and possibly malignancies that might not emerge in 1–2-year clinical trials.

Although the long-term risk-benefit profile of daclizumab-HYP is unknown, the results of Gold and colleagues' phase 2 study are encouraging, and extend previous findings suggesting that daclizumab-HYP could have a role in the growing arsenal of disease-modifying treatments for multiple sclerosis, and therefore warrants further study.

*Shiv Saidha, *Peter A Calabresi*
Department of Neurology, Beaumont University Hospital, Dublin, Ireland (SS); and Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA (PAC)
calabresi@jhmi.edu

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1 Gold R, Giovannoni G, Selmaj K, et al, for the SELECT study investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; published online April 4. http://dx.doi.org/10.1016/S0140-6736(12)62190-4.

2 Waldmann TA. Anti-Tac (daclizumab, Zenapax) in the treatment of leukemia, autoimmune diseases, and in the prevention of allograft rejection: a 25-year personal odyssey. *J Clin Immunol* 2007; **27:** 1–18.

3 International Multiple Sclerosis Genetics Consortium, Hafler DA, Compston A, et al. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med* 2007; **357:** 851–62.

4 Alcina A, Fedetz M, Ndagire D, et al. IL2RA/CD25 gene polymorphisms: uneven association with multiple sclerosis (MS) and type 1 diabetes (T1D). *PLoS One* 2009; **4:** e4137.

5 Saidha S, Eckstein C, Calabresi PA. New and emerging disease modifying therapies for multiple sclerosis. *Ann NY Acad Sci* 2012; **1247:** 117–37.

6 Morgan DA, Ruscetti FW, Gallo R. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* 1976; **193:** 1007–08.

7 Sheridan JP, Zhang Y, Riester K, et al. Intermediate-affinity interleukin-2 receptor expression predicts CD56(bright) natural killer cell expansion after daclizumab treatment in the CHOICE study of patients with multiple sclerosis. *Mult Scler* 2011; **17:** 1441–48.

8 Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. *Lancet Neurol* 2010; **9:** 381–90.

9 Martin JF, Perry JS, Jakhete NR, Wang X, Bielekova B. An IL-2 paradox: blocking CD25 on T cells induces IL-2-driven activation of CD56^{bright} NK cells. *J Immunol* 2010; **185:** 1311–20.

10 Wuest SC, Edwan JH, Martin JF, et al. A role for interleukin-2 trans-presentation in dendritic cell-mediated T cell activation in humans, as revealed by daclizumab therapy. *Nat Med* 2011; **17:** 604–09.

11 Bielekova B, Richert N, Howard T, et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. *Proc Natl Acad Sci USA* 2004; **101:** 8705–08.

12 Rose JW, Watt HE, White AT, Carlson NG. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* 2004; **56:** 864–67.

13 Smith FO, Downey SG, Klapper JA, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. *Clin Cancer Res* 2008; **14:** 5610–18.

14 Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. *Nat Immunol* 2008; **9:** 503–10.

Is vitamin D supplementation in pregnancy advisable?

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It has been suggested that high proportions of otherwise healthy pregnant women have deficient or insufficient vitamin D concentrations, as assessed by measurement of serum 25-hydroxyvitamin D (25[OH]D). Poor vitamin D status increases the risk of rickets in offspring, which has resulted in recommendations for routine maternal supplementation. For example, in the UK, the National Institute for Health and Clinical Excellence (NICE)[1] states that "All women should be informed at the booking appointment about the importance for their own and their baby's health of maintaining adequate vitamin D stores during pregnancy and whilst breastfeeding. In order to achieve this, women may choose to take 10 micrograms [equivalent to 400 IU] of vitamin D per day." In February, 2012, the UK Department of Health published a letter to raise awareness of the risk of vitamin D deficiency in specific groups of women, particularly pregnant and breastfeeding women.[2] The Canadian Paediatric Society currently indicates that "Consideration should be given to administering 2000 IU of vitamin D daily to pregnant and lactating women", which replaces the previously recommended dose of 200 IU per day.[3]

By contrast, the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists stated in July, 2011, that "At this time there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency" and suggested that "vitamin D supplementation during pregnancy beyond that contained in a prenatal vitamin should await the completion of ongoing randomized clinical trials".[4] A review of dietary reference intakes for calcium and vitamin D by the US Institute of Medicine, in 2010,[5] concluded that "More targeted research should continue. Higher levels have not been shown to confer greater benefits, and in fact, they have been linked to other health problems, challenging the concept that 'more is better'. There is emerging evidence

