in a study based on the third National Health and Nutrition Examination Survey (NHANES III), levels below 50 nmol/l were associated with a substantially increased risk of total and cardiovascular mortality[2]. Approximately one-third of participants fell into this deficiency category and this proportion is a large underestimate because in northern states samples were collected only in the summer months. Levels in the winter months in northern latitudes are of most concern for vitamin D deficiency. For example, in the winter months in northern states in the USA, almost all African Americans have levels below 50 nmol/l[3].

In contrast to downplaying any potential beneficial non-skeletal role for vitamin D, any evidence of potential harm was magnified. The IOM report cited a few studies that demonstrated an apparent U-shape or inverse J-shape for some health outcomes, and the potential for harm was prominently stated, even reflected in its two sentence summary statement. Some of the selected examples require a stretch of the imagination to see the evidence for a U-shaped pattern. For example, the results of one study of 25(OH)D and CVD[4] were described as: …'there was no additional reduction in risk at levels greater than 75 nmol/L and that the dose–response relationship may be U-shaped above 75 nmol/L'. Upon inspection of the figure for this 'U-shaped' relationship, there was no credible statistical evidence for an increased risk – because only six cases had levels >75 nmol/l, the confidence intervals were extremely wide and essentially uninformative. A better description of the results from this study is that risk of CVD decreases with increasing 25(OH)D but the benefit levels off at about 50–60 nmol/l.

Why the report placed large emphasis on the potential harm of high levels rather than the potential benefits may reflect largely the general approach for reviewing data, which, while appropriate for evaluating drug efficacy on specific diseases, may not be ideal to evaluate a 'lifestyle' biological factor, which I consider vitamin D to be. If we think of vitamin D as a pharmaceutical agent, we implicitly assume zero as the 'default' level and would look carefully for any evidence of risk, even from observational studies, and require evidence of benefit largely if not exclusively from randomized trials. However, 'natural' levels of 25(OH)D from healthy individuals with relatively high sun exposure (reflecting most of human history) are typically in the 125 to 175 nmol/l range. Because sun exposure tends to be low in current society, the highest levels are typically in the range of 75–100 nmol/l. Benefits and risks associated with vitamin D can be considered bidirectionally – for example, using 75 nmol/l as a starting point, the question of whether levels lower than this are deleterious is as relevant as the question of whether higher levels are harmful. The vast majority of studies for various endpoints including some cancers, total mortality, CVD, hypertension, skeletal health and some autoimmune and infectious diseases find higher risk at levels below 75 nmol/l; sometimes the trend appears inversely linear up to this point and sometimes the threshold for no further benefit may be lower (for example, at 50 nmol/l), but the group in the range of 75–100 nmol/l is typically the lowest-risk group. A much greater body of observational evidence supports that levels of 25(OH)D below 75 nmol/l are deleterious *v.* levels of 75 nmol/l or higher, than supports deleterious effects at higher levels.

Excessive concern for potential adverse effects may also extend from the example of β-carotene, where randomized trials did not support hypothesized benefits and even indicated harm. However, β-carotene trials tested intakes about tenfold higher than would be consumed by those on a diet naturally high in β-carotene, so any supraphysiological effects could not be predicted by experience in human subjects. I would not consider a seemingly high vitamin D dose of 25 μg (1000 IU/d), for example, as supraphysiological, as this amount could be made though several minutes of sun exposure. Ongoing and future randomized trials will undoubtedly generate important information, but are unlikely to address all relevant issues. For example, for some diseases, the timing of the relevant exposure could be decades before the diagnosis of the disease[5]. Given our current state of knowledge, it is a larger concern that many people are not getting enough vitamin D rather than many are getting too much.

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Vitamin D

Vitamin D and the limits of randomized controlled trials

Madam

Important decisions are now being made by the public health community regarding applications of vitamin D for

reducing the incidence of breast and colon cancer, type 1 diabetes, multiple sclerosis, bone fractures and other conditions caused mainly, in whole or part, by vitamin D deficiency.

Consensus on public health measures and methods of disease prevention is normally based on evaluation of the totality, consistency and reproducibly of available epidemiological evidence across study designs and throughout populations around the world. Evidence for effective prevention is not necessarily limited to results of randomized controlled trials (RCT), and few public health decisions in medical history have been based on them.

Science is built on observation and inference. By making an egregious decision to exclude most or all evidence from epidemiological observational studies, the authors of the recent US Institute of Medicine (IOM) monograph on vitamin D and calcium requirements[1] failed to provide readers with the benefit of a vast panoply of proof that has been acquired using observational studies. Inexplicably, a new RCT that used an aetiologically relevant dose of vitamin D_3 (1100 IU/d or 27·5 μg/d) and Ca (1450 mg/day)[2] also was excluded by the IOM. That RCT documented substantial prevention of all types of cancer combined in volunteers assigned to vitamin D and Ca.

The epidemiological evidence that vitamin D and Ca are able to prevent a substantial proportion of several important and common types of invasive cancer is consistent and compelling[3]. It includes approximately twenty-five major cohort studies of vitamin D intake, an equal number of nested case–control studies of serum 25-hydroxyvitamin D (25(OH)D) concentrations, a score of modern ecological studies, and the above new RCT.

Observational studies are subject to testing with well-defined and time-tested criteria for causation, the Hill criteria[4]. These criteria include strength of association, presence of a dose–response gradient, reasonable consistency among studies, temporal sequence and coherence with biological knowledge[3]. These criteria have been used to establish the cause of many diseases of public health importance, including all diseases related to use of cigarettes or other tobacco, and all occupationally or environmentally caused diseases.

