Author's reply to correspondence from Drs Grant, Garland, and Boucher.

Sir,

The primary function of calcitriol, 1,25-dihydroxyvitamin-D (1,25-D), is to activate the Vitamin D Nuclear Receptor (VDR), enabling transcription and transrepression of genes. Even pathways previously thought to be 'non-genomic' have been shown to rely upon gene transcription [1]. Thus, the measured level of 25-hydroxyvitamin-D (25-D) is not sufficient to determine "Vitamin D deficiency" or "Vitamin D status." Only the 1,25-D form of Vitamin D has the ability to activate the VDR to transcribe genes, and therefore only measurements including this metabolite can accurately describe the overall homeostasis of the Vitamin D metabolism in man [see ref. 2, Fig.1].

Dr Boucher has highlighted many of the difficulties confronting clinical medicine as it expands its knowledge-base from the level of tissues, as seen under the microscope, to that of individual genes and proteins, interacting at the sub-microscopic scale of the molecule. Even though there are decades of clinical studies attempting to delineate the association between health, disease, and the Vitamin D metabolites, any study conducted without reference to genes, or transcription, must necessarily lead to an incomplete characterization.

Drs. Grant and Garland correctly note that low levels of 25-D are ***associated*** with many diseases. Yet they extrapolate that observation to imply that a ***causal*** relationship should be expected between this (largely inactive) metabolite, and those disease states. This is a non sequitur, as our article shows there is not a first-order mass-action relationship between the dosage of exogenous Vitamin D and the measured level of the 25-D metabolite [ref. 2, Fig.1]. Not only are there multiple metabolic feedback control mechanisms, there are control inputs via Protein Kinase A (PKA), in addition to the steroid and xenobiotic ligands of PXR. Our article explains why the observed lower level of 25-D metabolite is a ***symptom*** of Vitamin D dysregulation resulting from the disease state, an attempt by the body to bring the level of the active metabolite back into its control range.

Exploring the cause of the obesity epidemic, we took the rhetorical question from Bajzer and Seeley [3], "are gut bacteria a factor in the obesity epidemic," and built a detailed putative pathogenesis, based on our molecular, and clinical, knowledge. Specifically cited were two carefully controlled studies [4,5] which had failed to show a causal relationship between lifestyle, nutritional choices, and obesity. It would have been helpful if Grant and Garland could have addressed any specific failings they might have seen in those controlled studies, rather than give the citation they chose [6] as the basis for their argument.

They suggest that deficiencies in the available clinical trials can be blamed on the low profit potential from sales of the secosteroid itself. Although the direct cost of Vitamin D supplements may not be great, there is money to be made from market positioning, enough to attract the interest of a large multinational. Our article explains how the Coca-Cola Company has petitioned the FDA to be allowed to add a high level of Vitamin D to their brands of orange juice, so that they can claim it reduces the risk of osteoporosis [7]. There is clearly money available for higher quality studies. However, because this secosteroid is still classified as a vitamin, rather than as a drug, the FDA has not yet begun insisting that a more rigorous understanding of the underlying biology be brought to bear upon Vitamin D trial design.

Grant and Garland accept that sarcoidosis is a chronic inflammatory diagnosis in which Vitamin D supplementation might do harm, but we feel they need to address why other autoimmune diagnoses might not be similarly exacerbated by supplementation. Our 2004 paper "Sarcoidosis succumbs to antibiotics - implications for autoimmune disease" [8] canvassed a homogeneity of inflammatory pathogeneses, a hypothesis which has subsequently been supported by the emerging clinical evidence [9,10,11].

We do not disagree with the primary premise of Grant and Garland, that Vitamin D supplementation of the food supply is one of the most important public health issues of our time. Our article is arguing that more sophisticated study designs will be needed if one is to definitively evaluate the metabolism responsible for expression of at least 913 genes. Only then can we determine if, and to what degree, addition of Vitamin D to the food chain might be beneficial to the public's health.

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