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that too much of these nutrients may be harmful." As a result, the minimum concentration of 25(OH)D in serum recommended for good bone health was reduced from 30·0 ng/mL to 20·0 ng/mL. An extensive review has confirmed that long-term safety data on vitamin D supplementation remain limited.[6] Moreover, some reports suggest no link between maternal 25(OH)D concentrations and important pregnancy outcomes, such as recurrent preterm birth,[7] diabetes,[8] or mode of delivery.[9] De-Regil and colleagues[10] showed in a 2012 systematic review that the evidence on use of vitamin D supplementation in pregnancy was too limited to draw any conclusions on usefulness and safety, and that further rigorous randomised trials are required.

In *The Lancet*, Debbie Lawlor and colleagues[11] present a large, prospective cohort study which challenges the assertion that vitamin D supplementation should be provided to pregnant women to prevent low bone-mineral content in offspring. They point out that the main available findings on this subject come from three small cohort trials and that the studies yielded inconsistent results. Lawlor and colleagues report on 3960 mother-and-child pairs enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC). This study cohort is ten times larger than the previous studies combined. Eligible pairs included women who had valid results for measurement of non-fasting 25(OH)D in serum assessed by high-performance liquid chromatography tandem mass spectrometry with an internal standard, and offspring with results from dual-energy x-ray absorptiometry done at age 9–10 years (mean 9·9 years). Among the mothers, 1035 (26%), 879 (22%), and 2046 (52%) had 25(OH)D concentrations assessed in the first, second, and third trimester, respectively. No association was found between maternal 25(OH)D concentration in any trimester and offspring bone-mineral content or other bone outcomes.

These findings contrast starkly with a previous study by the same group, which concluded that maternal ultraviolet B exposure (a proxy for maternal vitamin D status) during pregnancy was related to bone size in 6995 offspring enrolled in ALSPAC, at a mean age of 9·9 years.[12] That finding suggested that vitamin D status in pregnancy exerts direct effects on subsequent bone formation in offspring. The apparent contradiction between these two studies can be explained in several ways. First, in the latest study the researchers measured 25(OH)D to assess vitamin D status, rather than assigning status on the basis of estimated ultraviolet B exposure. Second, Lawlor and colleagues[11] discovered a quirk in the follow-up arrangements that led to children born in the late summer or autumn, when exposure to ultraviolet B is greatest, generally being older at the time of dual-energy x-ray absorptiometry. Thus, because bone-mineral content rises with age, their values were higher than those in children born at other times of year. Correction for these confounding effects completely explained the difference in results. The researchers conclude that there is no strong evidence to support the claims that maternal vitamin D status during pregnancy is an important determinant of postnatal offspring bone-mineral content, and they are to be congratulated on setting the record straight.

In view of the inconsistency in results, it might seem unclear why vitamin D supplementation is officially recommended for all pregnant and breastfeeding women. The reason might be reports of rickets from developed countries. Ward and colleagues, in 2007,[13] reported 104 cases of confirmed rickets, identified by respondents to a monthly survey of 2325 Canadian paediatricians between July, 2002, and June, 2004. Of the patients affected, 96 (92%) had intermediately dark or dark skin. The researchers concluded that there was an urgent need for heightened awareness among health-care providers and the general public about vitamin D deficiency and the risk of rickets. Sharma and

colleagues[14] reported 74 infants seen between January, 2006, and June, 2008, in four London hospitals, who had symptomatic vitamin D deficiency. Proactive implementation of vitamin D supplementation in pregnant and breastfeeding women was urgently recommended. Similar to the Canadian study, however, only one infant was white European (62% were Asian) whereas, in the ALSPAC study by Lawlor and colleagues, 3663 (92·5%) of participants were white European.

A particular difficulty in deciding who should be supplemented is the paucity of studies to define the normal range of 25(OH)D concentrations in serum, particularly during pregnancy. Yu and colleagues[15] noted the lack of standardised normal-range and cutoff values for diagnosis of vitamin D deficiency. The US National Institutes of Health has set a normal range of 30·0–74·0 ng/mL in non-pregnant women.[16] However, Yu and colleagues found that among 100 pregnant white European women with body-mass index in the normal range, who had spontaneously conceived, and had had vitamin D measured in the summer, the 50th percentile value was 30·7 ng/mL. Thus, almost half of this healthy group would have been deemed deficient by the National Institutes of Health standard. The 5th percentile value was 10·8 ng/mL; 45·5% of black and 53·7% of Asian patients had lower concentrations. In a 2012 report from the USA, Burris and colleagues[17] found that the mean vitamin D concentration in blood samples from 947 pregnant white women, measured in the second trimester, was 60·2 nmol/L (equivalent to 24·0 ng/mL), but for black women the corresponding value was only 46·0 nmol/L (equivalent to 18·4 ng/mL). 16·2% of the white women, compared with 60·2% of black women, had values of lower than 50·0 nmol/L (20·0 ng/mL), and 1·4% of white but 18·3% of black women had values lower than 25·0 nmol/L (10·0 ng/mL).

