Available online at www.sciencedirect.com
ScienceDirect
Journal of Steroid Biochemistry & Molecular Biology xxx (2007) xxx–xxx
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Sun protection and Vitamin D: Three dimensions of obfuscation

Barbara A. Gilchrest *

Boston University School of Medicine, Department of Dermatology, 609 Albany Street – J507, Boston, MA 02118, United States

Received 30 November 2006

Abstract

Ultraviolet (UV) radiation is a proven carcinogen, responsible for more than half of all human malignancies. It also compromises skin appearance and function. Since the UV action spectra for DNA damage, skin cancer and Vitamin D_3 (vit D) photosynthesis are identical and vit D is readily available from oral supplements, why has sun protection become controversial, now that some data suggest conventionally "sufficient" levels of vit D may be less than optimal for at least some population groups? First, the media and apparently some researchers are hungry for a new message. Nevertheless, after 50 years, UV exposure is still a major avoidable health hazard. Second, the controversy is fueled by a powerful special interest group: the indoor tanning industry. They target not the frail elderly or inner-city ethnic minorities, groups for whom evidence of vit D insufficiency is strongest, but rather fair-skinned teenagers and young adults, those at highest risk of UV photodamage. Third, evolution does not keep pace with civilization. When nature gave man the appealing capacity for vit D photosynthesis, the expected lifespan was far less than 40 years. Long-term photodamage was not a concern, and vit D was not available at the corner store. The medical community should avoid sensationalism and instead rigorously explore possible cause-and-effect relationships between vit D status and specific diseases while advocating the safest possible means of assuring vit D sufficiency.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: Skin cancer; Photodamage; Indoor tanning; Vitamin D photosynthesis

1. Introduction

The goal of this review and editorial comment is to place in perspective the "controversy" that is said to have arisen regarding the allegedly conflicting goals of sun protection and skin cancer prevention on the one hand and achieving optimal Vitamin D (vit D) homeostasis on the other hand. The curious and somewhat elusive basis of this "controversy" lies in the often unstated assumption that increasing vit D levels, specifically the levels of the inactive pre-vitamin 25(OH) vit D that is measured in serum, is best achieved by increased sun exposure in order to enhance cutaneous photosynthesis of the precursor molecule vit D within the irradiated epidermis. Despite the fact that all intervention studies suggesting a benefit for upward revision of the conventional "normal" or "sufficient" 25(OH) vit D level in specific population groups have examined the effect of oral vit D supplements, not increased exposure to sun or other UV sources; and that vit D obtained from diet or supplement can fully substitute for vit D synthesized in the skin, the media continue to report the "debate" between professional groups with primary interests in skin health versus endocrinologic health and to create confusion among the general public regarding recommended health behaviors. The sections below briefly review the relevant established facts and ongoing research in these complex areas, but principally seek to explain the otherwise inexplicable "controversy" that has dominated media coverage for several years.

2. Adverse effects of UV on skin

Ultraviolet (UV) is a proven carcinogen [1], responsible for the great majority of the estimated 1.3 million skin cancers per year in the US [2], more than half of all human malignancies. The causal role of UV irradiation in both non-melanoma skin cancer (NMSC) and melanoma has been suspected by experienced clinicians and epidemiologists for well more than a century and was demonstrated repeatedly in studies

* Tel.: +1 617 638 5538; fax: +1 617 638 5550.
E-mail address: bgilchre@bu.edu.

0960-0760/$ – see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2006.12.028

of hairless mice and other animal models beginning in the 1920s [3,4]. Particularly in the case of squamous cell carcinomas (SCCs) there is a clear direct relationship, with more UV irradiation resulting in earlier onset and higher prevalence of cancers in both mice and man [4,5]. A direct cause-and-effect relationship for UV irradiation and basal cell carcinomas (BCCs) has also been documented in a mouse model [6]. Although the dose–response relationship between UV irradiation and melanoma is less obvious than for NMSC, at least in man, cause-and-effect has similarly been documented in multiple animal models [7,8]. As well, patients with the rare disorder xeroderma pigmentosum (XP), caused by a mutation in one of eight DNA repair enzymes required to remove UV-induced DNA photoproducts, develop numerous NMSC as well as melanomas at rates greater than 1000 times the general population, often beginning in the first or second decade of life, even when they attempt to strictly avoid sun exposure [9].

In addition to this compelling evidence, research in numerous laboratories has identified specific "UV signature mutations" in the p53 tumor suppressor protein [10] that contribute to the development of more than 90% of SCCs and at least 50% of BCCs [11], in which mutations in *Ptch* or an interacting protein play the dominant role [6,12,13]. In melanoma, the molecular contribution of UV irradiation to malignant transformation of melanocytes has been more elusive [14], although UV signature mutations have been identified in gene products whose function is commonly lost (such as $p16^{INK4a}$) or amplified (such as N-Ras) in this tumor type [10,15] and, although the activating mutation in BRAF observed in up to 70% of melanomas is not specific for UV-induced DNA damage, it has not been observed in lesions arising on sun-protected mucosal body sites [16], suggesting that UV may nevertheless be responsible.

Although it has been noted that skin cancer is rarely fatal, there are approximately 10,000 deaths per year from skin cancer in the US, primarily due to metastatic melanoma [17]. Moreover, there is an enormous societal cost for treatment of these exceedingly common cancers [18]. Finally, treatment can be disfiguring.

Beyond the morbidity and mortality associated with NMSC and melanoma, lifelong cumulative UV damage to skin is responsible for the great majority of age-associated unwanted cosmetic changes in skin [19]. In addition, the associated xerosis, more properly altered epidermal differentiation with resulting stratum corneum barrier defects, leads to skin that is uncomfortable in addition to unsightly [19]. Photoaging changes, even aside from the strongly associated skin cancer risk, is a source of distress for a majority of fair-skinned adults beyond the age of 40–50 years and has spawned a multi-billion dollar skin rejuvenation market. The cause-and-effect relationship between UV exposure and photoaging, like the relationship with skin cancer, has been well documented in mouse models [20].

