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News and Views

The Evolution of Light Skin Color: Role of Vitamin D Disputed

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Vitamin D is essential for calcium and phosphorus homeostasis and for the growth, development, and structural integrity of the skeleton. Over 90% of the body's requirements for vitamin D derive from cutaneous photosynthesis, with dietary sources accounting for the remainder. Ultraviolet-B radiation (UVB) penetrates the epidermis where it photolyses 7-dehydrocholesterol to previtamin D_3, which is then converted to vitamin D_3. The latter is translocated to the circulation via the dermal vasculature; it is hydroxylated (enzymatically) in the liver to 25-hydroxyvitamin D (25-OHD) and then in the kidneys to 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) (Holick, 2007). Although the serum 25-OHD concentration gives the best index of an individual's vitamin D status, 1,25-$(OH)_2$D is the most active form biologically in mediating the effects on intestine (calcium absorption) and bone. The serum concentration of 1,25-$(OH)_2$D is tightly regulated and is not ordinarily dependent on sun exposure or diet.

Severe vitamin D deficiency causes nutritional rickets in children and adolescents, and osteomalacia and osteoporosis in adults. Rickets is caused by defective mineralization of the collagen matrix in newly formed osteoid tissue, with resultant bone softening. It is characterized by crippling deformities (notably bowing of the lower limb bones and narrowing of the pelvic outlet), muscle weakness, and, in neonates born to vitamin D-deficient mothers, by potentially fatal hypocalcaemia (manifesting as convulsions, heart failure) (Wharton and Bishop, 2003; Holick, 2006b).

Rickets is a sunlight deprivation disease, which emerged on an epidemic scale during the industrial revolution, when cities in Europe and North America were enveloped in a perpetual twilightlike haze of coal smoke. By the end of the 19th century, up to 90% of children in these centers suffered from rickets.

SKIN DEPIGMENTATION: THE VITAMIN D HYPOTHESIS

Originated by Murray (1934), the vitamin D hypothesis was revived and popularized by Loomis (1967), and, more recently, refined by Jablonski and Chaplin (2000) with the application of quantitative UVB data. It is based on the observation that the skin color of the world's indigenous peoples follows a clinical distribution: the darkest populations inhabit the equatorial and tropical belt; the most pale-skinned the regions above 50°N; and those of intermediate pigmentation the middle latitudes. Skin reflectances exhibit a high-positive and high-negative correlation with latitude and UVB measurements, respectively (Jablonski and Chaplin, 2000; Parra, 2007), i.e., higher reflectances (lighter skin color) are strongly associated with higher latitudes and lower UVB. At high latitudes, UVB intensity is reduced throughout the year but profoundly so in the winter months. At this latitude, solar elevation is low and UVB has to travel a more oblique and longer course to the earth, thereby being subjected to increased scattering and ozone absorption in the upper atmosphere.

Anatomically modern, and presumably deeply pigmented, humans (*Homo sapiens*) arose in sub-Saharan Africa 100,000–150,000 years ago. Some of them left the continent and advanced northward, arriving in Europe 35,000–40,000 years ago. The hypothesis proposes that as these northbound migrants proceeded to higher latitudes they underwent progressive depigmentation until they ultimately attained the light-colored appearance typical of contemporary northern Europeans. This pigmentary transformation was a physiological adaptation to the less intense UVB at these latitudes. The melanin of dark-skinned individuals would have impeded the epidermal transmission of an already attenuated UVB and inhibited the synthesis of previtamin D_3 and vitamin D_3. (Melanin is an excellent sunscreen.) The resultant vitamin D deficiency would have produced rickets, which, with its deformities and muscle weakness, would have seriously handicapped mobility and the ability to forage for food. In the female, a contacted pelvis would have led to obstructed labor and death of mother and baby (in the absence of Caesarean section); and even if the infant was successfully delivered, there was the danger of brain damage or life-threatening hypocalcaemia. There is little doubt that in the hostile environment of late-Pleistocene Europe rickets would have imperiled reproductive fitness and survival. Natural selection would have favored the genes for light skin color and promoted depigmentation. Conversely, in the topics (with their intense and perennial UVB), selection pressures would have driven the evolution of dark pigmentation owing to the remarkable photoprotective properties of melanin (Robins, 1991; Jablonski and Chaplin, 2000).

