CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES

Flower DR (1996) The lipocalin protein family: structure and function. *Biochem J* 318:1–14

Gower DB, Ruparelia BA (1993) Olfaction in humans with special reference to odorous 16-androstenes: their occurrence, perception and possible social psychological and sexual impact. *J Endocrinol* 137:167–87

Hasegawa Y, Yabuki M, Matsukane M (2004) Identification of new odoriferous compounds in human axillary sweat. *Chem Biodiversity* 1:2042–50

Jacoby RB, Brahms JC, Ansari SA *et al.* (2004) Detection and quantification of apocrine secreted odor-binding protein on intact human axillary skin. *Int J Cosmet Sci* 26:37–46

Labows JN, Preti G, Hoelzle E *et al.* (1979) Steroid analysis of human apocrine secretion. *Steroids* 34:249–58

Labows JN, McGinley KJ, Kligman AM (1982) Perspectives on axillary odor. *J Soc Cosmet Chem* 34:193–202

Leyden JJ, McGinley KJ, Hoelzle K *et al.* (1981) The microbiology of the human axillae and its relation to axillary odors. *J Invest Dermatol* 77:413–6

Martin A, Saathoff M, Kuhn F *et al.* (2010) A functional ABCC11 allele is essential in the biochemical formation of human axillary odor. *J Invest Dermatol* 130:529–40

Natsch A, Gfeller H, Gygax P *et al.* (2003) A specific bacterial aminoacylase cleaves odorant precursors secreted in the human axilla. *J Biol Chem* 278:5718–27

Natsch A, Schmid J, Flachsmann F (2004) Identification of odoriferous sulfanylalkanols in human axilla secretions and their formation through cleavage of cysteine precursors by a C-S lyase isolated from axilla bacteria. *Chem Biodiversity* 1:1058–72

Preti G, Wysocki CJ, Barnhart KT *et al.* (2003) Male axillary extracts contain pheromones that affect pulsatile secretion of luteinizing hormone and mood in female recipients. *Biol Reprod* 68:2107–13

Rennie PJ, Gower DB, Holland KT (1991) In-vitro and in-vivo studies of human axillary odour and the cutaneous microflora. *Br J Dermatol* 124:596–602

Sato K, Leidal R, Sato F (1987) Morphology and development of an apoeccrine sweat gland in human axillae. *Am J Physiol* 252:166–80

Shehadeh N, Kligman AM (1963a) The effect of topical antibacterial agents on the bacterial flora of the axillae. *J Invest Dermatol* 40:61–71

Shehadeh N, Kligman AM (1963b) The bacteria responsible for apocrine odor, II. *J Invest Dermatol* 41,1–5

Spielman AI, Zeng X-N, Leyden JJ *et al.* (1995) Proteinaceous precursors of human axillary odor: isolation of two novel odor binding proteins. *Experientia* 51:40–7

Spielman AI, Harmony JAK, Stuart WD *et al.* (1998) Identification and immunohistochemical localization of protein precursors to human axillary odor in apocrine gland secretions. *Arch Dermatol* 134:813–8

Troccaz M, Strakkenman C, Niclass Y *et al.* (2004) 3-Methyl-3-sulfanylhexan-1-ol as a major descriptor for the human axilla-sweat odour profile. *Chem Bioversity* 1:1022–35

Wysocki CJ, Preti G (2009) *Human pheromones: what's purported, what's supported*. A Sense of Smell Institute White Paper <http://senseofsmell.org/papers/Human_Pheromones_Final%207-15-09.pdf>

Zeng X-N, Leyden JJ, Lawley HJ *et al.* (1991) Analysis of the characteristic odors from human male axillae. *J Chem Ecol* 17:1469–92

Zeng X-N, Leyden JJ, Brand JG *et al.* (1992) An investigation of human apocrine gland secretion for axillary odor precursors. *J Chem Ecol* 18:1039–55

Zeng X-N, Leyden JJ, Spielman AI *et al.* (1996a) Analysis of the characteristic human female axillary odors: qualitative comparison to males. *J Chem Ecol* 22:237–57

Zeng C, Spielman AI, Vowels BR *et al.* (1996b) A human axillary odorant is carried by apolipoprotein D. *Proc Natl Acad Sci USA* 93:6626–30

See editorial on page 321 and related article on pg 546

Some Light on the Photobiology of Vitamin D

Antony R. Young[1]

In this issue, Bogh *et al*. report a study that begins to address the important public health question of skin surface area and UVB exposure dose, related to erythema, necessary to achieve a given level of vitamin D status. They demonstrate the importance of baseline vitamin D status in conducting such studies. A smaller substudy suggests that skin pigment is not a barrier to vitamin D photosynthesis.