In summary, common sense, clinical observation, animal experiments and mechanistic studies at the molecular level all support reducing sun exposure over the entire lifetime as the preferred means of avoiding the inter-related problems of skin cancer and photoaging.

3. Public attitudes toward sun exposure

In 1903 Finsen received the Nobel Prize for his observation that sun exposure was therapeutic for cutaneous tuberculosis [21], and the idea that UV exposure was "healthful" rapidly took hold among the public [22]. In the 1920s, Coco Chanel championed the idea that suntanning was glamorous [23], a position in sympathy with the Russian Revolution and the replacement of the traditionally sun-protected ruling aristocracy by a proletariat composed of outdoor workers. Like many of her pronouncements, the attractiveness of a tan became embedded in the public psyche and remains there to this day, nearly a century later, despite the revised medical and scientific perception of a tan as a DNA damage response [24] and widespread appreciation that UV exposure often leads to skin cancer [25].

The public perception that sunbathing is pleasant and that a suntan is attractive, and in many circumstances also prestigious, continues to motivate many individuals to attempt to tan their skin. This is particularly true for teenagers and young adults [26], who have a well documented inability to imagine themselves as middle-aged or elderly, affected by photoaging and skin cancer.

4. UV action spectra and biologic responses

In the 1980s, studies employing normal human volunteers and multiple narrow band UV light sources determined the relative efficacy of different wavelengths of light in producing sunburn and suntan [27] as well as epidermal DNA damage [28]. The action spectra for all these responses are strikingly similar, with peak efficacy in the short UVB portion of the spectrum (approximately 290–300 nm) and decreasing by approximately an order of magnitude at 313 nm (still in the UVB range) and by 4–5 orders of magnitude by 400 nm, the beginning of the visible spectrum [27,28]. The action spectrum for vit D photosynthesis in skin is extremely similar, also peaking at approximately 300 nm and falling off exponentially with longer wavelengths of light [29]. The virtual identity of these multiple action spectra has several implications. First, it implicates DNA damage as responsible for tanning, a relationship that has been confirmed experimentally [24]. Second, these data imply that vit D photosynthesis cannot occur in the absence of DNA damage, even though vit D production is a consequence of UV effects on cell membranes rather than on DNA itself [30].

It is also well established that formation of DNA photoproducts is linear with UVB dose over a very wide

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

range [28]. In contrast, vit D photosynthesis (conversion of 7-dehydrocholesterol to pre-vit D) is balanced in skin by conversion of pre-vit D to inactive photoproducts, lumisterol and tachysterol, so that the concentration of pre-vit D reaches a maximum value after a relatively short UV exposure, less than one minimal erythema dose (MED), and further UV exposure results only in more extensive conversion of the pre-vitamin to inactive metabolites [30]. Following formation of pre-vit D in the skin, there is a gradual thermal isomerization of this compound, yielding vit D, which then gradually leaches into the circulation and is sequentially hydroxylated in the liver and kidney to become the active hormone $1,25(OH)_2$ vit D [30]. The different UV-dose–response relationships for these biologic endpoints are shown diagrammatically in Fig. 1.

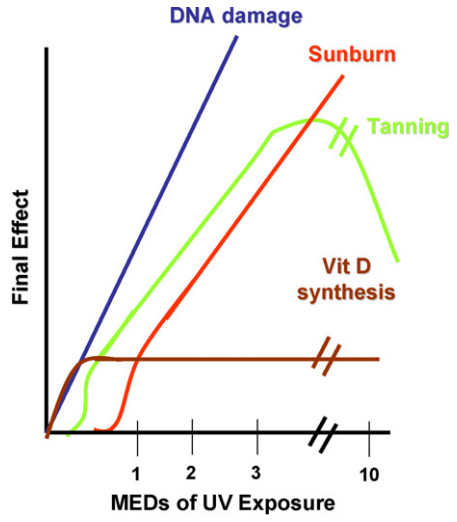

Fig. 1. UV dose relationships for sunburn, suntan, DNA photoproduct (thymine dimer) formation, and vit D photosynthesis. Sunburn and suntan reactions become clinically apparent following a threshold or greater UV dose (in the case of sunburn, by definition a minimal erythema dose or MED) after a considerable delay. The time to peak response is dose-dependent, approximately 12–24 h for sunburn and 2–5 days for suntan [31]. Larger doses result in more intense peak reactions in a roughly linear fashion, with the slope of the lines largely genetically determined. At very high UV doses, these responses are obscured by blistering and desquamation ("peeling"), respectively. In contrast, DNA photoproduct formation is instantaneous and increases linearly across very small to very large UV exposures, with absolute amount determined largely by epidermal melanin content. Rate of DNA photoproduct removal and the inversely related rate of mutation [70,71] are relatively poorly studied as a function of UV dose and not graphed here. The dose–response for vit D synthesis increases linearly at small UV doses but differs strikingly from the other curves in that it reaches a plateau at doses well below the threshold dose for erythema [30]. Pre-vit D forms rapidly, with excess compound converted to inactive metabolites. Remaining pre-vit D then thermally isomerizes over several hours to vit D that enters the circulation gradually over several days and is hydroxylated in the liver to 25(OH) vit D, the conventionally measured but still inactive "storage" form of the vitamin [41]. The plotted slopes for all curves are the author's arbitrary representations based on review of multiple publications and not on actual measurements.