WHY THE VITAMIN D HYPOTHESIS IS FLAWED

The hypothesis was initially predicated on data from the 1920s and 1930s, which showed that blacks in the

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United States had a twofold to threefold increase over whites in the prevalence of clinical rickets (Robins, 1991). Recent surveys also record substantially lower serum 25-OHD levels, and a markedly higher occurrence of vitamin D deficiency, in African Americans compared with white Americans (Looker et al., 2002; Nesby-O'Dell et al., 2002; Gordon et al., 2004). Exposure in vitro of isolated skin specimens and in vivo of human volunteers to UVB showed that hypopigmented (Caucasian) skin was five to 10 times more efficient at forming vitamin D_3 than melanized (African American) skin (Chen et al., 2007). Moreover, the UVB doses that dramatically raised serum vitamin D levels in whites by up to 60-fold had no significant effect on heavily pigmented African Americans (Clemens et al., 1982). At these doses, therefore, deep melanin pigment reduced cutaneous synthesis of vitamin D_3 by as much as 99%, the equivalent of a sunscreen with a sun protection factor of 15 (Holick, 2006a).

The hypothesis is weakened, however, because this epidermal melanin barrier is not absolute; it is surmountable provided that the UVB doses or the irradiation exposure times are increased according to the degree of pigmentation. For example, a sixfold increase in either of these variables brought vitamin D production in highly melanized skin in line with that of lightly pigmented skin (Holick et al., 1981; Clemens et al., 1982). Furthermore, single or repeated whole-body UVB (artificially administered) evoked similar increases in 25-OHD concentrations in Asian, black, and white subjects (Stamp, 1975; Lo et al., 1986; Brazerol et al., 1988). These experiments with simulated sunlight were confirmed in the natural setting by Ellis et al. (1977), who noted that groups of Asian, West Indian, and European adolescents with vitamin D deficiency and living in England showed marked and comparable increases respectively in serum 25-OHD concentrations during the spring and summer months (March to October). The conclusion from all of these studies is that there is an intrinsic capacity for vitamin D_3 synthesis regardless of skin color, provided that UVB exposure is adequate.

Skin pigmentation is not a primary factor in causing rickets, as exemplified in Britain where Asian immigrants and their families were far more susceptible to vitamin D deficiency and rickets than the more deeply pigmented West Indians (African Caribbeans) (Ellis et al., 1976; Ford et al., 1976). A survey in the high-latitude city of Glasgow, Scotland (56°N), found no cases of florid rickets in 100 African children, 100 Chinese children, or 100 Scottish children, but there were 10 cases in 200 Asian children (Goel et al., 1976). (The problem of Asian rickets and osteomalacia in Britain is probably due to multiple factors, e.g., diet, genetic predisposition, socio-cultural attitudes to clothing, and sun exposure.)

Webb et al. (1988) demonstrated that irrespective of skin pigmentation there was no photolysis of 7-DHC to previtamin D_3 in Boston (42°N) and Edmonton (52°N) from November to February (inclusive) and from October to March, respectively. This dormancy of vitamin D production for up to 6 months at these latitudes is offset by the synthesis, storage, and accrual of vitamin D_3 during sun exposure in summer. Mawer et al. (1972) established that vitamin D and 25-OHD are stored for extended periods in body tissues, predominantly fat. In their vitamin D-deficient patients, a large intravenous dose of radioactive vitamin D_3 was rapidly cleared from the circulation and, together with its 25-OHD metabolite, was distributed to the depleted storage sites. (These findings of Mawer et al. were misinterpreted by Jablonski and Chaplin (2000: 78) to imply that deficient subjects had a *reduced* potential for vitamin D storage.)

This cumulative storage property of vitamin D was neatly illustrated by a study of gardeners in Dundee, Scotland (56°N), who worked outdoors throughout the year. They not only had considerably higher serum 25-OHD levels than indoor workers, but these levels increased from July (the month of maximum UVB exposure) until they peaked in November and December (when UVB was in sharp decline) (Devgun et al., 1981). At high latitudes, therefore, where vitamin D_3 photosynthesis ceases during the winter months, the body maintains an acceptable vitamin D status on a year-round basis by mobilizing reservoirs in fat and other tissues that have been built up during the summer (Webb and Holick, 1988).

The question arises as to what extent early *Homo sapiens* at latitudes above 40°N would have been vulnerable to rickets. Historically, rickets is a product of urbanization, industrialization, and civilization; it was rampant in the smog-ridden cities of Europe and North America during the industrial revolution but conspicuously absent in the surrounding rural areas with their clean air and outdoor lifestyles. Sporadic cases of rickets were described in European skeletal material dating from the Neolithic period until medieval times, but its prevalence was very low; it occurred in about one percent of skeletons from Swedish and Danish cemeteries (AD 1100–1550), and there was no evidence of it in Anglo-Saxon remains from East Anglia. In pre-Columbian North and South America, it hardly existed (Wells, 1975).

