VITAMIN D and its essential role in curing rickets was discovered in the early part of the last century. The term vitamin is actually a misnomer as vitamin D is better characterized as a pre-hormone (see Fig. 1A for chemical modifications required for hormonal activity). Figure 1B illustrates where in the body vitamin D is modified and gives examples of target tissues. Vitamin D from the diet or from the UV-mediated conversion of 7-dehydro-cholesterol in the skin is hydroxylated by the liver in the 25 position to generate calcidiol (25-hydroxy vitamin D). This form of vitamin D serves as a pro-hormone. It circulates in serum, predominantly bound to the vitamin D binding protein, with a half-life of at least a couple of weeks in humans (http://www.drugbank.ca/drugs/DB00146) and is used to determine the vitamin D status. Currently, calcidiol levels of about 20 ng/ml (50 nM) are considered optimal for supporting health (8; http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx).

The biologically active, hormonal form of vitamin D requires hydroxylation of calcidiol in the 1-position to generate calcitriol (1,25-dihydroxy vitamin D). Calcitriol is synthesized mainly in renal proximal tubule cells and released into plasma as a canonical hormone to regulate intestinal calcium absorption and bone health (see endocrine system in Fig. 1B). Calcitriol is chemically a seco-steroid that regulates cellular functions by binding to the cytosolic vitamin D receptor (VDR) and activating a specific transcription program with >100 genes, i.e., by a cellular mechanism similar to that used by steroid hormones. The rate of calcitriol synthesis in proximal tubules is under the control of parathyroid hormone and FGF23 and therewith indirectly regulated by the plasma concentration of calcium and phosphate, respectively, as expected for a hormonal control loop. Interestingly, this rate is relatively independent of serum calcidiol concentrations over a wide range because proximal tubule cells have access to large amounts of calcidiol from the glomerular filtrate. Hence, insufficient intestinal calcium absorption due to decreased calcitriol is seen only at low serum calcidiol levels (<20 ng/ml). Calcitriol concentrations in human serum are ~0.1 nM (about 42 pg/ml) with a half-life of several hours (9).

During the past three decades, noncanonical sites of calcitriol generation and autocrine/paracrine effects have been discovered with the advent of methods to detect, quantify, and manipulate mRNA and protein products for VDR and CYP27B1, the cytochrome P450 enzyme responsible for 1-hydroxylation of calcidiol (7). Thus, through the use of transgenic and knockout mice models for Cyp27b1 and VDR, autocrine/paracrine effects of vitamin D are by now well established for skin and the immune system in mice, but are suspected to exist also in other tissues. This autocrine/paracrine system is crucial for differentiation of the epidermis and the regulation of balance between innate and adaptive immunity. Both VDR and Cyp27b1 expression are subject to regulation in a tissue-specific manner that is only partially understood at the present.

Evidence for these noncanonical autocrine/paracrine effects of vitamin D in humans comes mainly from studies that have correlated vitamin D status, as measured by serum calcidiol, and quantifiable parameters associated with specific diseases, such as tuberculosis, some autoimmune diseases, and certain types of cancer. Serum calcidiol is often found to correlate inversely with greater disease frequency in the population or disease severity (6). These results have caused a major debate in medical and nutritional circles about what constitutes vitamin D sufficiency and what should be the size of dietary vitamin D supplements. These questions are difficult to answer for humans because of constraints in experimentation, but answers are urgently needed because changes in lifestyle during the last century have substantially decreased exposure to sunshine and thus endogenous generation of vitamin D in skin. While endocrine functions can be assessed through serum concentrations of the cognate hormone, no such easy measure exists for autocrine/paracrine functions.

The Institute of Medicine created a major controversy with its report in the fall of 2010 about vitamin D and the recommendation for vitamin D supplementation only when serum calcidiol is <20 ng/ml (8; http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx). The report was based on the committee’s assessment that only the effects of vitamin D on bone health were firmly established in humans. Its recommendation clashed with that of the Endocrine Society which argued that serum levels of <30 ng/ml indicate vitamin D insufficiency because the noncanonical autocrine/paracrine effects (in the immune system, metabolism, and diabetes) require higher serum calcidiol than are needed for bone health (4–6). Optimal levels of serum calcidiol in humans appear to be two to three times higher for the noncanonical functions of vitamin D than for bone health. Part of the controversy involves a philosophical difference on how to view dietary vitamin D: On the one hand, if it is a drug that could harm then people should take only as much vitamin D as has been demonstrated to be clearly beneficial! On the other hand, if vitamin D was an abundant regulatory agent with separate endocrine and autocrine/paracrine functions during human evolution some million years ago in Africa, then exogenous vitamin D needs to replace what humans have lost in endogenous

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production by moving to higher latitudes and/or indoors (less exposure to the UV-B radiation of sunlight). The latter view assumes that optimal serum calcidiol is the one measured in people with daily full UV-B exposure, such as in African Masai herders who have levels of about 50 ng/ml (6).

The article by Chandel et al., entitled "Vitamin D receptor activation and downregulation of renin-angiotensin system attenuate morphine-induced T cell apoptosis" (2), makes a valuable contribution towards resolving the controversy by providing evidence that human T cells are a noncanonical target for calcitriol, the active form of vitamin D. The study sorts out the role of the vitamin D system in the cell signaling cascade between opiate receptors and T cell apoptosis. The results may help explain why opiate addicts are prone to infection. The authors use a combination of in vitro studies with a human T cell line and freshly isolated T cells to demonstrate that activation of opiate receptors in these cells results in a cascade of signaling/transcriptional events that begin with the downregulation of the calcitriol/VDR pathway, followed by upregulation of the renin-angiotensin system (RAS), and generation of reactive oxygen species (ROS) that promote DNA damage and apoptosis. This cascade can be interrupted or reversed at each step, i.e., by an agonist in the case of calcitriol/VDR or an antagonist/inhibitor/radical scavenger for the opiate receptor, RAS, or ROS, respectively.

While activated human T cells have relatively abundant levels of VDR, they are not known to express the 1-hydroxylase (CYP27b1) necessary to produce calcitriol. However, other studies have shown that macrophages are able to produce calcitriol, actually so much in some disease states that it can spill over into serum and lead to dysregulation of calcium balance (1). Macrophage calcitriol production is, at least in part, regulated by T cell cytokines, suggesting mutual interactions between human macrophages and T cells, which may occur locally and involve paracrine regulation of T cells via calcitriol (see paracrine system in Fig. 1B) (3). Moreover, rates of calcitriol generation by macrophages appear to be sensitive to serum calcidiol concentrations (1) and hence can be manipulated by dietary vitamin D supplements.

It is likely that the dependence of the rate of calcitriol generation on serum calcidiol differs between proximal tubule cells and macrophages because of obvious differences in access to calcidiol bound to the serum vitamin D binding protein: Proximal tubule cells extract calcidiol from the glomerular filtrate while tissue macrophages access calcidiol from the interstitial fluid. Therefore, it is not surprising that vitamin D sufficiency may be defined differently for renal endocrine and macrophage/T cell paracrine functions. Chandel et al.’s study (2) not only provides specific support for T cell regulation by vitamin D in humans, but also makes predictions that can be tested in patients: e.g., is there an inverse relationship between serum calcidiol and the extent of T cell apoptosis in opiate addicts? Or, is dietary vitamin D supplementation beneficial in terms of T cell numbers and resistance to infection? Thus, the study points to ways through which the importance of the paracrine vitamin D system and serum calcidiol levels (vitamin D status) for human health can be assessed.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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U.H. prepared the figure, drafted the manuscript, edited and revised the manuscript, and approved the final version of the manuscript.
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