5. Skin phototype influences acute and chronic UV responses

The effects of UV on human skin are substantially determined by the content of epidermal melanin, a large polymer that efficiently absorbs photons across the entire UV and visible light range, as well as by a related but less well understood set of determinants collectively termed "phototype" [31]. By definition, an individual's phototype reflects the extent of sunburning versus subsequent tanning following an initial moderate sun exposure after a long period of little or no exposure [32] (Table 1). Phototypes strongly affect the acute and chronic risks of UV exposure and also affect the rate of vit D photosynthesis (Fig. 2). A skin phototype I individual by definition will burn readily with a first moderate UV exposure and then tan minimally, if at all [31,32]. Such an individual will also rapidly achieve maximal vit D photosynthesis. For example, it is estimated that 2–8 min of midday spring or summer sun exposure in New York or Boston is adequate [33]. The required sun exposure in Alaska or Scandinavia is only minimally longer [33]. With longer and repeated sun exposures, such an individual will suffer very substantial DNA damage eventually manifested as photoaging and skin cancer; and will continue to sunburn without tanning. A skin phototype III individual, commonly someone with a reasonably light baseline complexion, will experience DNA damage and produce vit D comparably to a skin phototype I individual after a first UV exposure, but will burn less and tan more readily [31,32]. With multiple exposures, the tanning response will dominate, reducing the rate of vit D photosynthesis, and there will be considerably less cumulative DNA damage and hence less severe photoaging and less skin cancer risk [31]. A skin phototype VI individual, for example, someone of African or Aboriginal ancestry, will be protected by constitutive high epidermal melanin content from initial DNA damage, will not sunburn after a moderate UV exposure [31] but will also have relatively limited vit D photosynthesis, again because of UV absorption by melanin rather than other cellular targets [34]. With repeat exposures, such an individual will tan darkly and there will be only modest cumulative DNA damage with resulting minimal photoaging and skin cancer risk,

Table 1
Skin phototypes

Phototype	Reaction to sun exposure[a]
I	Always burn, never tan
II	Burn slightly, then tan slightly
III	Rarely burn, tan moderately
IV	Never burn, tan darkly
V	Oriental or Hispanic skin[b]
VI	Black skin[b]

[a] Specifically, a 30 min direct exposure after a long period of no sun exposure, e.g., on the first warm day of spring.

[b] In the original Fitzpatrick classification [32] these groups were defined by racial heritage alone but not all individuals who self-identify in these groups are more UV-protected than Caucasians.

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

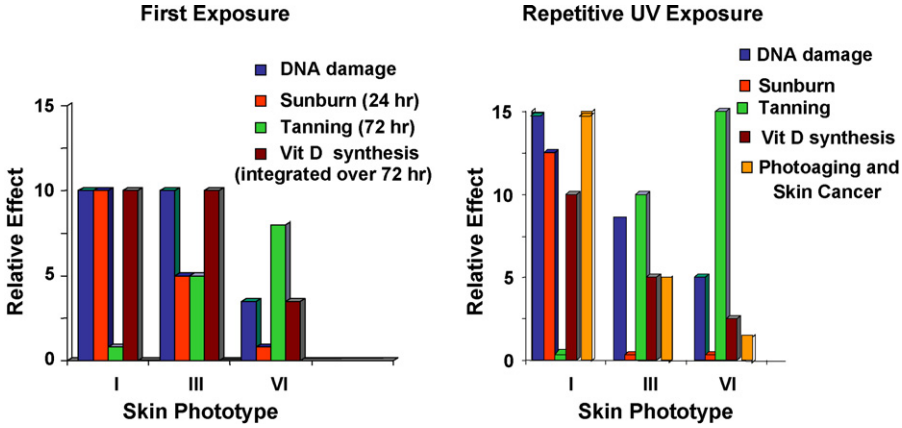

Fig. 2. Effect of skin phototype on specific UV responses. Relative consequences of a first and of multiple frequently spaced UV exposures on individuals of different complexion and genetic endowment are shown by bar heights. These are the author's arbitrary representations based on review of multiple publications and not on actual measurements.

but also far less vit D synthesis per sun exposure than for individuals of lighter complexion [34].

6. The pseudo-controversy

In recent years numerous newspaper reporters, freelance journalists and television news anchors have reported on the "medical controversy" that pits the unwanted effects of acute sunburns, photoaging and skin cancer against both well established and postulated benefits of vit D photosynthesis. Not often directly addressed in these reports is the fact that sun exposure also produces tanning, at least in those individuals genetically capable of tanning, a cosmetic and lifestyle goal of many in their reading/viewing audience. Simplistically stated, the question posed by these articles and reports is: should the public maximize vit D levels through intentional UV exposure in order to reduce their risk of internal cancers, hypertension, diabetes, multiple sclerosis, and a litany of other disorders felt by some to be due in part to "insufficient" vit D levels? [33] In essence, the issue is framed as needing to choose between the lesser of two evils: skin cancer and photoaging versus cancer of various internal organs and/or the long list of other ailments. This framework ignores the fact that ample vit D can be obtained from a combination of diet, supplements, and incidental protected sun exposure [35].

In many instances, a need to promote unprotected sun exposure is justified by reports that low or low normal levels of vit D have been measured in darkly pigmented individuals, such as inner-city minority groups, or among the frail elderly. However, such coverage rarely notes that these at-risk groups have inefficient cutaneous vit D photosynthesis, in the case of darkly pigmented individuals because melanin absorbs UV photons that otherwise generate vit D [34] and in the case of the elderly for less well understood reasons, but perhaps because their thinned epidermis has a reduced content of 7-dehydrocholesterol, the cell membrane constituent converted by UVB to pre-vit D [36,37]. Such media coverage also fails to note that population groups most attracted to sunbathing – healthy Caucasian teenagers and young adults, including many fair-skinned individuals who tan poorly [26] – are also at lowest risk of vit D insufficiency, yet at greatest risk of long-term photodamage.

The "safe sun" position, as articulated by the American Academy of Dermatology (AAD) [38] and other professional dermatologic organizations for many years, is based on the irrefutable fact that UV irradiation causes non-melanoma skin cancer, melanoma and photoaging; that the only established health benefit of UV irradiation is vit D photosynthesis; that vit D can be obtained from the diet or from oral supplements; and that lifelong sun protection is therefore recommended, especially for fair-skinned individuals at high risk of photodamage [35].

7. The true controversy

The real controversy is whether there is a health benefit to increasing an individual's serum 25(OH) vit D level, as has been suggested by some epidemiologic studies but certainly not yet confirmed in prospective randomized studies [35]. A thorough discussion of the quality and consistency of the epidemiologic and observational data interpreted by some to support a health benefit of serum 25(OH) vit D levels far above those associated with normal skeletal maintenance is provided elsewhere [35] and is beyond the scope of this article, but a recent example is illustrative.

