

Invited Commentary

The difference between a prophet and a madman

(First published online 7 June 2011)

Edgar Hope-Simpson was a self-taught young genius epidemiologist who turned into a gracious old man obsessed with his hypothesised ‘seasonal stimulus’ for epidemic influenza. He was the scientist who discovered the aetiology of shingles, but he was also the man who seemingly wasted the last 20 years of his life trying to untangle the manifold mysteries of influenza. Among his last written words, he cordially pleaded with the giants of influenzology, ‘it might be rewarding if persons, who are in a position to do so, would look more closely at the operative mechanisms that are causing such seasonal behaviour’⁽¹⁾. He died bereft of any recognition of his discovery that epidemiology of influenza is controlled by an unknown ‘seasonal stimulus’, whose character is dominated by a distinct aversion to sunlight.

Edgar Hope-Simpson had the rare gift of understanding the difference between fact and theory. For example, he knew that the statement, ‘children with rickets have frequent pneumonia because their rib cages are too weak to cough effectively’, contains one fact and one theory. Similarly, ‘influenza is more common in the winter due to overcrowding’, and ‘influenza is spread from person to person via respiratory droplets’, and ‘influenza spreads so rapidly because it is highly contagious’. He knew all these statements contain one fact and one theory and by distinguishing fact from theory, he wrote what is still the best book on influenza⁽¹⁾.

Indeed, his book led directly to two influenza publications from our group^(2,3), the last one of which we used vitamin D to explain nine major conundrums of influenza. We predicted that vitamin D will both prevent and treat influenza, once modern medicine learns proper maintenance dosage (25 µg/10 kg per d), not unlike the dosing of thyroxin.

The mechanism of action of vitamin D in preventing and treating various infections, a mechanism that led *Science News* to characterise vitamin D as the ‘the antibiotic vitamin’⁽⁴⁾, has become evident only very recently⁽⁵⁾. Both epithelial cells and macrophages increase expression of the antimicrobial cathelicidin upon exposure to microbes, an expression that is dependent upon the presence of vitamin D. Pathogenic microbes, much like the commensals that inhabit the upper airway, stimulate the production of a hydroxylase that converts 25(OH)D to 1,25(OH)₂D, a seco-steroid hormone. This, in turn, activates a suite of genes involved in defence.

In the epidermis, vitamin D induces additional PAMP (pathogen associated molecular pattern) receptors, enabling keratinocytes to recognise and respond to microbes⁽⁶⁾. Thus, vitamin D appears to both enhance the local capacity of the

epithelium to produce endogenous antibiotics and – at the same time – dampen certain arms of the adaptive immune response, especially those responsible for the signs and symptoms of acute inflammation.

All this leads to the recent paper by Berry *et al.* in this edition of the *British Journal of Nutrition*⁽⁷⁾, the first paper to take season, lifestyle and health factors into account while associating 25(OH)D levels and self-reports of respiratory infections. The effect size was large, about a 10% less risk of infection for every 10 nmol/l increase in 25(OH)D. Summer-time levels never reached 100 nmol/l, the level that some feel is the lower limit of health⁽⁸⁾.

The authors remain hesitant, for the reasons they list, to recommend vitamin D for asthmatic children. In the authors’ discussion of Ginde *et al.*⁽⁹⁾, they failed to note that the association between low vitamin D and infection was about four times stronger in asthmatic children than in non-asthmatic ones. Furthermore, while asthmatic numbers described by Urashima *et al.*⁽¹⁰⁾ were small, they were highly significant, finding that 30 µg/d of vitamin D effectively prevented exacerbations in asthmatic children ($P=0.006$) compared with placebo.

As a practitioner, I believe the medical community should consider vitamin D deficiency as a ‘known health hazard’, and aggressively treat it – in asthmatic individuals as well. Although anecdotal, I have observed high doses of vitamin D (50 µg/10 kg per d for 6 months then reduce to maintenance) seemingly ‘cure’ some childhood asthma in about 6 months. I hesitate to mention this but cannot find ethical reasons that allow me to exclude it from my comments.

Finally, to be sure, the study by Berry *et al.* speaks only of the respiratory system, yet antimicrobial effects of vitamin D may be more generalised. Recently, researchers in Tennessee wanted to know if vitamin D levels were associated with overall mortality in the intensive care unit (ICU)⁽¹¹⁾. They found patients were almost twice as likely to die during an ICU stay if they had vitamin D deficiency (<50 nmol/l).

Respiratory infections are but one failure of the immune system that lead children into the ICU. Meningitis is another, a grim winter time scythe that should be treated not only with conventional antimicrobials, but also (in my opinion) with pharmacological doses of vitamin D (500 µg/10 kg per d for several days). And, should any promising observer note an association between meningitis and a ‘seasonal stimulus’, and then suffer the scorn of their colleagues, remember

Edgar Hope-Simpson and remember also that time alone distinguishes a prophet from a madman.

Acknowledgements

Dr. Cannell is founder and principal of the educational organisation, the Vitamin D Council. In addition, he receives royalties from Purity Products on the sale of his 'Advanced Vitamin D Formula'.

John J. Cannell

Vitamin D Council
1241 Johnson Avenue
no. 134 San Luis Obispo
CA
USA

email jjcannell@vitamindcouncil.org

References

1. Hope-Simpson RE (1992) *The Transmission of Epidemic Influenza*, pp. 77. New York: Plenum Press.
2. Cannell JJ, Vieth R, Umhau JC, *et al.* (2006) Review: epidemic influenza and vitamin D. *Epidemiol Infect* **134**, 1129–1140.
3. Cannell JJ, Zasloff M, Garland CF, *et al.* (2008) On the epidemiology of influenza. *Virology* **25**, 29.
4. Raloff J (2006) The antibiotic vitamin: deficiency in vitamin D may predispose people to infection. *Science News*, Nov 11.
5. Zasloff M (2006) Fighting infections with vitamin D. *Nat Med* **12**, 388–390.
6. Schaubert J, Dorschner RA, Coda AB, *et al.* (2007) Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D dependent mechanism. *J Clin Invest* **117**, 803–811.
7. Berry DJ, Hesketh K, Power C, *et al.* (2011) Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr* **106**, 1433–1440.
8. Souberbielle JC, Body JJ, Lappe JM, *et al.* (2010) Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev* **9**, 709–715.
9. Ginde AA, Mansbach JM & Camargo CA Jr (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* **169**, 384–390.
10. Urashima M, Segawa T, Okazaki M, *et al.* (2010) Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* **91**, 1255–1260.
11. McKinney JD, Bailey BA, Garrett LH, *et al.* (2011) Relationship between vitamin D status and ICU outcomes in veterans. *J Am Med Dir Assoc* **12**, 208–211.