Skin-Pigment Regulation of Vitamin-D Biosynthesis in Man

Variation in solar ultraviolet at different latitudes may have caused racial differentiation in man.

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Vitamin D mediates the absorption of calcium from the intestine and the deposition of inorganic minerals in growing bone; this "sunshine vitamin" is produced in the skin, where solar rays from the far-ultraviolet region of the spectrum (wavelength, 290 to 320 millimicrons) convert the provitamin 7-dehydrocholesterol into natural vitamin D (*1*) (Fig. 1).

Unlike other vitamins, this essential calcification factor is not present in significant amounts in the normal diet; it occurs in the liver oils of bony fishes and, in very small amounts, in a few foodstuffs in the summer (see Table 1). Almost none is present in foodstuffs in winter.

Chemical elucidation of the nature of vitamin D has made it possible to eradicate rickets from the modern world through artificial fortification of milk and other foods with this essential factor. Before this century, however, mankind resembled the living plant in being dependent on sunshine for his health and well-being, a regulated amount of vitamin D synthesis being essential if he were to avoid the twin dangers of rickets on the one hand and an excess of vitamin D on the other.

Unlike the water-soluble vitamins, too much vitamin D causes disease just as too little does, for the calcification process must be regulated and controlled much as metabolism is regulated by the thyroid hormone. The term *vitamin D* is, in fact, almost a misnomer, for this factor resembles the hormones more closely than it resembles the dietary vitamins in that it is not normally ingested but is synthesized in the body by one organ—the skin—and then distributed by the blood stream for action elsewhere in the body. As in the case of hormones, moreover, the rate of synthesis of vitamin D must be regulated within definite limits if both failure of calcification and pathological calcifications are to be avoided.

Synthesis of too little vitamin D results in the bowlegs, knock-knees, and twisted spines (scoliosis) associated with rickets in infants whose bones are growing rapidly. Similar defects in ossification appear in older children and women deprived of this vitamin; puberty, pregnancy, and lactation predispose the individual toward osteomalacia, which is essentially adult rickets. In osteomalacia the bones become soft and pliable, a condition which often leads to pelvic deformities that create serious hazards during childbirth. Such deformities were common, for example, among the women of India who followed the custom of purdah, which demands that they live secluded within doors and away from the calcifying power of the sun's rays (*2*). Cod-liver oil or other source of vitamin D is a specific for rickets and osteomalacia, the usual recommended daily dosage being 10 micrograms of 400 international units (1 I.U.=0.025 microgram of vitamin D).

Ingestion of vitamin D in amounts above about 100,000 I.U. (2.5 milligrams) per day produces the condition known as hypervitaminosis D, in which the blood levels of both calcium and phosphorus are markedly elevated and multiple calcifications of the soft tissues of the body appear. Ultimate death usually follows renal disease secondary to the appearance of kidney stones (*3*). Although this condition has been described only in patients given overdoses of vitamin D by mouth, similarly toxic results would probably follow the natural synthesis of equal doses of vitamin D by unpigmented skin exposed to excessive solar radiation. The body appears to have no power to regulate the amount of vitamin D absorbed from food and no power to selectively destroy toxic doses once they have been absorbed. These facts suggest that the physiological means of regulating the concentration of vitamin D in the body is through control of the rate of photochemical synthesis of vitamin D in the skin.

It is the thesis of this article that the rate of vitamin-D synthesis in the stratum granulosum of the skin is regulated by the twin processes of pigmentation and keratinization of the overlying stratum corneum, which allow only regulated amounts of solar ultraviolet radiation to penetrate the outer layer of skin and reach the region where vitamin D is synthesized. According to this view, different types of skin—white (depigmented and dekeratinized), yellow (mainly keratinized), and black (mainly pigmented)—are adaptations of the stratum corneum which maximize ultraviolet penetration in northern latitudes and minimize it in southern latitudes, so that the rate of vitamin-D synthesis is maintained within physiological limits (0.01 to 2.5 milligrams of vitamin D per day) throughout man's worldwide habitat.

