Commentary

On the epidemiology of influenza: reply to Radonovich et al

John J Cannell*1, Michael Zasloff2, Cedric F Garland3, Robert Scragg4 and Edward Giovannucci5

Address: 1Department of Psychiatry, Atascadero State Hospital, 10333 El Camino Real, Atascadero, CA 93423, USA, 2Departments of Surgery and Pediatrics, Georgetown University, Washington, DC, USA, 3Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, USA, 4Department of Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand and 5Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA, USA

Email: John J Cannell* - jcannell@ash.dmh.ca.gov; Michael Zasloff - maz5@georgetown.edu; Cedric F Garland - cgarland@earthlink.net; Robert Scragg - r.scragg@auckland.ac.nz; Edward Giovannucci - egiovann@hsph.harvard.edu

* Corresponding author

Published: 11 August 2009

Received: 24 June 2009

Accepted: 11 August 2009

Virology Journal 2009, 6:121 doi:10.1186/1743-422X-6-121

This article is available from: http://www.virologyj.com/content/6/1/121

© 2009 Cannell et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

On the epidemiology of influenza: reply to Radonovich LJ, Martinello RA, Hodgson M, Milton DK, Nardell EA. Influenza and ultraviolet germicidal irradiation. Virol J. 2008, 5:149

Commentary

To the Editor:

We thank Radonovich et al [1] for commenting on our paper [2], in which we attempted to use the epidemiology of vitamin D to clarify the manifold mysteries surrounding the epidemiology of influenza. Since our publication, Ginde et al [3] have produced additional evidence in support of our theories. They studied the relationship between 25-hydroxy-vitamin D [25(OH)D] levels and recent upper respiratory tract infections (URI) in 18,883 participants in the Third National Health and Nutrition Examination. Compared to individuals with serum 25-hydroxy-vitamin D levels of > 30 ng/ml, those with levels < 10 ng/ml had 53% higher odds of a recent URI. Furthermore, very recent evidence indicates 25(OH)D levels of even 30 ng/ml often signify chronic substrate starvation [4], thus the full antimicrobial properties of vitamin D may be understated.

Radonovich et al did not supply any evidence against the main hypotheses proposed in our paper, only to a speculation we made about ultraviolet germicidal air irradia-

tion. They take factual issue with our theory that the ultraviolet C radiation (UVC) lamps, used in the past to sterilize the upper air in some VA hospitals, may have exerted some, or most, of their effects – not by sanitizing air – but by increasing 25(OH)D levels.

Radonovich et al assert there was no patient exposure from UVC germicidal lamps, as they were installed to irradiate only the upper air and never shone directly on patients, thus "minimizing UV exposure in the occupied space below." Careful inspection of such an arrangement, in a 1957 Baltimore VA hospital, is illuminating [5]. Photographs show lights that seemed to shine indirectly on patients, apparently 24 hours per day, seven days a week. Depending on the characteristics of the reflective surfaces, it seems possible – even likely from the photographs – that a small amount of UVC was reflected downward toward the patients.

Radonovich et al then assert that even if some UVC reflected downward, it could not produce Vitamin D, as UVC radiation does not do so, citing MacLaughlin et al [6]. The belief that UVC radiation cannot produce vitamin
D may be a widespread misconception. Fortunately for humans, as UVC is highly carcinogenic, UVC does not penetrate the atmosphere and certainly does not trigger cutaneous Vitamin D during the course of normal human affairs. However, closer reading of their MacLaughlin et al reference [6] would have revealed that significant photosynthesis of vitamin D from 7-dehydrocholesterol (7-DHC) occurs at UVC wavelengths in the epidermal lipids the authors extracted [as illustrated in MacLaughlin et al’s figure 1(B)]. Indeed, per photon, UVC photosynthesis is greater than UVB [as illustrated in MacLaughlin et al’s figure 1(C)].

Furthermore, several animal studies indicate that UVC, which should never be used in man, is highly effective in both producing vitamin D and in treating rachitic rats [7]. Knudson and Benford studied numerous UV wavelengths in rats, finding UVC as effective as any of the UVB wavelengths studied in curing rickets [8]. If all human Vitamin D production is intra-epidermal, the academic question appears to be, how deep does UVC penetrate human epidermis? Campbell et al found evidence that significant amounts of UVC penetrate through the stratum corneum, stratum lucidum, stratum granulosum, and small amounts of UVC even reach the upper layers of the 7-DHC-rich stratum spinosum [9]. Thus, UVC penetrates far enough into the epidermis to trigger some intra-epidermal vitamin D production. Again, because UVC is so mutagenic, we are heartened to find no studies that directly test this theory in living humans.

However, even if no UVC penetrated the stratum corneum, Helmer and Jensen published a remarkable human/animal study in 1937, showing that significant amounts of Vitamin D are made on the surface of human skin [10]. They collected surface oils from young men, irradiated the oils, and showed those oils rapidly cured rachitic rats. Then, they tested a very practical and important question, can those oils be removed by washing. Indeed they found a simple water wash removed much of the Vitamin D from the surface of human skin. Holick et al’s landmark study showing most human Vitamin D production occurs in the deep epidermis was based on surgically obtained (and assumedly surgically prepared) skin samples that then had surface oils removed again by washing in hot water [11]. Indeed, to accurately address the question, one would need to obtain unwashed human skin, difficult to do even from cadavers.