There is a distinguished history of using observational studies to determine aetiology in public health. To his undying credit, Dr John Snow, the founder of modern epidemiology, used only observational studies. He did not randomly allocate the inhabitants of London's Broad Street to drink or not drink contaminated water. Instead he used ecological mapping studies, cohort studies and case–control studies to reach and confirm his compelling observation that cholera is transmitted mainly by drinking contaminated water.

One hundred and fifty years after Snow's landmark observations, the public health community is at a moment in medical history where it cannot ethically conduct an experiment withholding vitamin D from persons who are in need of it to avoid several serious diseases. Vitamin D, with its many preventive benefits, can no longer be ignored by the public health community. The nearly universal deficiency that exists in most developed countries must be eradicated. Sufficiency should logically be restored to the physiological levels of the outdoor-dwelling equatorial ancestors of modern humanity, in the range from 60–80 ng/ml (150–200 nmol/l). Fortunately this can be achieved using new IOM guidelines without waiting years for another RCT.

The 'no observed adverse effect level' (NOAEL) recently recognized by the US IOM is 10 000 IU (250 μg)/d[1]. Now is the time for the public health community to act upon this important statement from the IOM and begin large-scale field trials of vitamin D for prevention of chronic diseases. Such field trials could to include whole communities, states or countries. Dosages should be in the range of 4000–10 000 IU (100–250 μg)/d. Serum 25(OH)D ideally should be measured routinely when possible, with the goal of establishing a range of 60–80 ng/ml (150–200 nmol/l).

The vitamin D revolution will occur without performance of additional RCT, as most great public health measures have. Major sound and reasonable public health measures have been widely adopted without trials. These include smoking prohibitions and warnings, use of seat belts and motorcycle helmets, and posting of speed limits along roadways.

Society is speeding along a dangerous course of vitamin D and Ca deficiency. The public health risks are visible around us as breast and colon cancers, multiple sclerosis, type 1 diabetes, some forms of IHD and other diseases now known to be due in whole or part to vitamin D deficiency.

Based on the new IOM guidelines, it is now not only unnecessary to allow vitamin D deficiency to continue unchecked at such high prevalence, needlessly predisposing the population to many serious chronic diseases – it is morally unjustifiable.

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Vitamin D

Era or error?

Madam

The recent conclusions of the Institute of Medicine's Food and Nutrition Board (FNB)[1] will not damage the vitamin D juggernaut. People consistently take a supplement, first and foremost, because that supplement makes them feel better. True, a large minority of supplement users takes supplements to try to prevent disease, such as cancer, but my experience is that such users tend to fade over time. They tend to fade even faster if the supplement in question is shown to cause – not prevent – death, as was the case with vitamin A.

For years, many nutritionists believed retinol reduced the risk of cancer. However, later studies showed the opposite. In one randomized controlled trial (RCT), retinol actually increased – not decreased – death; the effect was so clear the RCT had to be stopped early because the retinol arm had a 46% increased risk of dying, mostly from cancer[2]. The dose of retinol used didn't seem like too much, equivalent to a couple of tablespoonfuls of cod-liver oil per day, but it appears it was enough to kill some of the volunteers taking it.

One can argue that the subjects (smokers) in the above study were at high risk of cancer, that the treatment arm included β-carotene along with retinol, and that another small epidemiological study found cod-liver oil reduced the risk of lung cancer, not increased it. However, hovering over all of this is the fact that a large RCT had to be stopped when it was found that retinol increased, not decreased, the risk of death.

Indeed, a recent Cochrane review found that retinol supplements increase total mortality rate by 16%[3]. Warnings about vitamin A began as early as 1933, when Alfred Hess *et al.*, who discovered that sunlight both prevented and cured rickets, wrote in the *Journal of the American Medical Association*, '…as to a requirement of thousands of units of vitamin A daily, the unquestionable answer is that this constitutes therapeutic absurdity, which, happily, will prove to be only a passing fad'[4].

The authors of the recent FNB report on vitamin D appear to believe we are in the throes of another dangerous fad. The problem is that their attempt to convince us that the vitamin D revolution is an error, and not an era, is so filled with logical errors that I have difficulty in taking the document seriously.

For example, they warn that 25-hydroxyvitamin D (25(OH)D) levels of 30–40 ng/ml may be dangerous (the U-shaped curve) and then turn around and contend that 100 μg/d (the new Upper Limit) is safe. Earlier in the document they reported that intakes of 100 μg/d will lead to 25(OH)D levels of 30–40 ng/ml. Such internal inconsistencies plague the document.

Another? Visualize the valiant pregnant woman pushing down and breathing hard, about to give birth. According to the FNB, the woman and her *in utero* infant require only 15 μg/d. Pop and all of a sudden the requirement almost doubles. Now the mother still needs 15 μg daily but the infant also requires 10 μg. Simple logic leads to the conclusion the FNB believes the *in utero* infant required none but magically acquired the need the moment of that last push.

What about the 350 lb interior lineman playing for the New York Giants? 15 μg/d replies the FNB. What about his one-year-old 20 lb son, how much does he need? The same 15 μg/d, mumbles the FNB.

Perhaps the fear of making another mistake – similar to the vitamin A type mistake made a decade ago – loomed so large over the committee they were willing to forswear logic to protect the world. Perhaps they let their special adviser, Professor Hector DeLucca, make the tough decisions. In my experience, when one finds a committee making so many simple errors of logic, one usually finds a committee with an agenda.

As far as stopping the vitamin D juggernaut is concerned, the FNB report will not. Once you take 125 μg/d for several months, most people notice a difference in how they feel, how they think and how they move. Not only do they buy another bottle (about $US 2·00/month) at the pharmacy, they buy a bottle for a friend.

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