Journal of Investigative Dermatology (2010) **130**, 346–348. doi:10.1038/jid.2009.419

Introduction

The benefits of vitamin D and how best to obtain and maintain optimal levels are highly controversial topics that have enormous potential implications for human health. Nature has provided humans with two sources of vitamin D: solar UVB radiation and diet. However, most foods provide very little vitamin D, especially in typical Western diets. The exception is oily fish. Manmade interventions include food fortification in some countries, supplementation, and the use of tanning devices with UVB. Any discussion on vitamin D status should be based on facts. There is a surprising lack of careful, published investigation (as opposed to observation/extrapolation/calculation) into the photobiology of vitamin D *in vivo* and its interaction with skin color. Furthermore, there is a lack of data that compare the effects of UVR with other approaches to maintaining vitamin D status performed in the same laboratories to minimize experimental variation.

The significance of this study

The study by Bogh *et al*. (2010, this issue) is a welcome and timely addition to our knowledge in the photobiology field. The baseline data show that 85% of 182 people screened for the study were either vitamin D (25(OH)D) insufficient (67% < 50 nmol l^{-1}) or deficient (18% < 25 nmol l^{-1}) in Denmark at 56°N during the winter. The limitation of these definitions of vitamin D status is discussed in this issue's Editorial, by Reddy and Gilchrest (2010). The backs and chests of volunteers with skin types I–VI were exposed to three standard erythema doses (SEDs) of UVB for 4 days over 1 week. The UVB source used was very rich in the spectral region that converts 7-dehydrocholesterol to pre–vitamin D in the skin. The sites exposed represent

[1]*Division of Genetics and Molecular Medicine, St John's Institute of Dermatology, King's College London, London, UK*

Correspondence: Antony R. Young, King's College London, Division of Genetics and Molecular Medicine, St John's Institute of Dermatology, Tower Wing (9th floor), Guy's Hospital, London SE1 9RT, UK. E-mail: antony.r.young@kcl.ac.uk

~25% body surface area as estimated by the approach of Augustsson *et al*. (1992). It should be stressed that an SED is independent of personal UVR sensitivity and is a measure of erythemal efficacy that is independent of source spectrum. A dose of 3 SEDs is equivalent to about 1 minimal erythema dose (MED) in skin types I/II and would be suberythemogenic (approximately 0.5 MED) in skin types III/IV (Harrison and Young, 2002). The authors show that baseline 25(OH)D is the determinant of the response to UVB exposure. The lower the baseline level, the greater the response, which supports homeostatic control. The regression line in Figure 3 in the article by Bogh *et al*. indicates that individuals in the insufficient/deficient baseline range had an increase of 20–30 nmol l^{-1} 25(OH)D, a very substantial response, in about 1 week. This essentially brought people who were insufficient into sufficiency and those who were deficient into insufficiency. However, it must be stressed that a relatively large surface area was exposed, and, at least in skin types I/II, the exposure doses would have been approximately erythemogenic.

The UVR doses used in the study by Bogh and co-workers should be placed into context. The same authors have performed several studies in which UVR exposure was measured over extended periods in different populations in spring/summer in Denmark (56°N) using time-stamped personal electronic dosimeters. In people working indoors without engaging in sun-seeking behavior, the median daily dose was 0.3 SED (range: 0–3.9) on working days and 0.6 SED (range: 0.1–3.5 SED) on their days off (Thieden *et al*., 2004). The measurements were taken on subjects' wrists, and it is estimated that the dose to the face is twofold greater. Thus, the doses used in Bogh and colleagues' study were 5–10 times higher than median wrist exposures at the same latitude. Not surprisingly, higher daily exposures have been measured in Queensland, Australia, with, for example, home workers in Brisbane (27.4°S) having weekday shoulder exposure medians of 2.0–8.0 SEDs, depending on the time of year. Outdoor workers at the same latitude showed values of 3.0–10.0 SEDs (Parisi *et al*., 2000). It has been estimated that the average American is exposed to about 250 SEDs per working year, mostly in the spring and summer (Godar *et al*., 2001). This can be increased by 78 SEDs (i.e., about 30%) with a 3-week vacation (i.e., by 3.7 SEDs per day). It is perhaps surprising that even studies in sunny climates have demonstrated suboptimal vitamin D status. This conundrum remains to be investigated and explained.