The safest approach is probably routinely to supplement pregnant women at greatest risk, as defined by the NICE guidelines:[1] women of south Asian, black African, black Caribbean, or Middle Eastern origin, women who have limited exposure to sunlight (eg, those who are predominantly housebound or are generally fully covered when outdoors), women who eat a diet particularly low in vitamin D (eg, no oily fish, eggs, meat, or vitamin D-fortified margarine or breakfast cereal), and women with a body-mass index higher than 30 kg/m² before pregnancy. For other women, the optimum approach is unclear, and long-term randomised trials of supplementation are justified.

Philip J Steer
Division of Cancer, Faculty of Medicine, Imperial College London, London, UK, and Academic Department of Obstetrics and Gynaecology, Chelsea and Westminster Hospital, London SW10 9NH, UK
p.steer@imperial.ac.uk

I declare that I have no conflicts of interest.

1 National Institute for Health and Clinical Excellence. Antenatal care. Issued March 2008, last modified June, 2010. http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf (accessed Feb 4, 2013).
2 Department of Health. Vitamin D—advice on supplements for at risk groups. Feb 2, 2012. http://www.dh.gov.uk/health/2012/02/advice-vitamin-d (accessed Feb 4, 2013).
3 Godel JC. Position statement: vitamin D supplementation: recommendations for Canadian mothers and infants. Oct 1, 2007, reaffirmed March 1, 2012. http://www.cps.ca/en/documents/position/vitamin-d (accessed Feb 4, 2013).
4 Committee on Obstetric Practice. Opinion Number 495: vitamin D—screening and supplementation during pregnancy. July, 2011. http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Obstetric_Practice/Vitamin_D_-_Screening_and_Supplementation_During_Pregnancy (accessed Feb 4, 2013).
5 Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Nov 30, 2010. http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx (accessed Feb 8, 2013).
6 Macdonald HM. Contributions of sunlight and diet to vitamin D status. *Calcif Tissue Int* 2013; **92:** 163–76.
7 Thorp J, Camargo C, McGee P, et al. Vitamin D status and recurrent preterm birth: a nested case-control study in high-risk women. *BJOG* 2012; **119:** 1617–23.
8 Makgoba M, Nelson SM, Savvidou M, Messow CM, Nicolaides K, Sattar N. First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. *Diabetes Care* 2011; **34:** 1091–93.
9 Savvidou MD, Makgoba M, Castro PT, Akolekar R, Nicolaides KH. First-trimester maternal serum vitamin D and mode of delivery. *Br J Nutr* 2012; **108:** 1972–75.
10 De-Regil LM, Palacios C, Ansary A, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2012; **2:** CD008873.
11 Lawlor DA, Wills AK, Fraser A, Sayers A, Fraser WD, Tobias JH. Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study. *Lancet* 2013; published online March 19. http://dx.doi.org/10.1016/S0140-6736(12)62203-X.
12 Sayers A, Tobias JH. Estimated maternal ultraviolet B exposure levels in pregnancy influence skeletal development of the child. *J Clin Endocrinol Metab* 2009; **94:** 765–71.
13 Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin D-deficiency rickets among children in Canada. *CMAJ* 2007; **177:** 161–66.
14 Sharma S, Khan N, Khadri A, et al. Vitamin D in pregnancy-time for action: a paediatric audit. *BJOG* 2009; **116:** 1678–82.
15 Yu CK, Ertl R, Samaha R, Akolekar R, Nicolaides KH. Normal range of maternal serum vitamin D at 11–13 weeks' gestation. *Fetal Diagn Ther* 2011; **30:** 94–99.
16 National Institutes of Health. 25-hydroxy vitamin D test. http://www.nlm.nih.gov/medlineplus/ency/article/003569.htm (accessed Feb 4, 2013).
17 Burris HH, Rifas-Shiman SL, Camargo CA Jr, et al. Plasma 25-hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. *Ann Epidemiol* 2012; **22:** 581–86.