Crystal Rogers

From: Pekula, Joyce M. [JOYCEPEKULA@creighton.edu]
Sent: Thursday, March 10, 2011 5:52 AM
To: Crystal Rogers
Cc: carole@grassrootshealth.org
Subject: IOM report
Attachments: JBMR RPH_MFH 2011.pdf; The IOM Report on Vitamin D Misleads eLetter Mar 4 2011.docx; Endocr Prac Holick_IOM_2011.pdf; Critical responses IOM report Feb 2011_Grant.docx

Crystal:

Dr. Heaney is traveling, and he asked me to get you this information.

The Academy of Dermatology has a position against tanning booths because of skin damage. So they oppose any effort which points out that we need more vitamin D than we are now getting, since they see that as an opening that would be exploited by the tanning industry. We take no position with respect to tanning and do not want to be caught in that crossfire. But we do insist that almost everybody needs more vitamin D than they are currently getting. And, incidentally, we note that getting your vitamin D through tanning is the expensive way.

I am attaching, at Dr. Heaney's instruction, four documents that may be helpful. First is his brief rebuttal of the IOM report in the Journal of Bone and Mineral Research; second is a necessarily even briefer rebuttal in the Journal of Clinical Endocrinology & Metabolism, in response to the official Journal publication in that same outlet; third is a rebuttal by Dr. Michael Holick published in Endocrine Practice which goes into much more detail about nonskeletal endpoints; and finally is a partial list of such rebuttals compiled by Dr. William Grant. You cannot get all of these, of course, by the time of the hearing. The list should help representative Seaton confirm that there is a lot of opposition to the IOM report, coming from a broad base of support within the vitamin D investigative community.

Regards,

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PERSPECTIVE

JBMR

Why the IOM Recommendations for Vitamin D Are Deficient

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ABSTRACT

The IOM recommendations for vitamin D fail in a major way on logic, on science, and on effective public health guidance. Moreover, by failing to use a physiological referent, the IOM approach constitutes precisely the wrong model for development of nutritional policy.

KEY WORDS: VITAMIN D; NUTRITIONAL POLICY; EVOLUTIONARY PHYSIOLOGY

Introduction

In the past two years, vitamin D supplement sales to consumers have increased by more than 100% per year.[1] Now, following publication of the report[2] on Dietary Reference Intakes (DRIs) for calcium and vitamin D by the Institute of Medicine (IOM), many physicians report that they are decreasing their vitamin D recommendations to patients. This change was explicitly proposed by members of the IOM panel in their various media statements. While a small fraction of consumers may well have all the vitamin D they need, on balance, we consider a general downward trend to be harmful to the health of the public.

Both the authors of this Perspective served as members of the panel that drafted the 1997 report of the IOM on the DRIs for calcium and vitamin D. That report was the first issued by the IOM under the then-new evidence-based guidelines for evaluating studies and making recommendations. We are thus familiar with the process and, most important, with vitamin D itself. On the basis of this experience, we respectfully dissent from many of the findings and recommendations in the current report, and we set forth here a small fraction of the reasons for that dissent.

The IOM report (and its presentation to the media) stressed that its recommendations for vitamin D were based primarily on the intake (and serum 25-hydroxyvitamin D concentration) needed to ensure skeletal health and that, in the panel's judgment, there was insufficient evidence to make any recommendations with respect to nonskeletal benefits, if any. Second, the report concluded that a serum level for 25-hydroxyvitamin D [25(OH)D] of 20 ng/mL was sufficient to ensure bone health. And third, the panel concluded that since the bulk of the American public had 25(OH)D values that were above 20 ng/mL, most individuals were getting all the vitamin D they needed and had no reason for further supplementation. These conclusions fail on three grounds: logic, science, and guidance.

First, logic. Since the panel, in its judgment, concluded that it did not know whether there might be nonskeletal benefits (or at what blood level they could be ensured), then it is patently incorrect to say that they know that people are getting enough. The most the panel could have said logically was, "Here's what you need for bone; most people get that much; we do not know whether more would confer possible nonskeletal benefits." That, at least, would have been an honest communication of the state of the issue as the panel apparently understands it. However, to state publicly that the general public does not need more goes well beyond what the panel admits it knows.

Second, science. The statement that skeletal health can be ensured at serum 25(OH)D levels of 20 ng/mL is simply incorrect. Without going into an exhaustive recital of all the evidence pointing to a skeletal need for higher levels, we cite here three illustrative observations that, in our collective judgment, indicate that instead of 20 ng/mL, a serum level of 30 ng/mL is closer to the bottom end of the acceptable range for skeletal health. First, there is the large randomized, controlled trial in the United Kingdom that raised serum 25(OH)D level from 21 to 29 ng/mL and produced a 33% reduction in all major osteoporotic fractures combined.[3] The fact that other trials, with less good compliance, failed to reproduce that effect does not negate the evidence of a well-conducted trial. Second, there are the many meta-analyses of Bischoff-Ferrari and colleagues[4,5] demonstrating that, taken overall, fracture reduction with vitamin D does not occur reproducibly below serum 25(OH)D

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For further discussion on this topic, please see Reid and Avenell (J Bone Miner Res. 2011;452–454. DOI: 10.1002/jbmr.327).

