

the concerns of Morrison and Cushman here. Cotch et al. included candidal culture and gold-standard assessment for bacterial vaginosis by Gram's staining³ in their comprehensive study of vaginal flora and pregnancy outcomes; there was no association between candidiasis and preterm birth in that study. The review cited by Morrison and Cushman describes two studies of vaginal infections and preterm birth. Kiss et al.⁴ used Gram's staining for bacterial vaginosis, *Trichomonas vaginalis*, and candida. Two critical limitations of that study are the lack of candidal cultures and the fact that approximately 11% of women with candidiasis also received treatment for bacterial vaginosis. The other study⁵ was a retrospective case-control study that did not use standardized methods to detect candidiasis but relied on prescription use of clotrimazole as a surrogate indicator of presumed candidiasis. No data regarding other microbiologic covariates were included.

The relationships among vaginal flora, sexually transmitted infections, and the immunologic

milieu are complex, and the mechanisms by which they converge to increase the risk of preterm birth is probably even more complex. We caution against the interpretation of evidence cited by the correspondents to suggest causation or association.

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Vitamin D Deficiency

TO THE EDITOR: Holick's review of vitamin D deficiency (July 19 issue)¹ is timely. We agree² that the serum concentration of 25-hydroxyvitamin D should exceed 20 ng per milliliter to avoid bone problems. Data supporting much higher levels for bone or general health are weak and do not fulfill the criteria of evidence-based medicine.³⁻⁵ Requiring levels above 32 ng per milliliter implies that more than 80% of the European population and half of the world population are vitamin D-deficient. In Table 3 of his review, Holick recommends about 800 IU of vitamin D per day but also states that several thousand international units of vitamin D per day is acceptable. Toxicity studies in a few hundred healthy subjects cannot be extrapolated to proven safety over a lifetime for millions of people. In particular, data do not support advising pregnant or lactating women that up to 4000 IU of vitamin D per day is safe.

Recommending increased exposure to sunlight or ultraviolet B tanning equipment will undoubtedly result in increased skin photoaging and carcinogenesis.

To eradicate widespread genuine vitamin D de-

ficiency is a formidable task. Prospective studies should clarify whether higher vitamin D intake can further improve bone and general health and can do so safely.

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TO THE EDITOR: Holick proposes a minimum target level of 30 ng of 25-hydroxyvitamin D per milliliter in a healthy population. Many of his references cite a high incidence of vitamin D deficiency in at-risk populations.

We have been measuring 25-hydroxyvitamin D levels in unselected outpatients in an affluent suburb of sunny South Florida. Data are available for 170 women and 76 men (age range, 18 to 85 years) between 2005 and 2007. A total of 22 women (12.9%) had levels under 15 ng per milliliter, and 110 women (64.7%) had levels under 30 ng per milliliter. Sixteen men (21.1%) had 25-hydroxyvitamin D levels under 15 ng per milliliter, and 50 (65.8%) had levels under 30 ng per milliliter.

The majority of our vitamin D-deficient patients have been treated with 50,000 IU of vitamin D weekly for up to 2 years, without clinical evidence of toxicity or hypercalcemia or elevated serum levels.

We believe that 25-hydroxyvitamin D screening should be included in standard screening laboratory batteries, and replacement doses of 50,000 IU weekly are well tolerated for up to 2 years without toxicity.

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TO THE EDITOR: Holick overstates the degree to which sunscreen use reduces levels of vitamin D₃, because few people apply the large amount of sunscreen that would correlate with the controlled laboratory tests he references.¹⁻³ Instead of exposing people to higher levels of a known carcinogen — ultraviolet light — dietary vitamin D supplementation and a balanced diet may be a better choice for achieving healthy levels of vitamin D.⁴