Several much referenced reports link incidence of colorectal cancer [39–41] to "low" vit D levels within the conventional normal range or to a presumptive proxy, little sun exposure, usually as deduced from residence in a poorly insolated[1] area. Although other epidemiologic or observational studies of similar size and design (grade B level 2 or

[1] Insolation refers to amount and intensity of incident UV irradiation. It is affected by latitude, altitude, season, cloud cover, smog and other variables, being generally high near the equator and low near the poles.

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

3 in the hierarchy of evidence-based medicine) [42] found no statistical relationship or even an inverse relationship for colorectal cancer or closely related diseases [43–47], the positive reports have been selectively and prominently cited in popular media coverage of the topic. However, a recently published prospective randomized placebo-controlled trial (grade A level 1 for medical decision making) [42] of vit D supplementation (400 IU/day) for 7 years or longer, involving over 36,000 post-menopausal women, found no relationship whatever between colorectal cancer risk (incidence or mortality; tumor grade, stage, or size) and use of supplements, total vit D intake, amount of sun exposure (crudely and indirectly calculated, as in the positive epidemiologic studies), or baseline serum 25(OH) vit D levels [48]. An accompanying editorial [49] and the investigators themselves noted that 7 years may be too short a period of supplementation, the subjects may have been given too low a dose of vit D, or had too healthy a lifestyle and/or been too young (62 years on average) to develop this cancer in large numbers. In brief, they concluded that no result is ever definitively negative. Nevertheless, it is most unlikely that even larger, longer-lasting randomized controlled trials than this multi-million dollar effort will ever be performed. Yet, less than two months later a far less definitive multivariable model study inversely linking cancer risk, including colorectal cancer, statistically to six historical indirect measures of sun exposure and presumptively correlated vit D levels [50] received prominent media coverage with no reference to the "gold standard" completely negative colorectal cancer study [48].

8. Irrelevance of both controversies to sun protection

The neglected but critical point is that the "true" optimal level of 25(OH) vit D for musculoskeletal health, cancer prevention, or any of the other claimed benefits is irrelevant to the proven value of sun protection. Whatever this optimal level, ample vit D can be obtained from diet, supplements, and incidental sun exposure [51–54]. Intentional unprotected sun exposure with the goal of increasing vit D photosynthesis is not only unnecessary; as discussed above, it is also least efficient for those population groups highest risk of vit D deficiency [34,36,37]. In contrast, the groups most responsive to the media's unprotected sun exposure message are those at statistically lowest risk of vit D deficiency: healthy fair-skinned adolescents and young adults. Indeed, surveys show that more than 70% of tanning bed users are Caucasian women aged 16–49 years [26] and that 95% of all users exceed the FDA recommended exposure levels [55] anticipated to maximize vit D photosynthesis. The composition and exposure habits of the sunbathing public are similar, although the average age is likely even younger and exposures even greater. The safe sun message promulgated by individual dermatologists and the AAD does not target dark-skinned individuals, who already have excellent endogenous sun protection in the form of epidermal melanin. Of note, the "UV advantage" message [33] is also not so targeted and has not been embraced by the groups at demonstrated risk of vit D insufficiency.

The interest among the media and public in the pseudo-controversy is nevertheless real and persistent. Why? It must first be noted that the sun protection message is old, dating back at least 23 years [56], and like the "buckle up" seatbelt message is viewed by its intended audience as wimpy. Real men do not wear sunscreen (or seatbelts). Neither do many rebellious, fun loving and spontaneous adolescents. Moreover, many people, especially teenagers, want to sunbathe . . . not to decrease their risk of age-associated disease decades later, but to acquire a "sexy" tan [25]. In addition, relaxing in the sun and making one's own vit D have a back-to-nature holistic appeal for many individuals. It is therefore not surprising that reporters representing the print and electronic media continue to cover the pseudo-controversy. It sells. Of note, however, this natural tendency for the media to pursue a "new" and controversial story, especially if it is one of their audience wishes to hear, has been greatly facilitated by press releases crafted by representatives and employees of the indoor tanning industry.

9. The indoor tanning industry

In the United States alone, indoor tanning is a $5 billion per year business [57,58] with more than 50,000 tanning facilities and 28 million customers annually [59], greater than 1 million visits per day [60]. In some regions of the US, more than half of all teenage girls have visited a tanning facility at least 3 times in the previous year [61]. Because the concerns discussed above have led professional groups such as the AAD to request stricter guidelines and better enforcement of existing regulations governing indoor tanning, over the past decade 29 states have enacted legislation restricting access for teenagers, with similar legislation in place or under consideration in at least 3 additional states [62]. The indoor tanning industry is vigorously opposing such legislation through paid lobbyists and a well orchestrated media campaign. The cornerstone of the industry's argument to curtail proposed restrictions on teenage use and general overuse by many customers is that more UV exposure is healthy, that indoor tanning is safer than natural tanning, and that UV exposure reduces the risk of multiple diseases [63]. The message shared with state legislatures and the media by the tanning industry is the same as recited on the UV Foundation's website: "Vitamin D from UV exposure is free and easy to get—why pass up the simplest way to improve your odds of preventing cancer?" [64] This and similar sites also detail industry funding of research by the principal and perhaps only academically-based proponent of UV exposure to increase vit D levels.

The sincerity of the industry's concern for the public health would be more credible if their coverage of the issues were more balanced and if the campaign had not been preceded

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

by a decade or so of extolling the virtues of UVA lamps, as opposed to UVB lamps that they now tout as "healthful" [1,65,66]. In the years preceding the publication of the epidemiologic studies questioning the adequacy of conventional recommendations for vit D levels, the industry argued strenuously that indoor tanning was superior to natural sun exposure precisely because tanning could be obtained with relatively less UVB exposure [67] (and, of course, less vit D photosynthesis). Indeed, a review of the industry's public postures over the 30 years of its dramatic growth in annual revenues [22] reveals a series of opportunistic contradictory positions. There can be no mistake that the business of the tanning industry is to sell tanning sessions, the more the better, not to safeguard the public's health.

