currently pregnant, of childbearing age). Once these large groups are identified, a precise behavioral or attitudinal goal must be developed for each group. This is the beginning of the communication-planning process.

Communication program planning

The large groups noted above are further refined based on demographic, psychological, and behavioral factors; all other communication variables are considered at this point such as possible settings, channels, activities, and materials. Formative research is used to develop message content as well as to identify appropriate spokespersons, tone, and other message variables. For example, focusing only on women, the vitamin D message strategy needs to be researched and developed so that messages to add supplements do not result in a decrease in breastfeeding or too early introduction of complementary foods. Timing is a critical factor, as most women have made their breastfeeding decision by the second trimester of pregnancy. The literature suggests that this decision is easily undermined. The supplement message is possibly

one that is better delivered during postpartum visits, once breastfeeding is established.

Discussion of Dr. Parvanta's presentation by expert panel members and guests

There was discussion of the Canadian experience. In Canada, vitamin D supplementation is recommended for all babies because of the latitude of the country, and breastfeeding has increased, rather than decreased. Most mothers give vitamin D to their children in the winter. In the United States and Canada, infants fed with commercial formula, all of which is supplemented with 10 µg (400 IU) of vitamin D per liter, receive extra vitamin D beyond that obtained through sun exposure. Because the amounts are not large enough to cause harm, it is not considered a problem. The message should not be that breast milk is inadequate but that formula-fed babies are getting something breastfed babies are not.

Concern was expressed about the international impact the AAP recommendation would have. Expert panel members from AAP responded that its recommendations were for its constituents- i.e., North America, not the entire world.

It was stressed that, for people to go along with the recommendation, it must be consistent with those made by other entities. Panel members from AAP responded that it communicated with many groups, all of whom have the opportunity to review and comment on the recommendation before it is published. It was pointed out that the breastfeeding handbook was inconsistent with the current AAP recommendations. This will not be the case with the next published handbook.

Panel members from AAP were urged by other panel members to meet with formula manufacturers to stress that AAP's recommendation could not be used as a vehicle for selling formula. AAP panel members responded that they would do so but added that they had no authority to forbid use of their recommendation for commercial purposes.

Concluding remarks - Dr. William Dietz, CDC

- It is clear that the public health perspective must include vitamin D deficiency and not just rickets. Because little is known about the consequences for children who are vitamin D deficient, population-based longitudinal assessments are needed.
- Although no consensus was achieved, many panel members think universal supplementation is warranted. Still others think targeted supplementation is a better idea. Even if universal supplementation is recommended, targeted marketing campaigns may be essential.
- It would be useful to look at functional outcomes of vitamin D deficiency, including any

outcomes after treatment, to determine the implications of subclinical disease.

- Research is needed on whether high-dose supplementation of mothers, infants, or both will work to prevent vitamin D deficiency in infants and for which groups it is feasible. A single high dose is appealing, but not enough is known about safety.
- Other unresolved issues include the following: when to start supplementation, the impact of supplementation, how supplementation should be delivered, the taste of the supplement, and how to market supplementation.
- The risk of formula manufacturers trying to push formula over breastfeeding in response to the occurrence of rickets among breastfed infants and the recommendation to supplement vitamin D is of great concern.
- The AAP and any CDC recommendations will have worldwide implications that must be considered.
- The research agenda in the field has not been adequately addressed. Funding for such research deserves higher priority.

Final discussion points raised by expert panel members and guests

It was suggested that CDC put together a slide show on the topic that could be used by others to gain support for research and action. North Carolina already has a slide show available, and AAP has a teaching set on breastfeeding under review to which the vitamin D aspect can be added.

The meeting adjourned at noon.

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