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levels of 30 ng/mL and for some fractures even 40 ng/mL. Finally, there is the demonstration, in a large German autopsy series (strangely misinterpreted by the panel), that osteoid seam width—the histologic hallmark of vitamin D deficiency—does not reach fully normal values until serum 25(OH)D levels are above 30 ng/mL.[6] [N.B.: Of 33 patients with 25(OH)D values between 20 and 30 ng/mL, more than half (18) had elevated osteoid volume. A Recommended Daily Allowance (RDA), by definition, meets the need of 97.5% of the population.] In a closely related finding, investigators from South Australia[7] showed seasonal variation in osteoid seam width and mineral appositional rate, reflecting variations in serum 25(OH)D precisely within the 20 to 30 ng/mL range, that is, above the IOM panel's "adequate" level.

Additionally, there is an apparent inconsistency between the recommended intake (600 IU/day for all individuals up through age 70) and the bottom end of the acceptable 25(OH)D serum concentration range (let alone higher values). As virtually universal experience with vitamin D supplementation demonstrates, 600 IU/day, if the body's sole input of vitamin D, would not be enough to produce a value of even 10 ng/mL, let alone 20 ng/mL or above. There is a generally recognized "rule of thumb" to the effect that each additional 100 IU of vitamin D per day raises serum 25(OH)D concentration by approximately 1 ng/mL. That is, in fact, a "rounding up" for convenience of calculation. Several studies indicate that the response increment is closer to 0.7 ng/mL/100 IU.[8,9] Either way, 600 IU/day will not suffice without appreciable solar and dietary input. Furthermore, as is also widely recognized, 600 IU/day produces barely perceptible changes in individuals who are overweight or obese (now better than 50% of the US adult population). Hence the increase from the 1997 DRIs, while welcome, and certainly in the right direction, is simply inconsistent with current professional experience. It not only is inadequate, by itself, to meet even the panel's recommended serum levels, but this internal inconsistency detracts from the credibility of the whole report inasmuch as it flies in the face of the everyday experience of clinicians who recommend supplements to their patients and measure the resulting responses.

Finally, guidance. At already noted, the panel indicated that it was uncertain about extraskeletal benefits—benefits that might accrue at intakes above the new intake recommendations. At the same time, the panel raised the upper-level intake "TUIL" to 4000 IU/day. (The report acknowledges that intakes up to 10,000 IU/day are probably safe for everyone and applied an uncertainty factor[10] to that 10,000-IU figure to generate the 4000-IU TUIL. It is important to stress that the TUIL is not a limit but instead constitutes an assurance of safety for such an intake.) One should have thought that even a very simplistic game-theory approach would have led to a guidance statement such as the following: "We do not know whether taking more vitamin D than we are currently recommending will help you, but it could, and we can assure you that supplemental intakes up to at least 4000 IU/day are safe." Such a statement, couched, perhaps, in less straightforward language, nevertheless would provide guidance that both the public and governmental agencies could find useful. Instead, we now have only a confused public.

Beyond these errors and inconsistencies, though, serious as they are, lies a much deeper flaw in the approach taken by the panel, exemplified by a quote from one of the panel members to the *New York Times* at the time of release of the report.[11] The statement was simply that the "onus" (ie, burden of proof) fell on anyone who claimed benefits for intakes higher than the panel's current recommendations. This is an approach that is correct for drugs, which are foreign chemicals and which do carry an appropriately heavy requirement for proof. For drugs, the position of privilege is given to the placebo. And in the current IOM report, the privilege is given to a serum 25(OH)D level that is effectively the status quo. We judge that this is exactly backward for nutrients. The privilege instead must be given to the intake that prevailed during the evolution of human physiology, the intake to which, presumably, that physiology is fine-tuned. So far as can be judged from numerous studies documenting the magnitude of the effect of sun exposure,[12,13] the primitive intake would have been at least 4000 IU/day and probably two to three times that level, with corresponding serum 25(OH)D levels ranging from 40 to 80 ng/mL. The fact that primitive levels would have been higher than current IOM recommendations does not, of course, prove their necessity today. But such intakes should be given the presumption of correctness, and the burden of proof must be placed on those who propose that lower intakes (and lower serum levels) are without risk of preventable dysfunction or disease. The IOM, in its report, has utterly failed to recognize or meet that standard.

Finally, we commend the IOM panel for their concern about safety, certainly an appropriate posture for a body crafting public policy. However, the standards adopted by the panel for taking into evidence papers indicating possible risk were, we note, far lower than those the panel required to indicate benefit. Additionally, many of the purported risks were, on their face, implausible and inconsistent with the experience of population subgroups that routinely have serum levels in the range mentioned by the panel as possibly risky (eg, approximately 50 ng/mL). We note that one of the widely accepted Hill[14] criteria for acceptance of observational data is precisely biologic plausibility. Furthermore, we consider it highly implausible that serum levels such as prevailed during hominid evolution could carry more risk than benefit for the populations concerned. Had that been the case, one should have expected that natural selection would have eliminated those prone to such risks.

In this Perspective, we have deliberately avoided a mind-numbing laundry list of the vast number of factual inaccuracies and misinterpretations in the report. We are informed that there is a request, through the Freedom of Information Act, to obtain the external review comments submitted to the IOM in response to a prepublication draft. When those materials become available, those interested can review the many problems with the IOM report in detail. For now, our recommendation to the American public is that the IOM report should be taken with a grain of salt (another nutrient the IOM finds risky).