10. The appeal of natural solutions

Over millions of years, life has beautifully adapted to the earth's environment. Nature has devised elegant, efficient, and often surprising solutions to complex problems; and it would appear that man is rarely able to improve on them. The exceptions to this general rule involve instances in which the rate of change imposed by civilization has outpaced evolution by modifying the environment and/or altering the situation in ways that create previously non-existent downsides for the natural solution. Vit D photosynthesis is a prime example.

Humans evolved as relatively hairless darkly pigmented beings in a highly insolated tropical subsistence environment. Their abundant epidermal melanin absorbed most of the incident UV photons, allowing them to avoid painful sunburns while hunting and gathering food, but the high UVB content in sunlight nevertheless permitted epidermal photochemistry to occur. This photochemistry included conversion of membrane lipids to vit D, the biologically inactive precursor of the hormone $1,25(OH)_2$ vit D that requires hydroxylation steps in the liver and kidney before acquiring the ability to modulate genes in cells throughout the body [41]. Overproduction of the precursor molecule was prevented by metabolic spillover pathways that convert excess vit D to inactive metabolites in the skin during prolonged UV exposure. The ability to photosynthesize vit D avoided the requirement for dietary vit D in this environment with its unpredictable and often inadequate food supply. Life expectancy was far less than 40 years [68] and therefore there was an enormous priority for health in the first decades, a time sufficient to permit reproduction. Very gradually humans migrated away from the equator to far less insolated climates and skin color gradually lightened, giving rise to the fair-skinned blue-eyed blonde populations of Scandinavia and Northern Europe, for example. Although quite speculative, one appealing explanation for the complexion change with migration north is that acute UV damage became less of a problem, while maintaining adequate vit D levels became a priority.

In recent centuries, human beings have become far more mobile, migrating thousands of miles in a matter of weeks or more recently hours. Simultaneously, cities have been created, and many people live indoors predominantly. Among the consequences of this population mobility and rapid industrialization are large populations of dark-skinned individuals now living largely indoors in poorly insolated climates, as well as many fair-skinned people living in relatively well insolated places, recreating if not working outdoors, and intermittently traveling to highly insolated places for business or pleasure. Compounding these trends, life expectancy has increased dramatically in recent centuries and now approaches or exceeds 80 years in much of the first world [69], giving rise to decades of progressive photoaging and the accompanying exponential increase in annual skin cancer incidence between the fourth and eighth decades, due at least in part to an age-associated decrease in DNA repair capacity [70,71]. The results include the emergence of childhood rickets among dark-skinned inner-city ethnic minorities in the northern United States and Europe [72,73], as well as a one in three lifetime risk of skin cancer among fair-skinned Caucasians.

These facts imply that a fair-skinned individual will benefit enormously from regular lifelong safe sun practices. Moreover, while wearing a high SPF sunscreen in season, such an individual will probably maximally generate vit D in exposed areas during incidental sun exposure [35]. Although sunscreens have been stated to block all UV and hence, all vit D photosynthesis [74], this is not the case. By definition sunscreens allow continuous transmission of a fraction of incident UV photons equal to 1/SPF (sun protection factor) of the total, for example, 1/15th or 7% in the case of an SPF 15 product. Moreover, studies have documented that sunscreen users customarily apply half or less of the FDA-stipulated amount of product required to generate the stated level of protection ($2\ mg/cm^2$) [75] and hence achieve far less protection [75]. If 2–8 min of unprotected summer sun exposure is required to optimize cutaneous vit D synthesis [33], this would be accomplished in approximately 10–20 min of exposure while wearing an SPF 15-30 sunscreen in the customary manner [75,76]. Most critically, regardless of one's complexion or extent of UV exposure, daily oral vit D supplementation can completely compensate for lack of cutaneous vit D photosynthesis [35].

11. Common ground for the Vitamin D and dermatology communities

It is likely that all clinicians and investigators interested in vit D biology, photocarcinogenesis, and/or skin biology and pathophysiology can agree that more research in overlap areas would be desirable. Perhaps the questions of greatest clinical importance include: is there a cause-and-effect inverse relationship between higher 25(OH) vit D levels and cancer incidence, hypertension, diabetes, multiple sclerosis, and other conditions for which inverse epidemiologic associations have been noted? [35] Is there an individual health

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

benefit of having a higher than conventionally recommended serum 25(OH) vit D level for "healthy" children and adults? If there is a benefit, what is the minimum length of time during which high 25(OH) levels must be maintained, for example, throughout life or only for a period of months or years? Implicit in these questions is the fact that cause-and-effect relationships cannot be deduced from epidemiologic studies which classically are confounded by socioeconomic factors, racial/genetic factors, lifestyle associations, and the like.

In contrast to the as-yet-understudied areas referenced above, randomized prospective controlled trials conducted among groups of frail elderly strongly suggest that such individuals do benefit from daily oral supplementation of at least 800 IU of vit D in that muscle strength is enhanced and falls are decreased, decreasing the risk of bone fractures in this vulnerable population [35]. These data imply that the present recommended daily allowance (RDA) for vit D in those >70 years old (600 IU/day) [77] is likely inadequate and that enhancing vit D intake in older frail individuals, particularly those who are housebound or institutionalized, would be likely to confer a health benefit. Other research has established that doubling or tripling the standard vit D supplement doses and/or enriching more foods with vit D would be very safe [51,78]. Daily doses exceeding 10,000 IU appear to be required for signs of vit D toxicity [51], creating a broad safety margin.

Finally, overwhelming data summarized above establish UV as a carcinogen responsible for more than 1 million skin cancers per year in the United States alone [2], as well as for photoaging [19], an essentially universal problem among Caucasians in middle age and beyond; and that lifelong safe sun practices minimize both risks.

12. Conclusions and recommendations

The medical research community has an obligation to determine optimal vit D levels in different population groups. If supplementation of apparently healthy individuals to higher than conventionally recommended vit D levels can be shown to confer a health benefit, in the present or in the future, the same community should advocate strongly for increased vit D RDAs and increased availability of vit D in standard vitamin supplements and enriched foods. However, there is an equal obligation not to confuse epidemiologic associations with cause-and-effect relationships and not to unwittingly undermine a public health message of proven benefit. Safe sun practices are fully compatible with achieving optimal vit D levels.