Where instances of rickets occurred in preindustrial times, these were most likely due to sunlight deprivation. Ortner and Mays (1998) identified eight cases of active rickets (out of a sample of 687 excavated skeletons) from a churchyard in North Yorkshire, England, dating to the Middle Ages. All were infants aged from 3 to 18 months, and it was conjectured that these children had been sickly and thus kept indoors in dark, smoky houses. An examination of graveyard material from medieval cities in Hungary showed an increase in the frequency of rickets from 0.7% to 2.5% from the 10th to the 13th centuries AD, respectively (Wells, 1975), probably because of the proliferation of windowless houses during that period.

The strongest case against the hypothesis is that the smoky and rickets-producing urban environments of the industrial revolution (and even earlier) were diametrically opposed to the sparsely inhabited, open-air, and unpolluted landscapes in which Upper Paleolithic Europeans lived and roamed. These individuals would have spent their daylight hours during late spring and summer under open skies and, partly clad in animal skins, they would have exposed a relatively large body area to an intensity of UVB that was optimal for cutaneous vitamin D_3 photosynthesis. This quality and quantity of UVB (possibly enhanced during glacial periods by reflectivity from snow and ice), maintained daily for 4 or 5 months, would have amply fulfilled their physiological vitamin D requirements for the rest of the year.

The decisive question though is whether early, deeply pigmented *Homo sapiens* in northern Europe would have benefited from the ambient summer UVB or whether they would have been deprived of vitamin D by virtue of melanin blockade. As discussed earlier, dark-skinned persons are endowed with the same capability to

manufacture vitamin D_3 as their lighter counterparts. Estimates are that fair-skinned people living in North America or Europe require only 5–10 min sun exposure of the arms and legs between 10:00 and 15:00 three times a week (except winter) to prevent vitamin D insufficiency (Webb and Holick, 1988; Holick, 2006a; Holick, 2007). If we assume that very dark individuals at latitudes above 50° need 10–20 times that duration of exposure to override the melanin barrier, then this would equate to about 1–3 h thrice weekly, a quota that would have been achievable within 1 or 2 days of the hunter-gatherer life of Upper Paleolithic Europeans. It is highly improbable that rickets ever emerged in that setting. Thus, vitamin D status could not have constituted the fitness differential between lightly pigmented and darkly pigmented individuals at high latitudes that favored the evolutionary selection of the former. There was no risk of vitamin D toxicity from prolonged UVB exposure, as mistakenly contemplated by Loomis (1967), because excessive sunlight degrades previtamin D_3 and vitamin D_3 into inert photoproducts (Holick et al., 1981; Webb and Holick, 1988).

In recent times, there has been a resurgence of vitamin D insufficiency and deficiency, not only in high-latitude countries but in some of the sunniest regions in the world (Holick, 2006b). The explanation is that present-day populations receive inadequate solar insolation for various reasons: indoor working and living conditions, deliberate sun avoidance, and the wearing of concealing clothing.

A survey conducted across three regions of Australia of differing latitudes (27°S, 38°S, and 43°S) noted the high prevalence of vitamin D insufficiency but found, unexpectedly, that season and latitude together accounted for less than 20% of the variation in serum 25-OHD levels (van der Mei et al., 2007). This indicated that interindividual differences in sun-related behavior (duration of exposure, amount of clothing) vastly outweighed the more obvious seasonal and latitudinal differences in determining vitamin D status. Similarly, the marked black–white disparity in the United States in the occurrence of vitamin D inadequacy is not predominantly a consequence of skin color but rather a reflection of behavior or circumstances that restrict sun exposure. An example is a study in Cincinnati (39°N) where black breast-fed infants had strikingly lower 25-OHD levels compared with their white counterparts: the former were confined indoors and had negligible solar exposure, whereas the latter had regular outings in the sunshine (Specker et al., 1985).

Socioeconomic circumstances largely account for the chronic sunlight deprivation experienced by many black babies. Compared with their white compatriots, African-American mothers tend to be financially and educationally disadvantaged and to live in crowded neighborhoods. Consequently, they lack the leisure time, the amenities (ready access to gardens and parks), and the resources (baby carriages and cars) to take their infants on regular outdoor excursions in spring and summer, thereby maximizing vitamin D production. It is not surprising that, where cases of rickets have been reported in the United States in recent times, these have affected predominantly black children.