Disclosures

Both authors state that they have no conflicts of interest.

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The IOM Report on Vitamin D Misleads

4 March 2011

Robert P. Heaney, M.D.
Creighton University,
William B. Grant,
Michael F. Holick,
Michael Amling

Send letter to journal:
Re: The IOM Report on Vitamin D Misleads

Email Robert P. Heaney, et al.

The Commentary by Ross et al. (1), concerning the recent calcium and vitamin D recommendations of the Institute of Medicine (IOM) has the potential to be substantially misleading. First, the title ("What clinicians need to know") is incorrect. The focus of all recommendations from the Food and Nutrition Board is, as the text of the article states, "normal healthy persons". Those recommendations have no applicability for patients with disease, or for physicians attempting to prevent disease in at-risk populations. That distinction is something clinicians need to know.

The Commentary also gives no hint of the substantial dissent which the recommendations have evoked from the vitamin D investigative community. The draft report had been submitted to external experts, and it is to be presumed that their findings were made available to the panel. While the details of these reviews are shrouded behind a pledge of secrecy, it is clear from the published comments of several of them that the review uncovered errors both factual and strategic/analytic. Some acknowledgement of this dissent would have been useful. One infers that there must also have been dissent within the panel itself, as one of its members was a co-author of Canadian guidelines (2) which specifically recommended cholecalciferol intakes approximately three times higher than the IOM. Thus, rather than being a settled issue, clinicians need to know that the IOM recommendations do not represent a consensus.

There is not room here to recount the many factual errors in the IOM report, some described elsewhere (3,4). But two in particular are, we judge, suggestive of how the panel approached evidence. In a study by one of us (MA), describing the relation of osteoid volume to vitamin D status (5), it was shown that serum 25(OH)D $\geq$ 30 ng/mL was necessary to ensure that there was no residue of osteomalacia. Specifically there were no instances of osteoid volume (OV/BV) above 1% for 25(OH)D > 32 ng/mL. Nevertheless the IOM panel accepted 20 ng/mL as the lower bound of normal, despite the fact that approximately half of the individuals between 20 and 32 had OV/BV values above 1% (and ranging up to 4.5%).

In another instance, the panel attempted to discredit on methodologic grounds the results of one of us (RPH), showing that calcium absorption efficiency was not fully normalized below 30-32 ng/mL (6,7). This was despite the fact that the method used was the gold standard in Europe and its results in this context had been confirmed by others. In both instances, there seemed to have been an effort to discredit or distort studies that were incompatible with the panel's proposed 20

ng/mL lower bound for normal vitamin D status.

Finally, in their conclusion, Ross et al. call for more randomized controlled trials. This is such a part of the conventional wisdom that it would seem to be entirely reasonable. Instead it dodges the panel's responsibility to deal with the available evidence. Most of the "needed" randomized trials are simply unfeasible (8), as they would require low intake contrast groups with serum 25(OH)D levels below even the IOM's already low recommendation. Such trials would be unethical. Since they cannot be done, this purported "need" leaves critical nutritional policy issues in a kind of permanent limbo.

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the nutritional context. [Appendix: Amplification on certain of the points discussed in the paper (online only).] Nutr Rev 68:478-484

6/30

Commentary

VITAMIN D
IOM

THE D-BATABLE INSTITUTE OF MEDICINE REPORT: A D-LIGHTFUL PERSPECTIVE

Michael F. Holick, PhD, MD

Abbreviations:
IOM = Institute of Medicine;
25(OH)D = 25-hydroxyvitamin D

During the past decade, several thousand articles have been written about the health benefits of vitamin D and sun exposure (1-4). Being born or living at lower latitudes and being exposed to more sunlight reduces the risk of type 1 diabetes mellitus, multiple sclerosis, hypertension, and dying of cancer. Numerous studies have reported an inverse association with vitamin D status, ie, lower serum 25-hydroxyvitamin D (25[OH]D) levels are associated with increased risk for cancers of the breast, prostate, and colon among others; type 2 diabetes mellitus; cardiovascular disease; multiple sclerosis; rheumatoid arthritis; osteoarthritis; preeclampsia; cesarean delivery; depression; Alzheimer disease; infectious diseases; and neurocognitive dysfunction (1-5). However, because these studies were association and observational studies, they were dismissed by the recent Institute of Medicine (IOM) report on dietary reference intakes (6) as not qualifying as a high enough level of evidence to confirm the beneficial effect of vitamin D on these nonskeletal-related health outcomes.

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To put this into perspective, the adage a picture is worth 1000 words can also be applied to digesting the more than 700 pages of documentation in the IOM report (6), represented with Figures 1 and 2. The committee focused on the role of vitamin D and bone health and reviewed studies on parathyroid hormone plateaus. They concluded that discrepancies at the level parathyroid hormone plateaued could be due in part to differences in populations studied and statistical methods used. In postmenopausal women, parathyroid hormone levels continued to decrease until a blood 25(OH)D concentration of approximately 30 ng/mL was reached and there was no further decline in the prevalence of secondary hyperparathyroidism (7) (Fig. 1A and 1B). The committee recognized the work of Priemel et al (8) who examined 675 iliac crest biopsy specimens from male and female German patients (401 males, mean age of 58.2 years, and 270 females, mean age of 68.2 years) for structural and histomorphometric parameters including osteoid indices. Priemel et al (8) could not establish a minimum 25(OH)D concentration that was inevitably associated with mineralization defects and did not find pathologic accumulation of osteoid in any patient with circulating 25(OH)D concentrations above 30 ng/mL. They concluded a minimum 25(OH)D threshold of 30 ng/mL along with adequate calcium intake was necessary for maintaining skeletal health. The IOM Committee, however, concluded from the same study that a 25(OH)D concentration of 20 ng/mL was adequate to prevent osteomalacia in at least 97.5% of the population (6).