The confusing and misleading media coverage of the "vit D controversy" over the past few years has unfortunately indeed undermined the campaign to reduce the current excessive sun exposure in our society. This situation can best be corrected by joint efforts of the vit D and dermatology communities, speaking with one voice. A mandatory first step toward this goal is discussion between these groups in order to exchange perspectives and reach consensus. The first of such meetings has already occurred. In July 2004 the AAD convened a consensus conference between interested Academy members, researchers in the vit D area, and representatives of government agencies [79]. In April 2006 the Vitamin D Workshop invited the author to participate in its every 3-year meeting, resulting in the present manuscript. Additional joint meetings are contemplated.

A major opportunity presented by joint meetings among investigators and thought leaders in both fields is the development of responsible, mutually satisfactory public health messages. Once such messages have been crafted, they need to be communicated to the major professional organizations in both fields, so as to have them formally adopted. Once this is accomplished, the messages can be shared both with the general membership, for their information and use in personal communications, as well as with the media, to be included in future relevant stories with a goal of providing sound public education and dispelling the appearance of disagreement among mainstream professionals in this area.

The above agenda has already been accomplished in part. With continued good will and enhanced communication, the obfuscation surrounding the sunshine vitamin will hopefully become a thing of the past.

References

[1] US DoH, U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Report on carcinogens, 11th ed., Exposure to sunlamps or sunbeds. Available from: http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s183uvrr.pdf, accessed 23 September 2005.
[2] A. Jemal, R.C. Tiwari, T. Murray, et al., Cancer statistics 2004, CA Cancer J. Clin. 54 (1) (2004) 8–29.
[3] G.M. Findlay, Ultraviolet light and skin cancer, Lancet 215 (1928) 1070.
[4] H.F. Blum, Carcinogenesis by Ultraviolet Light, Princeton University Press, Princeton, NJ, 1959.
[5] B.C. Vitasa, H.R. Taylor, P.T. Strickland, et al., Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen, Cancer 65 (12) (1990) 2811–2817.
[6] M. Aszterbaum, J. Epstein, A. Oro, et al., Ultraviolet and ionizing radiation enhance the growth of BCCs and trichoblastomas in patched heterozygous knockout mice, Nat. Med. 5 (11) (1999) 1285–1291.
[7] F. Yamazaki, H. Okamoto, Y. Matsumura, K. Tanaka, T. Kunisada, T. Horio, Development of a new mouse model (xeroderma pigmentosum a-deficient, stem cell factor-transgenic) of ultraviolet B-induced melanoma, J. Invest. Dermatol. 125 (3) (2005) 521–525.
[8] K. Kannan, N.E. Sharpless, J. Xu, R.C. O'Hagan, M. Bosenberg, L. Chin, Components of the Rb pathway are critical targets of UV mutagenesis in a murine melanoma model, Proc. Natl. Acad. Sci. U.S.A. 100 (3) (2003) 1221–1225.
[9] K.H. Kraemer, M.M. Lee, A.D. Andrews, W.C. Lambert, The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm, Arch. Dermatol. 130 (8) (1994) 1018–1021.
[10] M.R. Hussein, Ultraviolet radiation and skin cancer: molecular mechanisms, J. Cutan. Pathol. 32 (3) (2005) 191–205.