It is often said that short solar exposures to the face and the back of the hands are adequate to maintain optimal vitamin D status, but this does not seem to have been experimentally verified. Using the technique of Augustsson *et al*. (1992), this would be equivalent to ~10% of the body surface and would increase to ~20% if the lower arms are included, which is still less than the ~25% surface area in Bogh and colleagues' study. Whether this is sufficient with lower UVR doses, which are more typical of daily exposure at given latitudes, over a longer period of time, remains to be tested under laboratory and/or field conditions. In this context it should also be noted that an SED of solar UVR will be less effective at vitamin D synthesis than an SED from the very UVB-rich source used in this study. This is because UVA in sunlight makes a much greater contribution to erythema than with the source used by Bogh *et al*.

Clinical Implications

- Baseline 25(OH)D is a determinant of UVB-induced vitamin D synthesis.
- Vitamin D photosynthesis is independent of skin pigmentation for a fixed UVB dose and similar baseline 25(OH)D level.
- Is adventitious solar exposure of face and hands sufficient to maintain vitamin status?

Skin color and vitamin D synthesis

Of particular interest is the substudy on the effect of pigmentation (see Table 2 in the article by Bogh *et al*.) on vitamin D synthesis; people with darker skin tend to have suboptimal vitamin D status. Although the sample size is small (n = 9 pairs matched with similar baseline 25(OH)D), the data indicate that skin type and measured pigmentation have no effect on the synthesis of vitamin D after exposure to the same fixed doses of UVB; this means that from an erythemal (MED) point of view the darker skin types, which included V and VI, had lower doses. This study should be confirmed with a larger sample size, and broadened in its remit, but it calls into question much of the dogma about the relationship between pigmentation and vitamin D status, and perhaps even the hypothesis that vitamin D was a major factor in the evolution of skin color (Yuen and Jablonski, 2009). However, the data of Bogh *et al*. are in contrast with those recently published by Armas *et al*. (2007) in a larger study. Armas *et al*. exposed 90% of the body surface area three times per week for 4 weeks. The doses given to skin types I/II would be expected to be in the MED range, and doses up to fourfold greater were given to individuals with darker skin types. The estimated increase of 25(OH)D in skin types I/II for a dose of 30 mJ/cm^2 over 4 weeks was comparable to that obtained in 1 week in Bogh and colleagues' study. Higher doses were required for darker skin types. Thus, overall, the outcomes of the two studies, with very different designs, are contradictory. However, it should be noted that the study population of Armas *et al*. (2007) indicated a relationship between skin color and baseline 25(OH)D, with higher values for fairer skin types. The current study shows that this difference in baseline 24(OH)D levels could have influenced the outcome.

How best to obtain vitamin D

Some three decades ago, some studies compared daily UVR with daily vitamin D supplementation, at different doses, for 3 weeks in vitamin D-deficient/insufficient people (Stamp *et al*., 1977). The UVR details are not comprehensive but would appear to be for whole-body exposure to a source with a peak at 290 nm. The initial "dose" was 1 minute, on dorsal and ventral surfaces, but this was increased by 1 minute each day, except when erythema was present (Stamp, 1975), indicating that the doses

were at the high end of suberythemal. This UVR protocol was equivalent to a vitamin D dose of 250 μg/day, which is 10,000 international units. A level of about ~100 nmol l^{-1} was reached at 3 weeks, with about 70 nmol l^{-1} reached in 2 weeks. This daily supplement dose is 10 times higher than that recommended by the US Department of Health and Human Services and the US Department of Agriculture (Johnson and Kimlin, 2006).

Much of the advice pertaining to "safe sun" is based on the prevention of erythema because it is a readily accessible clinical readout, and sunburn is a risk factor for malignant melanoma in susceptible skin types. It is possible to compare, in theory, the relative risks and benefits of solar exposure using action spectra (wavelength dependence) for erythema and the synthesis of pre–vitamin D (not 25(OH)D) as biological weighting functions with solar spectra with different UVB/UVA ratios. The amount of UVB increases with the height of the sun, which is dependent on latitude, season, and time of day. Such calculations indicate that the optimal benefit-to-risk ratio occurs when the sun is high in the sky (Sayre and Dowdy, 2007), which is when people are advised to avoid the sun (e.g., about noon). These calculations are based on action spectra, which are likely to have large margins of error, and it would be desirable to test these results under field or laboratory conditions using 25(OH)D as the readout.