The IOM report (6) reviewed the literature regarding vitamin D intake in women of childbearing age and concluded that being pregnant or lactating did not increase their need for their vitamin D intake above what was recommended for a woman of the same age, ie, 600 IU of vitamin D daily despite what others have reported (9). However, as noted in Figure 1C, of 40 mostly black pregnant women who were documented to be ingesting a prenatal vitamin (400 IU vitamin D_2) and drinking on average 2 glasses of milk (200 IU of vitamin D) a day, thus consuming approximately 600 IU of vitamin D a day, at the time that they gave

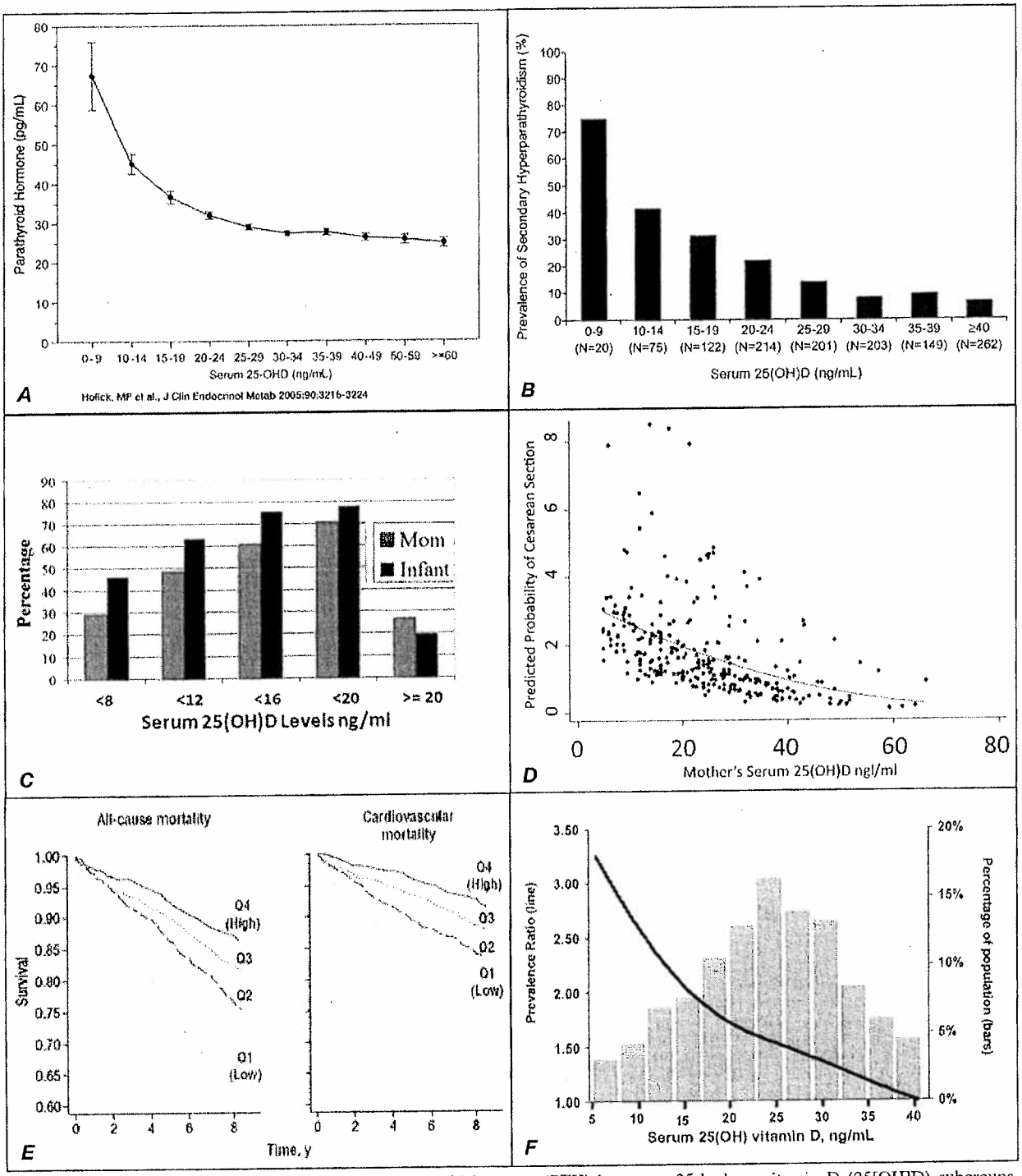

Fig. 1. ***Panel A.*** Mean (±standard error) serum parathyroid hormone (PTH) by serum 25-hydroxyvitamin D (25[OH]D) subgroups. Participants' PTH concentrations relative to serum 25(OH)D concentrations sorted by subgroups delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. Serum PTH values begin to increase with 25(OH)D concentrations less than 29.8 ng/mL. Adapted from *J Clin Endocrinol Metab*, 90:3215-3224, Holick MF, Siris ES, Binkley N, et al, Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy, Copyright (2005), with permission from The Endocrine Society. ***Panel B.*** Percentage of subjects with secondary hyperparathyroidism by 25(OH)D level. The percentage of subjects with secondary hyperparathyroidism (parathyroid hormone greater than 40 pg/mL) sorted by subgroups with serum 25(OH)D concentrations delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. Adapted from *J Clin Endocrinol Metab*, 90:3215-3224, Holick MF, Siris ES, Binkley N, et al, Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy,