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

[11] M.R. Gailani, D.J. Leffell, A. Ziegler, E.G. Gross, D.E. Brash, A.E. Bale, Relationship between sunlight exposure and a key genetic alteration in basal cell carcinoma, J. Natl. Cancer Inst. 88 (6) (1996) 349–354.
[12] Z. Holikova, D. Massi, T. Lotti, J. Hercogova, Insight into the pathogenesis of sporadic basal cell carcinoma, Int. J. Dermatol. 43 (12) (2004) 865–869.
[13] J.P. Lacour, Carcinogenesis of basal cell carcinomas: genetics and molecular mechanisms, Br. J. Dermatol. 146 (Suppl. 61) (2002) 17–19.
[14] J.M. Elwood, J. Jopson, Melanoma and sun exposure: an overview of published studies, Int. J. Cancer 73 (2) (1997) 198–203.
[15] D.E. Brash, A. Ziegler, A.S. Jonason, J.A. Simon, S. Kunala, D.J. Leffell, Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion, J. Investig. Dermatol. Symp. Proc. 1 (2) (1996) 136–142.
[16] R.H. Edwards, M.R. Ward, H. Wu, et al., Absence of BRAF mutations in UV-protected mucosal melanomas, J. Med. Genet. 41 (4) (2004) 270–272.
[17] D.L. Cummins, J.M. Cummins, H. Pantle, M.A. Silverman, A.L. Leonard, A. Chanmugam, Cutaneous malignant melanoma, Mayo Clin. Proc. 81 (4) (2006) 500–507.
[18] T.S. Housman, S.R. Feldman, P.M. Williford, et al., Skin cancer is among the most costly of all cancers to treat for the Medicare population, J. Am. Acad. Dermatol. 48 (3) (2003) 425–429.
[19] M. Yaar, B.A. Gilchrest, Aging of skin, in: I.M. Freedberg, A.Z. Eisen, K. Wolff, K.F. Austen, L.A. Goldsmith, S.I. Katz (Eds.), Fitzpatrick's Dermatology in General Medicine, vol. 2, McGraw-Hill, New York, 2003, pp. 1386–1398.
[20] L.H. Kligman, R.M. Sayre, An action spectrum for ultraviolet induced elastosis in hairless mice: quantification of elastosis by image analysis, Photochem. Photobiol. 53 (2) (1991) 237–242.
[21] A.C. Geise, Is sunlight good for you? in: K.C. Smith (Ed.), Living With Our Sun's Ultraviolet Rays, Premium Press, New York, 1976, p. 35.
[22] M.R. Albert, K.G. Ostheimer, The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 3 J. Am. Acad. Dermatol. 49 (6) (2003) 1096–1106.
[23] B. Gilchrest, Anti-sunshine Vitamin A, Nat. Med. 5 (4) (1999) 376–377.
[24] B.A. Gilchrest, M.S. Eller, The tale of the telomere: implications for prevention and treatment of skin cancers, J. Invest. Dermatol. Symp. Proc. 10 (2) (2005) 124–130.
[25] A.C. Geller, D.R. Brooks, G.A. Colditz, H.K. Koh, A.L. Frazier, Sun protection practices among offspring of women with personal or family history of skin cancer, Pediatrics 117 (4) (2006) 688–694.
[26] A.J. Swerdlow, M.A. Weinstock, Do tanning lamps cause melanoma? An epidemiologic assessment, J. Am. Acad. Dermatol. 38 (1) (1998) 89–98.
[27] J.A. Parrish, K.F. Jaenicke, R.R. Anderson, Erythema and melanogenesis action spectra of normal human skin, Photochem. Photobiol. 36 (1982) 187–191.
[28] S.E. Freeman, H. Hacham, R.W. Gange, D.J. Maytum, J.C. Sutherland, B.M. Sutherland, Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated in situ with ultraviolet light, Proc. Natl. Acad. Sci. U.S.A. 86 (14) (1989) 5605–5609.
[29] J.S. Adams, T.L. Clemens, J.A. Parrish, M.F. Holick, Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and Vitamin-D-deficient subjects, N. Engl. J. Med. 306 (12) (1982) 722–725.
[30] M.F. Holick, J.A. MacLaughlin, M.B. Clark, et al., Photosynthesis of previtamin D3 in human skin and the physiologic consequences, Science 210 (4466) (1980) 203–205.
[31] S.L. Walker, J.L.M. Hawk, A.R. Young, Acute and chronic effects of ultraviolet radiation on the skin, in: I.M. Freedberg, A.Z. Eisen, K. Wolff, K.F. Austen, L.A. Goldsmith, S.I. Katz (Eds.), Fitzpatrick's Dermatology in General Medicine, vol. 1, sixth ed., McGraw-Hill, New York, NY, 2003, pp. 1275–1282.
[32] T.B. Fitzpatrick, The validity and practicality of sun-reactive skin types I through VI, Arch. Dermatol. 124 (6) (1988) 869–871.
[33] M.F. Holick, M. Jenkins, The UV Advantage: ibooks, Incorporated, 2004.
[34] T.L. Clemens, J.S. Adams, S.L. Henderson, M.F. Holick, Increased skin pigment reduces the capacity of skin to synthesise Vitamin D3, Lancet 1 (8263) (1982) 74–76.
[35] D. Wolpowitz, B.A. Gilchrest, The Vitamin D questions: how much do you need and how should you get it? J. Am. Acad. Dermatol. 54 (2) (2006) 301–317.
[36] N.H. Bell, Vitamin D metabolism, aging, and bone loss, J. Clin. Endocrinol. Metab. 80 (4) (1995) 1051.
[37] A.G. Need, H.A. Morris, M. Horowitz, C. Nordin, Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D, Am. J. Clin. Nutr. 58 (6) (1993) 882–885.
[38] J.K. Robinson, R. Amonette, S.W. Wyatt, B.A. Bewerse, W.F. Bergfeld, P.K. Farris, Executive summary of the national "sun safety: protecting our future", in: Proceedings of the Conference on American Academy of Dermatology and Centers for Disease Control and Prevention, New York, NY, 1–2 May 1997, J. Am. Acad. Dermatol. 38 (5, Part 1) (1998) 774–780.
[39] C.F. Garland, F.C. Garland, E.D. Gorham, Can colon cancer incidence and death rates be reduced with calcium and Vitamin D? Am. J. Clin. Nutr. 54 (Suppl. 1) (1991) 193S–201S.
[40] C.F. Garland, F.C. Garland, E.D. Gorham, Calcium and Vitamin D. Their potential roles in colon and breast cancer prevention, Ann. N. Y. Acad. Sci. 889 (1999) 107–119.
[41] M.F. Holick, Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications, in: M. Favus (Ed.), Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, fourth ed., Lippincott Williams & Wilkins, Philadelphia, PA, 1999, pp. 92–98.
[42] M. Bigby, M. Szklo, Evidence-based dermatology, in: I.M. Freedberg, A.Z. Eisen, K. Wolff, K.F. Austen, L.A. Goldsmith, S.I. Katz (Eds.), Fitzpatrick's Dermatology in General Medicine, vol. 2, sixth ed., McGraw-Hill, New York, 2003, pp. 2301–2311.
[43] M.V. Grau, J.A. Baron, R.S. Sandler, et al., Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial, J. Natl. Cancer Inst. 95 (23) (2003) 1765–1771.
[44] P. Tuohimaa, L. Tenkanen, M. Ahonen, et al., Both high and low levels of blood Vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries, Int. J. Cancer 108 (1) (2004) 104–108.
[45] M.D. Gross, Vitamin D and calcium in the prevention of prostate and colon cancer: new approaches for the identification of needs, J. Nutr. 135 (2) (2005) 326–331.
[46] T.J. Hartman, P.S. Albert, K. Snyder, et al., The association of calcium and Vitamin D with risk of colorectal adenomas, J. Nutr. 135 (2) (2005) 252–259.
[47] S. Majewski, M. Skopinska, M. Marczak, A. Szmurlo, W. Bollag, S. Jablonska, Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis, J. Invest. Dermatol. Symp. Proc. 1 (1) (1996) 97–101.
[48] J. Wactawski-Wende, J.M. Kotchen, G.L. Anderson, et al., Calcium plus Vitamin D supplementation and the risk of colorectal cancer, N. Engl. J. Med. 354 (7) (2006) 684–696.
[49] M.R. Forman, B. Levin, Calcium plus Vitamin D3 supplementation and colorectal cancer in women, N. Engl. J. Med. 354 (7) (2006) 752–754.
[50] E. Giovannucci, Y. Liu, E.B. Rimm, et al., Prospective study of predictors of Vitamin D status and cancer incidence and mortality in men, J. Natl. Cancer Inst. 98 (7) (2006) 451–459.
[51] R. Vieth, Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety, Am. J. Clin. Nutr. 69 (5) (1999) 842–856.
[52] B.J. Boucher, Sunlight "D"ilemma, Lancet 357 (9260) (2001) 961.
[53] M.S. Calvo, S.J. Whiting, C.N. Barton, Vitamin D intake: a global perspective of current status, J. Nutr. 135 (2) (2005) 310–316.
[54] R.D. Utiger, The need for more Vitamin D, N. Engl. J. Med. 338 (12) (1998) 828–829.
[55] R.L. Hornung, K.H. Magee, W.J. Lee, L.A. Hansen, Y.C. Hsieh, Tanning facility use: are we exceeding Food and Drug Administration limits? J. Am. Acad. Dermatol. 49 (4) (2003) 655–661.