The above arguments do not negate the effect of melanin pigmentation on vitamin D_3 production, but they shift its influence from a primary to a secondary role, i.e., where UVB exposure is already marginal, a dark-skin color will accentuate the problem and contribute significantly to vitamin D deficiency.

It is crucial to recognize that the overwhelming majority of people worldwide with vitamin D insufficiency and deficiency have the subclinical form; they are apparently healthy and free of skeletal deformities (Gordon et al., 2004; Rockell et al., 2005; Holick, 2006b). A survey of 232 black (East African) immigrant children living in Melbourne, Australia (37°S), found that although vitamin D insufficiency and the more severe vitamin D deficiency occurred in 81% and 44%, respectively, none showed clinical signs of rickets (McGillivray et al., 2007). In the event that early, dark-skinned humans at high latitudes did develop vitamin D deficiency, it is highly probable that they would have remained asymptomatic. In an evolutionary context, vitamin D deficit per se would not have exerted a negative selective action against dark pigmentation unless it translated into florid rickets, with the attendant deformities and disabilities that curtailed reproductive fitness and survival.

There is another perspective that undermines the hypothesis. Matsuoka et al. (1991) demonstrated that after single-dose, whole-body UVB exposure black subjects had distinctly lower serum vitamin D_3 levels than whites; but differences between the two groups narrowed after liver hydroxylation to 25-OHD and disappeared after kidney hydroxylation to 1,25-$(OH)_2$D. These findings suggest that there is a compensatory mechanism whereby, in the presence of vitamin D_3 suppression by melanin, the liver and kidney hydroxylating enzymes are activated in tandem to ensure that the concentration of the biologically active 1,25-$(OH)_2$D metabolite is normalized and kept constant regardless of ethnic pigmentation (Matsuoka et al., 1991, 1995).

Homeostatic control of bone metabolism and function is mediated by a complex series of feedback interactions between vitamin D, calcium, phosphorus, and parathyroid hormone (one action of which is to enhance the enzymatic conversion of 25-OHD to 1,25-$(OH)_2$D) (Holick, 2007). Blacks have optimally modulated this vitamin D endocrine system to protect the skeleton from the adverse consequences of reduced vitamin D_3 synthesis (Looker et al., 2002; Harris, 2006). These adaptive processes fail in extreme vitamin D deficiency (and possibly also in the elderly), but they are decidedly effective in the moderate vitamin D deficit state that affects nearly half of African Americans. The latter, for example, have a lower prevalence of osteoporosis, a lower incidence of fractures and a higher bone mineral density than white Americans, who generally exhibit a much more favorable vitamin D status (Henry and Eastell, 2000; Hannan et al., 2008).

In the past decade, there has been an increasing focus on the nonskeletal functions of vitamin D. The biologically active metabolite 1,25-$(OH)_2$D is produced locally in organs such as breast, colon, and prostate, where it is believed to regulate cellular growth and potentially to inhibit cancer development and progression. It is active in the immune system (macrocytes and lymphocytes) and it may promote immunity against infectious diseases such as tuberculosis. It is also claimed to prevent conditions such as cardiovascular disease, hypertension, diabetes, and rheumatoid arthritis (Holick 2006a, 2007). Much of this work is still speculative and experimental, and the evidence linking vitamin D to the various disease states is inconsistent and dogged by confounding variables (Wolpowitz and Gilchrest, 2006). Proponents of the vitamin D hypothesis have not yet been able to structure these ideas into a specific evolutionary formulation; indeed many of the diseases mentioned above manifest

later in life (after the reproductive period) and so have negligible fitness consequences. Infectious diseases tend to occur within high-density populations and not within small and scattered nomadic groups such as those that characterized Upper Paleolithic humans. But, since the thrust of this work has been to exclude vitamin D deficiency in these early Europeans, neither the skeletal nor the nonskeletal effects of such deficiency would pertain to the skin color debate.

CONCLUSION

The vitamin D hypothesis has gained widespread acceptance as the standard explanation for light skin color in northern Europe. It has received strong endorsement in two recent and reputable review publications (Jablonski, 2004; Parra, 2007), and it threatens to become enshrined in evolutionary lore. Although I have previously advanced detailed counter-arguments (Robins, 1991), in this work I have reformulated and updated the opposing position in the hope that it will evoke discussion and reassessment. I believe that this hypothesis, which superficially appears elegant and convincing, is invalidated by current research. Alternative hypotheses deserve to be revisited but, more important, new ideas need to be sought to unravel the enigma of human depigmentation.

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