Fig. 1 Legend ***(Continued)***

Copyright (2005), with permission from The Endocrine Society. ***Panel C.*** The percentages of mostly black women and their neonates with serum 25(OH)D concentrations below predefined cut-off values of <8, <12, <16, <20, and ≥20 ng/mL. At the time of birth, the pregnant women were documented to be ingesting a prenatal vitamin (400 IU vitamin D_2) and drinking on average 2 glasses of milk (200 IU of vitamin D) a day, thus consuming approximately 600 IU of vitamin D a day. Adapted from *Clin Pediatr (Phila)*, 46:42-44, Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF, Vitamin D deficiency in a healthy group of mothers and newborn infants, Copyright (2007), with permission from Sage Publications. ***Panel D.*** Blood concentrations of 25(OH)D in 253 pregnant women, demonstrating an association between the mother's increased 25(OH)D levels and decreased predicted probability of having a cesarean vs vaginal delivery, with a quadratically fit line. Adapted from *J Clin Endocrinol Metab*, 94:940-945, Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF, Association between vitamin D deficiency and primary cesarean section, Copyright (2009), with permission from The Endocrine Society. ***Panel E.*** Kaplan-Meier plots of all-cause and cardiovascular mortality in the 25(OH)D quartiles (Q). Log-rank test indicated a significant difference across all 25(OH)D quartiles (P<.001). Multivariate-adjusted hazard ratios for patients in the lower 2 25(OH)D quartiles (median, 7.6 and 13.3 ng/mL) were higher for all-cause mortality (hazard ratio, 2.08; 95% confidence interval, 1.60-2.70; and hazard ratio, 1.53; 95% confidence interval, 1.17-2.01; respectively) and for cardiovascular mortality (hazard ratio, 2.22; 95% confidence interval, 1.57-3.13; and hazard ratio, 1.82; 95% confidence interval, 1.29-2.58; respectively) compared with patients in the highest 25(OH) D quartile (median, 28.4 ng/mL). Adapted from *Arch Intern Med*, 168:1340-1349, Dobnig H, Pilz S, Scharnagl H, et al, Independent association of low serum 25-hydroxyvitamin D and 1,25-dihyroxyvitamin D levels with all-cause and cardiovascular mortality, Copyright (2008), with permission from the American Medical Association. All rights reserved. ***Panel F.*** Multivariable adjusted prevalence ratio of peripheral artery disease associated with serum 25(OH)D levels between 5 and 40 ng/mL. Adapted from *Arterioscler Thromb Vasc Biol*, 28:1179-1185, Melamed ML, Muntner P, Michos ED, et al, Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: Results from NHANES 2001 to 2004, Copyright (2008), with permission from Wolters Kluwer Health.

birth, 76% were vitamin D deficient as defined by the IOM cutoff of less than 20 ng/mL. Eighty-one percent of their newborns were vitamin D deficient according to this same cutoff (10). The IOM report focused on vitamin D's effect on musculoskeletal health and fall reduction, especially in adults older than 70 years (6), but disregarded vitamin D's effect on muscle function in pregnant women at the time of birthing. Figure 1D shows blood concentrations of 25(OH)D in 253 pregnant women, demonstrating an association between a mother's increased 25(OH)D levels and decreased predicted probability of having a cesarean vs vaginal delivery (11).

The association of vitamin D deficiency with a 50% increased risk of myocardial infarction (12) and more than 100% increased chance of dying of the event (13) (Fig. 1E) was also dismissed as not being supported by randomized clinical trials (6). The IOM did note that 25(OH)D concentrations lower than 15 ng/mL were associated with increased risk of mortality and that some, but not all, studies observed that increasing the blood 25(OH)D concentration above 30 ng/mL was associated with increased mortality (6), including the report by Melamed et al (14). The major cause for mortality was cardiovascular disease. However, Melamed et al concluded that there was a lower risk of mortality for 25(OH)D concentrations of 30 to 49 ng/mL and concentrations greater than 50 ng/mL were associated with a higher risk of mortality in women, but not in men. The same authors also reported a strong inverse association with peripheral vascular disease and serum 25(OH) D levels (15) (Fig. 1F). This observation is supported by the findings of a randomized controlled trial conducted by Dong et al (16). In 49 normotensive black boys and girls aged 16.3 ± 1.5 years who received 2000 IU of vitamin D_3 daily for 4 months, Dong and colleagues reported a significant increase in plasma 25(OH)D levels from 11 ng/mL to 34 ng/mL and a reduction in arterial wall stiffness, a prelude to hypertension and atherosclerotic deposition, as determined by carotid-radial pulse wave velocity. No effect was observed in the children who received 400 IU of vitamin D_3 daily and increased their blood 25(OH)D concentration from 11 ng/mL to 24 ng/mL. This mirrors the observation that serum 25(OH)D levels less than 30 ng/mL are strongly associated with hypertension and metabolic syndrome in adolescents (17).