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028

[56] J.K. Robinson, D.S. Rigel, R.A. Amonette, Trends in sun exposure knowledge, attitudes, and behaviors: 1986 to 1996, J. Am. Acad. Dermatol. 37 (2, Part 1) (1997) 179–186.
[57] R.P. Dellavalle, E.R. Parker, N. Cersonsky, et al., Youth access laws: in the dark at the tanning parlor? Arch. Dermatol. 139 (4) (2003) 443–448.
[58] M.F. Demierre, Time for the national legislation of indoor tanning to protect minors, Arch. Dermatol. 139 (4) (2003) 520–524.
[59] H.T. Kwon, J.A. Mayer, K.K. Walker, H. Yu, E.C. Lewis, G.E. Belch, Promotion of frequent tanning sessions by indoor tanning facilities: two studies, J. Am. Acad. Dermatol. 46 (5) (2002) 700–705.
[60] S.E. Whitmore, W.L. Morison, C.S. Potten, C. Chadwick, Tanning salon exposure and molecular alterations, J. Am. Acad. Dermatol. 44 (5) (2001) 775–780.
[61] J.A. Oliphant, J.L. Forster, C.M. McBride, The use of commercial tanning facilities by suburban Minnesota adolescents, Am. J. Public Health 84 (3) (1994) 476–478.
[62] R. Bohannon, State Affairs Division, AAD Association, personal communication, May 2006.
[63] ITA responds to flawed study on links between indoor tanning, skin cancer, The National Tanning Training Institute, available from: http://www.tanningtraining.com/hotnews/61h181519848010.html.
[64] UV Foundation Applauds Vitamin D Research Results, U.S. Newswire http://releases.usnewswire.com/GetRelease.asp?id=58835, accessed January 4, 2006.
[65] J. Westerdahl, C. Ingvar, A. Masback, N. Jonsson, H. Olsson, Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity, Br. J. Cancer 82 (9) (2000) 1593–1599.
[66] J.M. Spencer, R.A. Amonette, Indoor tanning: risks, benefits, and future trends, J. Am. Acad. Dermatol. 33 (2, Part 1) (1995) 288–298.
[67] J.A. Levine, M. Sorace, J. Spencer, D.M. Siegel, The indoor UV tanning industry: a review of skin cancer risk, health benefit claims, and regulation, J. Am. Acad. Dermatol. 53 (6) (2005) 1038–1044.
[68] J. Oeppen, J.W. Vaupel, Demography. Broken limits to life expectancy, Science 296 (5570) (2002) 1029–1031.
[69] D.L. Hoyert, M.P. Heron, S.L. Murphy, H.C. Kung, Deaths: final data for 2003, Natl. Vital Stat. Rep. 54 (13) (2006) 1–120.
[70] V.A. Bohr, R.M. Anson, DNA damage, mutation and fine structure DNA repair in aging, Mutat. Res. 338 (1–6) (1995) 25–34.
[71] S. Moriwaki, S. Ray, R.E. Tarone, K.H. Kraemer, L. Grossman, The effect of donor age on the processing of UV-damaged DNA by cultured human cells: reduced DNA repair capacity and increased DNA mutability, Mutat. Res. 364 (2) (1996) 117–123.
[72] T.R. Welch, W.H. Bergstrom, R.C. Tsang, Vitamin D-deficient rickets: the reemergence of a once-conquered disease, J. Pediatr. 137 (2) (2000) 143–145.
[73] S.R. Kreiter, R.P. Schwartz, H.N. Kirkman Jr., P.A. Charlton, A.S. Calikoglu, M.L. Davenport, Nutritional rickets in African American breast-fed infants, J. Pediatr. 137 (2) (2000) 153–157.
[74] L.Y. Matsuoka, L. Ide, J. Wortsman, J.A. MacLaughlin, M.F. Holick, Sunscreens suppress cutaneous Vitamin D3 synthesis, J. Clin. Endocrinol. Metab. 64 (6) (1987) 1165–1168.
[75] N. Bech-Thomsen, H.C. Wulf, Sunbathers' application of sunscreen is probably inadequate to obtain the sun protection factor assigned to the preparation, Photodermatol. Photoimmunol. Photomed. 9 (6) (1992) 242–244.
[76] S.R. Pinnell, Cutaneous photodamage, oxidative stress, and topical antioxidant protection, J. Am. Acad. Dermatol. 48 (1) (2003) 1–19, quiz 20–12.
[77] 1997 RDA Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, National Academy Press, Washington, DC, 1997.
[78] B.W. Hollis, Circulating 25-hydroxyvitamin D levels indicative of Vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for Vitamin D, J. Nutr. 135 (2) (2005) 317–322.
[79] H.W. Lim, B.A. Gilchrest, K.D. Cooper, et al., Sunlight, tanning booths, and Vitamin D, J. Am. Acad. Dermatol. 52 (5) (2005) 868–876.

Please cite this article in press as: B.A. Gilchrest, Sun protection and Vitamin D: Three dimensions of obfuscation, J. Steroid Biochem. Mol. Biol. (2007), doi:10.1016/j.jsbmb.2006.12.028