Conclusions

The dermatology community is very mindful of the well-established detrimental effects of UVB. The community is increasingly aware of the role of UVB in vitamin D synthesis but is still skeptical of many of the health benefits attributed to vitamin D. Researchers are justifiably concerned about the misuse of information for financial gain or the inadvertent promotion of sun-seeking/tanning behavior. However, much work remains to be done in risk-versus-benefit assessment of UVR exposure, which will depend on a range of individual/demographic/cultural/geographic factors and on the communication of research outcomes and advice to the public. There is a clear need for a much better understanding of the relationship among UVR spectrum, skin area and exposure dose, skin color, tanning, photoprotection, and vitamin D outcome. Some of these issues in the context of risk/benefit are currently being investigated in a multinational European Community–funded project, "ICEPURE: The Impact of Climatic and Environmental Factors on Personal Ultraviolet Radiation Exposure and Human Health" (see http://www.icepure.eu for details). Furthermore, we need a much better understanding of the relationship between the maintenance of vitamin D status by UVB versus diet/supplementation and their interactions.

CONFLICT OF INTEREST

The author states no conflict of interest.

REFERENCES

Armas LA, Dowell S, Akhter M *et al.* (2007) Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol* 57:588–93

Augustsson A, Stierner U, Rosdahl I *et al.* (1992) Regional distribution of melanocytic naevi in relation to sun exposure, and site-specific counts predicting total number of naevi. *Acta Derm Venereol* 72:123–7

Bogh MKB, Schmedes AV, Philipsen PA *et al.* (2010) Vitamin D production after UVB exposure depends on baseline vitamin D and total cholesterol but not on skin pigmentation. *J Invest Dermatol* 130:546–53

Godar DE, Wengraitis SP, Shreffler J *et al.* (2001) UV doses of Americans. *Photochem Photobiol* 73:621–9

Harrison GI, Young AR (2002) Ultraviolet radiation-induced erythema in human skin. *Methods* 28:14–9

Johnson MA, Kimlin MG (2006) Vitamin D, aging, and the 2005 Dietary Guidelines for Americans. *Nutr Rev* 64:410–21

Parisi AV, Meldrum LR, Kimlin MG *et al.* (2000) Evaluation of differences in ultraviolet exposure during weekend and weekday activities. *Phys Med Biol* 45:2253–62

Reddy KK, Gilchrest BA (2010) What is all this commotion about vitamin D? *J Invest Dermatol* 130:321–6

Sayre RM, Dowdy JC (2007). Darkness at noon: sunscreens and vitamin D3. *Photochem Photobiol* 83:459–63

Stamp TC (1975) Factors in human vitamin D nutrition and in the production and cure of classical rickets. *Proc Nutr Soc* 34:119–30

Stamp TC, Haddad JG, Twigg CA (1977) Comparison of oral 25-hydroxycholecalciferol, vitamin D, and ultraviolet light as determinants of circulating 25-hydroxyvitamin D. *Lancet* 1:1341–3

Thieden E, Philipsen PA, Heydenreich J *et al.* (2004) UV radiation exposure related to age, sex, occupation, and sun behavior based on time-stamped personal dosimeter readings. *Arch Dermatol* 140:197–203

Yuen AW, Jablonski NG (2009) Vitamin D: in the evolution of human skin colour. *Med Hypotheses* 74:39–44

See related article on pg 563

Cutaneous T-Cell Lymphoma: Two Faces of the Same Coin

Magdalena B. Wozniak[1] and Miguel Á. Piris[1]

Primary cutaneous anaplastic large-cell lymphoma (C-ALCL) and cutaneous peripheral T-cell lymphoma not otherwise specified (C-PTL-NOS) are cutaneous T-cell lymphomas with distinct clinical behaviors. Whereas C-ALCL has a favorable prognosis with frequent spontaneous disease regression, C-PTL-NOS runs a more aggressive course. The molecular pathogenesis of these cutaneous T-cell lymphoma types has not yet been studied in detail. In this issue, van Kester *et al.* report new imbalances that could contribute to our understanding of the differences between these two lymphoma types.

Journal of Investigative Dermatology (2010) **130**, 348–351. doi:10.1038/jid.2009.373

Cutaneous T-cell lymphomas (CTCLs) are non-Hodgkin´s lymphomas characterized by the clonal proliferation of skin-homing mature T lymphocytes. The

[1]*Molecular Pathology Program, Spanish National Cancer Research Centre, Madrid, Spain*

Correspondence: Miguel Á. Piris, Spanish National Cancer Research Centre (CNIO), Melchor Fernández Almagro 3, Madrid 28029, Spain. E-mail: mapiris@cnio.es