It has been estimated that more than 70% of children aged 6 to 11 years in the United States have a blood 25(OH) D concentration less than 30 ng/mL (18). Infectious diseases have enormous health implications globally, not only increasing risk of morbidity, but also mortality. Urashima et al (19) reported a multicenter, double-blind, placebo controlled, parallel-group trial to assess the effect of supplementing school children aged 6 to 15 years with 1200 IU of vitamin D_3 daily from December through March on the incidence of seasonal influenza A infection (diagnosed with influenza antigen testing and nasopharyngeal swab specimen analysis). They observed a 42% relative risk reduction in the children who received 1200 IU of vitamin D daily for 4 months. Furthermore, those children who took 1200 IU of vitamin D daily and who had a previous diagnosis of asthma had a relative risk reduction of 93% for having an asthma attack compared with the children taking placebo. This observation is supported by a study of 1024 children with a history of mild-to-moderate persistent asthma who were vitamin D insufficient and had a one and a half times higher odds ratio for any hospitalization or emergency department visit (20). Serial concentrations of

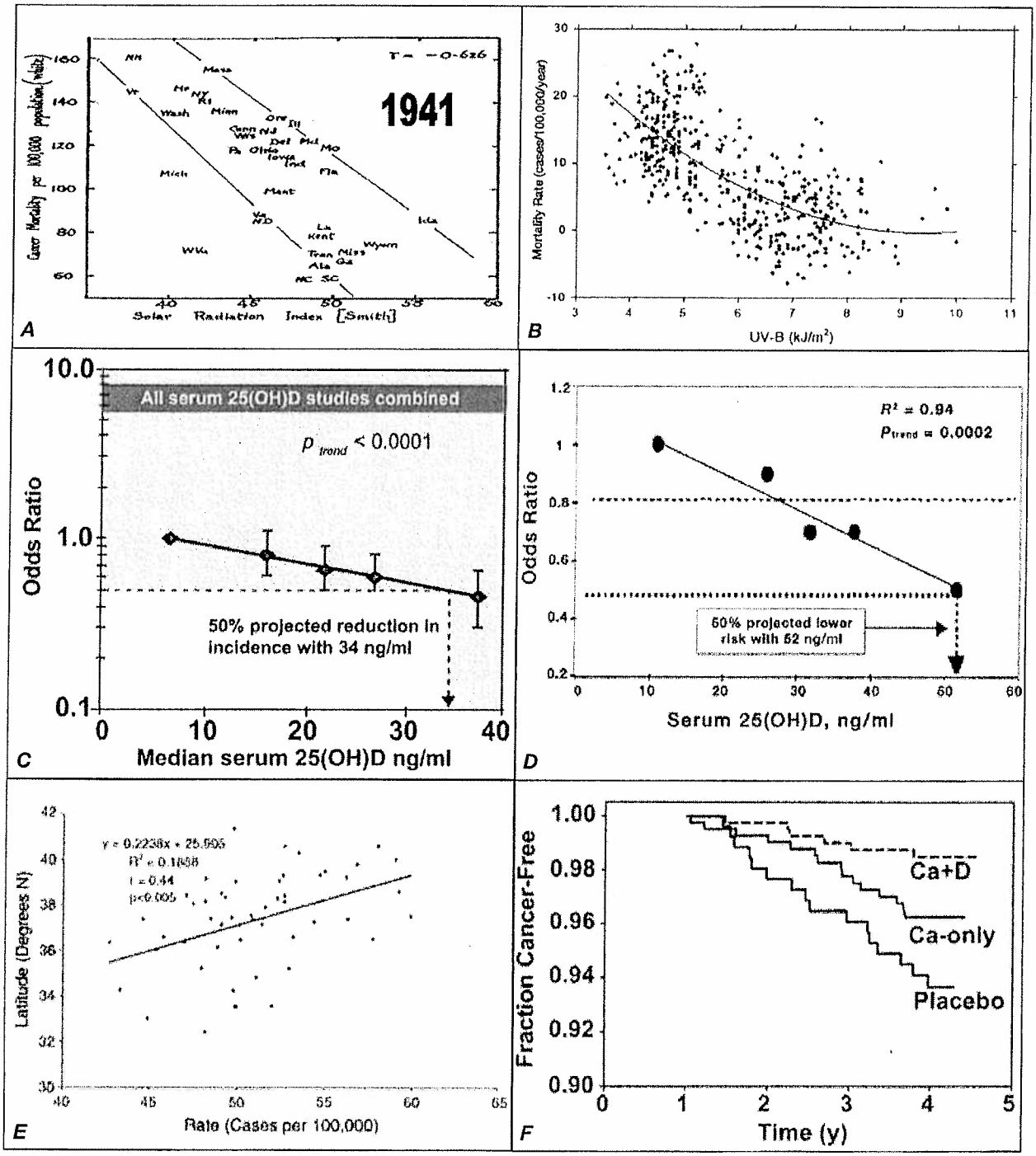

Fig. 2. ***Panel A***. Cancer mortality per 100000 population (white) and solar radiation index. Adapted and reprinted from *Cancer Res*, 1:191-195, Apperly FL, The relation of solar radiation to cancer mortality in North America, Copyright (1941), with permission from the American Association for Cancer Research. ***Panel B***. Mortality rate of cancer cases compared with solar UV-B index. Reprinted from *Cancer*, 94:1867-1875, Grant WB, An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation, Copyright (2002), with permission from John Wiley and Sons. ***Panel C***. Dosage-response gradient for colorectal cancer according to serum 25-hydroxyvitamin D (25[OH]D) concentration of 5 studies combined. The 5 points are the odds ratios for each quintile of 25(OH)D on the basis of the combined data from the 5 studies. Reprinted from *Am J Prev Med*, 32:210-216, Gorham ED, Garland CF, Garland FC, et al, Optimal vitamin D status for colorectal cancer prevention: A quantitative meta analysis, Copyright (2007), with permission from Elsevier. ***Panel D***. Dose-response gradient of breast cancer risk according to serum 25(OH)D concentration, pooled analysis. Reprinted from *J Steroid Biochem Mol Biol*, 103:708-711, Garland CF, Gorham ED, Mohr SB, et al, Vitamin D and prevention of breast

Fig. 2 Legend ***(Continued)***

cancer: Pooled analysis, Copyright (2007), with permission from Elsevier. ***Panel E***. Latitude vs the number of adults diagnosed with colon cancer independent of race in the state of California. The R^2 value is a measure of how well the data fit the linear regression. The larger the value, the better the fit. Pearson correlation coefficient (r) calculated for the rate of colon cancer vs latitude, independent of race was measured to be $r = 0.44$ ($P<.005$), demonstrating a significant positive linear relationship. The strongest possible value is 1.0 and no correlation measured as 0. Reprinted from *J Steroid Biochem Mol Biol*, 97:111-120, Spina C, Tangpricha V, Yao M, et al, Colon cancer and solar ultraviolet B radiation and prevention and treatment of colon cancer in mice with vitamin D and its Gemini analogs, Copyright (2005), with permission from Elsevier. ***Panel F***. Kaplan-Meier survival curves (ie, free of cancer) for the 3 treatment groups randomly assigned in the cohort of women who were free of cancer at 1 year of intervention (n = 1085). Sample sizes are 266 for the placebo group, 416 for the calcium-only (Ca-only) group, and 403 for the calcium plus vitamin D (Ca+D) group. The survival at study end for the Ca+D group is significantly higher than that for the placebo group, by logistic regression. (Reproduced with permission from Dr. Robert Heaney, 2007.)

25(OH)D in 198 healthy adults revealed that a concentration of 38 ng/mL or higher reduced the risk of developing acute viral respiratory tract infections and numbers of days ill 2-fold (21).