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TO THE EDITOR: Holick reports that for children up to 1 year of age who are breast-fed without vitamin D supplementation, 400 IU of vitamin D per day prevents vitamin D deficiency. However, the current recommendation by the American Academy of Pediatrics (AAP) for adequate intake of vitamin D in breast-fed infants is 200 IU per day; this amount can maintain the serum 25-hydroxyvitamin D level at or above 11 ng per milliliter (27.5 nmol per liter), which is considered a cutoff for preventing vitamin D deficiency.¹ Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter).^{2,3} There is an evident discrepancy between Holick's suggestions and those of the AAP.¹ Independently of the cutoff value for the serum 25-hydroxyvitamin D level that is used to diagnose vitamin D deficiency, to my knowledge, there is no evidence of vitamin D-deficiency rickets in breast-fed infants receiving 200 IU of vitamin D per day. Vitamin D supplementation to prevent rickets should be efficacious and cost-effective.

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THE AUTHOR REPLIES: Bouillon, Norman, and Lips voice concern about the recommendations I made about vitamin D doses. The observations that the maximum calcium transport, lowest parathyroid hormone levels, and greatest muscle strength and bone density occur when 25-hydroxyvitamin D levels are above 30 ng per milliliter

and that, among women who received 1100 IU of vitamin D₃ per day, the risk of cancer was reduced by 60% are evidence-based and compelling, in my view.¹⁻³

In my opinion, poorly substantiated reports that outbreaks of vitamin D intoxication in the 1950s occurred from the addition of pharmacologic doses of vitamin D to milk have led to unjustified fear in the medical community of inducing vitamin D toxicity. Moderate sun exposure and ultraviolet irradiation are effective methods for maintaining serum 25-hydroxyvitamin D levels, as noted by Norman and Lips and their colleagues.^{2,4}

The recommendation to avoid any direct sun exposure because of the risk of skin cancer has resulted in a global pandemic of vitamin D deficiency. At least half of the European and U.S. populations currently have insufficient vitamin D.² Indeed, Cava and Javier observe that vitamin D insufficiency is common. Their patients received 50,000 IU of vitamin D₂ per week (equivalent to taking more than 7000 IU of vitamin D₂ per day) for two years without toxicity; in my experience, 50,000 IU of vitamin D₂ twice a month for up to 5 years has no toxic effects. In my opinion, a recommendation of 1000 to 2000 IU per day is reasonable, as also suggested by Norman and colleagues.²

Howe and Dellavalle question the effect of sunscreen in reducing vitamin D synthesis. Many sunscreen products have a sun protection factor (SPF) of 30 to 50. Even if only 30% of the total

volume were applied, vitamin D₃ synthesis would be reduced by 95 to 99%. One cannot get an adequate amount of vitamin D from a balanced diet alone; for that reason, vitamin D supplementation should be recommended.

I agree with Baroncelli's observation that there is a discrepancy between what the AAP recommends and what I and others have recommended with respect to vitamin D intake for neonates and children.² My hope is that the AAP will reconsider the scientific evidence that vitamin D deficiency in childhood is associated with an increased risk of several chronic conditions, as outlined in my review, and might thus revise its recommendation to be equivalent to the Canadian Paediatric Society's current recommendation of 400 IU per day for all neonates.

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¹¹C-Labeled Methionine and Evaluation of Malignant Pleural Mesothelioma

TO THE EDITOR: Assessing responses to treatment on the basis of computed tomographic (CT) measurements in patients with malignant pleural mesothelioma is challenging because of the pattern of growth of this disease.¹ There is evidence that ¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG-PET) can detect the response of a tumor to chemotherapy or chemoradiotherapy early in the course of treatment.² A few pilot studies have explored the role of FDG-PET in patients with malignant pleural mesothelioma who were treated with chemotherapy, with promising

results.³ Nevertheless, the usefulness of FDG is limited by its uptake in inflammatory cells such as macrophages and activated lymphocytes, which can cause false positive findings in patients treated with palliative talc pleurodesis. False negative results in early epithelial malignant pleural mesothelioma have been reported.⁴

Measurement of the uptake of ¹¹C-labeled methionine has been useful for metabolic imaging of brain tumors.⁵ This uptake is related to the overexpression of the LAT-1 amino acid transporter. After administration, the tracer is incor-