It appears to us that the percentage of Vitamin D made on the surface of the human epidermis, compared to that made intra-epidermally, is unknown at this time and in need of additional and careful research. What percentage of the Vitamin D made in human skin after sun exposure is removed by simply washing? Furthermore, as the percentage made of the surface is significant, studies of cutaneous Vitamin D production in modern humans, unless unwashed, will not give accurate estimates of Vitamin D production in early man and thus an estimate of the “natural” 25(OH)D levels present when the human genome evolved.

We repeat our aside hypothesis that the patients in UVC irradiated hospitals may have been the beneficiaries of more than just cleaner air. Much more importantly, influenza is just one of many seasonal infections sensitive to the broad spectrum anti-microbial peptides (AMP) that vitamin D up-regulates [2]. Invasive pneumococcal disease, meningococcal disease, and group A streptococcal disease are all highly seasonal [12-14] and all are sensitive to AMP [15-17]. Would vitamin D be an effective adjuvant in these devastating diseases?

As research into vitamin D’s remarkable effects on innate immunity quickens [18], we hope to see the day when infectious disease experts use all available antimicrobial strategies, including testing the serum 25(OH)D level in all patients with severe infections. In our opinion, physicians treating such patients should vigorously replete them, quickly achieving 25(OH)D levels in the high range of normal.

References
1. Radonovich LJ, Martinello RA, Hodgson M, Milton DK, Nardell EA: Influenza and ultraviolet germicidal irradiation. Viral J 2008, 5:149.
2. Cannell JJ, Zasloff M, Garland CF, Scragg R, Giovannucci E: On the epidemiology of influenza. Viral J 2008, 5:29.
3. Ginde AA, Plansch BM, Camargo CA Jr: Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009, 169(4):384-390.
4. Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW: 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr 2008, 87(6):1738-1742.
5. Riley RL, Wells WF, Mills CC, Nyka W, Mclean RL: Air hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward. Am Rev Tuberc 1957, 75:420-431.
6. MacLaughlin JA, Anderson RR, Holick MF: Spectral character of sunlight modulates photosynthesis of previtamin D3 and its photoisomers in human skin. Science 1982, 216(4549):1001-1003.
7. Bunker JWM, Harris KS, Mosher LM: Relative efficiency of active wave-lengths of ultraviolet in activation of 7-dehydrocholesterol. J Am Chem Soc 1940, 62(3):508-511.
8. Knudson A, Benford F: Quantitative studies of the effectiveness of ultraviolet radiation of various wavelengths in rickets. J Biol Chem 1938, 124:287-299.
9. Campbell C, Quinn AG, Angus B, Farr PM, Rees JL: Wavelength specific patterns of p53 induction in human skin following exposure to UV radiation. Cancer Res 1993, 53(12):2697-2699.
10. Helmer AC, Jensen CH: Vitamin D precursors removed from the skin by washing. Studies Inst Divi Thomea 1937, 1:207-216.
11. Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT Jr, Anderson RR, Blank IH, Parrish JA, Elias P: Photosynthesis of previtamin D3 in human skin and the physiologic consequences. Science 1980, 210(4466):203-205.
12. Dowell SF, Whitney CG, Wright C, Rose CE Jr, Schuchat A: Seasonal patterns of invasive pneumococcal disease. Emerg Infect Dis 2003, 9(5):573-9.
13. Jensen ES, Lundbye-Christensen S, Pedersen L, Sørensen HT, Schønhøjer HC: Seasonal variation in meningococcal disease in Denmark: relation to age and meningococcal phenotype. Scand J Infect Dis 2003, 35(4):226-9.

14. Vlaminckx BJ, van Pelt W, Schouls LM, van Silfhout A, Mascini EM, Elzenaar CP, Fernandes T, Bosman A, Schellekens JF: Long-term surveillance of invasive group A streptococcal disease in The Netherlands, 1994–2003. Clin Microbiol Infect 2005, 11(3):226-231.

15. Lee HY, Andalibi A, Webster P, Moon SK, Teufert K, Kang SH, Li JD, Nagura M, Ganz T, Lim D: Antimicrobial activity of innate immune molecules against Streptococcus pneumoniae, Moraxella catarrhalis and nontypeable Haemophilus influenzae. BMC Infect Dis 2004, 4:12.

16. Bergman P, Johansson L, Wan H, Jones A, Gallo RL, Gudmundsson GH, Hekfelt T, Jonsson AB, Agerberth B: Induction of the antimicrobial peptide CRAMP in the blood-brain barrier and meninges after meningococcal infection. Infect Immun 2006, 74(12):6982-6991.

17. Ryan MA, Akinbi HT, Serrano AG, Perez-Gil J, Wu H, McCormack FX, Weaver TE: Antimicrobial activity of native and synthetic surfactant protein B peptides. J Immunol 2006, 176(1):416-425.

18. White JH: Vitamin D signaling, infectious diseases, and regulation of innate immunity. Infect Immun 2008, 76(9):3837-3843.