The IOM assessed the effect of UV-B exposure and vitamin D status on cancer risk and mortality on the basis of several large studies, including those from the Agency for Healthcare Research and Quality in the United States and Canada and the Women's Health Initiative. As a whole, the studies are not supportive of a role for vitamin D with or without calcium in reducing cancer risk (6,22-24). These conclusions are eerily similar to how the scientific and medical communities responded to what Sniadecki in 1822 and Palm in 1889 reported regarding their observations on the effect of latitude and sun exposure on the incidence of rickets (25). They had concluded that the incidence of rickets increased in the inner cities because of lack of sun exposure and that rickets was also was associated with living at higher latitudes. It was inconceivable during the 19th century that exposure to sunlight on the skin would have any beneficial effect on bone health, and these observations were quickly dismissed without further study; thus, rickets continued to be a devastating consequence of living in sun-deprived environments. It was only later in the 1920s when Hess and Unger exposed children to UV-B radiation and sunlight when it was finally accepted that this was a "definite and dependable cure of rickets" (26). Hoffman (27) was the first to appreciate that living in cities and higher latitudes between 1908 and 1912 was associated with increased cancer mortality. In the 1930s, Peller and Stephenson analyzed cancer incidence in a population with increased exposure to solar UV radiation—the United States Navy—and reported the rate of skin cancer in the US Navy was 8 times higher than in the civilian population, but that the total number of deaths resulting from other cancers was 60% less (28). In 1941, Apperly demonstrated a significant correlation between reduced cancer mortality in adults who lived in the south compared with those living in the northeast (29) (Fig. 2A). In the 1980s and 1990s, Garland et al (30), and then later many other investigators (31-35), began reporting on epidemiologic studies that evaluated the correlation between cancer, sun exposure, and cutaneous production of vitamin D. They demonstrated a strong negative correlation between latitude, sun exposure, and vitamin D status and the risk of many cancers including colon, breast, ovarian, and prostate (Figs. 2C and 2D). Grant (36) reported an inverse relationship with cancer mortality in both men (Fig. 2B) and women and exposure to solar UV-B radiation. Grant calculated that over a span of 24 years (between 1970 and 1994) a total of 566400 Americans died prematurely of 1 of the 13 cancers because of inadequate exposure to solar UV-B radiation. Even in California where there is a wide range of latitudes, the incidence of colon cancer was significantly affected by living at a higher latitude and was associated with decreased solar UV-B exposure. An overall increase in occurrence of colon cancer was observed by 7.5% to 10.5% per degree latitude independent of race (Fig. 2E) (37). The IOM countered with the Agency for Healthcare Research and Quality reports (6,22,23) and made special note that the Women's Health Initiative trial examined the effect of combined supplementation of vitamin D and calcium (400 IU of vitamin D in 1000 mg of elemental calcium), and that over an average of 7 years follow-up, no significant trend towards risk reduction for cancer mortality was observed in postmenopausal women (24). However, what the IOM and Agency for Healthcare Research and Quality did not note was that many of the studies that were reviewed, including the Women's Health Initiative, stated that more than 50% of the participants admitted not taking the calcium and vitamin D on a daily basis and blood levels of 25(OH)D were often not measured at baseline and/or at study end. The authors of the Women's Health Initiative acknowledged that the 400 IU of vitamin D was inadequate to raise the blood level of 25(OH)D above 30 ng/mL, which is what most studies (31-33) have suggested is required to reduce cancer risk. Virtually all of the subjects in the Women's Health Initiative study were vitamin D insufficient, ie, 25(OH)D less than 30 ng/mL, both at the beginning and end of the 7-year trial. Of great interest, and what should have been considered an important finding from this study, was that women in the lowest quartile of 25(OH)D levels (less than 12 ng/mL) had an incidence of colorectal cancer that was 253% higher than the incidence

in women who had a baseline 25(OH)D level in the highest quartile (serum 25[OH]D of ≥24 ng/mL) (38). Lappe et al (39) reported a 60% reduction in all cancers in postmenopausal women who ingested 1100 IU of vitamin D and 1000 mg of elemental calcium daily for 4 years (Fig. 2F). They even accounted for the possibility that some cancers were developing during the first year; when they considered this, they showed a 77% reduction after only 3 years of enhanced vitamin D and calcium intake.

The IOM committee did a careful and thoughtful analysis of the vitamin D literature and recognized that the IOM's 1997 recommendations for adequate vitamin D intakes (40) were woefully inadequate and recommended a 3-fold increase in the vitamin D intake for most children and adults. They recognized that vitamin D is not as toxic as once thought and substantially raised the upper limit from 2000 IU to 4000 IU for children older than 12 years and all adults and noted that 10 000 IU is the dosage considered to have no observed adverse effect. They also concluded that the definition of vitamin D deficiency defined in the 1997 report as a 25(OH)D concentration less than 10 ng/mL was also in need of an upward adjustment to at least less than 20 ng/mL. Thus, they appreciated what many experts had been reporting for the past decade: a vitamin D intake of 200 IU daily put both children and adults at high risk for vitamin D deficiency and all of its health consequences (1-5). The IOM committee disregarded association studies and mainly relied on randomized controlled trials for the recommendations. Yet, curiously, there are few if any randomized controlled trials that have demonstrated that 600 IU of vitamin D daily for either children or adults up to the age of 70 years will maintain their blood 25(OH)D concentration above 20 ng/mL. Six hundred IU of vitamin D daily in the absence of any sun exposure will not maintain blood 25(OH)D levels even at 20 ng/mL. This is demonstrated by the fact that people of color have much lower blood levels of 25(OH)D than white persons (18,41,42); the main reason is due to the sunscreening of their skin melanin content in reducing vitamin D synthesis (43). Humans, and in fact most vertebrates, have always depended on sun exposure for most if not all of their vitamin D requirement, and this source of vitamin D should not be dismissed as inconsequential (1,6). It is well known that excessive exposure to sunlight increases risk of nonmelanoma skin cancer, which is easy to detect and easy to treat. Melanoma, the most deadly form of skin cancer, occurs on the least sun-exposed areas, and occupational and environmental sun exposure reduces risk for this highly invasive cancer (44). Thus, it is not unreasonable to consider sensible sun exposure as a good source of vitamin D (34,35,43).

As more randomized controlled trials report on the nonskeletal health benefits of vitamin D, the recommendation will likely be to increase vitamin D intake to at least 1000 IU of vitamin D daily for children and 2000 IU of vitamin D daily for adults (43). There is no downside to increasing vitamin D intake, just as there is no downside to considering a serum level of 25(OH)D of 21 to 29 ng/mL as being vitamin D insufficient and 30 to 100 ng/mL as being sufficient (1-5,33-35,45). Because vitamin D toxicity is a very rare occurrence and is not observed until the blood 25(OH)D concentration is greater than 150 ng/mL (1), maintaining a concentration up to 100 ng/mL is considered safe. The fact that the IOM recognized the wide variability in the 25(OH)D assay is all the more reason that to guarantee vitamin D sufficiency (with the exception of patients with granulomatous disorders), children and adults should maintain a blood 25(OH)D concentration of 30 ng/mL or higher, not only to maximize bone health, but also to reduce risk of infectious diseases, autoimmune diseases, type 2 diabetes, cancers, and cardiovascular disease.

One has to wonder whether during Copernicus's time, if an Agency for Astronomical Research and Quality (AARQ) had reviewed all of the astronomical observations by the experts and included Copernicus's and Galileo's observations, would they have concluded that the world was round? We know what happened to them when they voiced their opinions and published their observational studies proposing that the world was round. How many more randomized controlled astronomical trials (RCATs) would have been needed for AARQ to conclude that the world was round, as Copernicus and Galileo proclaimed?

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The author has no multiplicity of interest to disclose.

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