Figure 2 provides evidence in support of this view, for it is apparent that there is a marked correlation between skin pigmentation and equatorial latitudes. In addition, the reversible summer pigmentation and keratinization activated by ultraviolet radiation and known a suntan represents a means of maintaining physiologically constant rates of vitamin-D synthesis despite the great seasonal variation in solar ultraviolet radiation in the northern latitudes.

Ultraviolet Transmission and Vitamin-D Synthesis

In 1958 Beckemeier (*4*) reported that 1 square centimeter of white human skin synthesized up to 18 I.U. of vitamin D in 3 hours. Using this figure, we calculate that an antirachitic preventive dose of 400 I.U. per day can

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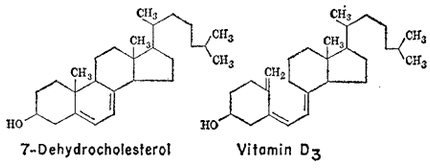

Fig. 1. Chemical structures of 7-dehydrocholesterol and vitamin D_3.

be synthesized by daily exposure of an area of skin approximately equal to that of the nearly transparent pink cheeks of European infants (about 20 square centimeters). Perhaps this explains why mothers in northern climates customarily put their infants out of doors for "some fresh air and sunshine" even in the middle of winter.

From this high rate of synthesis by only a small area of thin unpigmented skin, one can calculate the daily amount of vitamin D that would be synthesized at the equator by the skin of adults who exposed almost all their 1½ square meters (22,500 square centimeters) of body surface during the whole of a tropical day. Such a calculation shows that the skin of such individuals would synthesize up to 800,000 I.U. of vitamin D in a 6-hour period if the stratum corneum contained no pigment capable of filtering out the intense solar ultraviolet radiation.

Direct evidence that pigmented skin is an effective ultraviolet filter was provided by Macht, Anderson, and Bell (*5*), who used a spectrographic method to show that excised specimens of whole skin from Negroes prevented the transmission of ultraviolet radiation of wavelengths below 436 millimicrons, while excised specimens of white skin allowed radiation from both the 405- and the 365-millimicron bands of the mercury spectrum to pass through.

These early studies with whole skin were refined by Thomson (*6*), who used isolated stratum corneum obtained by blistering the skin with cantharides. He found that the average percentage of solar radiation of 300- to 400-millimicron wavelength transmitted by the stratum corneum of 22 Europeans was 64 percent, while the average for 29 Africans was only 18 percent. There was no overlapping of values for the two groups (Fig. 3), but there was considerable variation within each group, the values for the Europeans varying from 53 to as high as 72 percent and those for the Africans (who were mainly Ibos but also included men from most of the Nigerian tribes) varying from 36 to as low as 3 percent.

In his careful studies, Thomson measured skin thickness as well as pigmentation and found that the former was a minor variable. Studies on the degree of blackness of the various African specimens were made by skin-reflectance measurements. These showed that the darker the skin is, the lower is the percentage of ultraviolet radiation transmitted. One specimen from an albino African showed transmission of 53 percent—a value within the range for the European group. Thomson concluded from these studies that skin pigmentation was mainly responsible for protecting the African from excessive solar ultraviolet radiation, the thickness of the horny layer in Africans playing only a minor role. Thomson did not mention the fact that skin pigmentation and thickening of the horny layer in Africans would protect against excessive vitamin-D synthesis as well as sunburn.

Thomson's results indicate that African stratum corneum filters out solar ultraviolet radiation equivalent to between 50 and 95 percent of that which reaches the vitamin-D-synthesizing region of the skin of Europeans. This explains "the fact, agreed to by all, that of all races the Negro is most susceptible to rickets" (*7*). It is clear from Thomson's figures that exposure of the face of Negro infants to winter sunlight in Scandinavia would result in synthesis of too little vitamin D to meet the infant's body requirements.

It was Hess who first proved that sunlight could cure rickets (*8*). Seeking

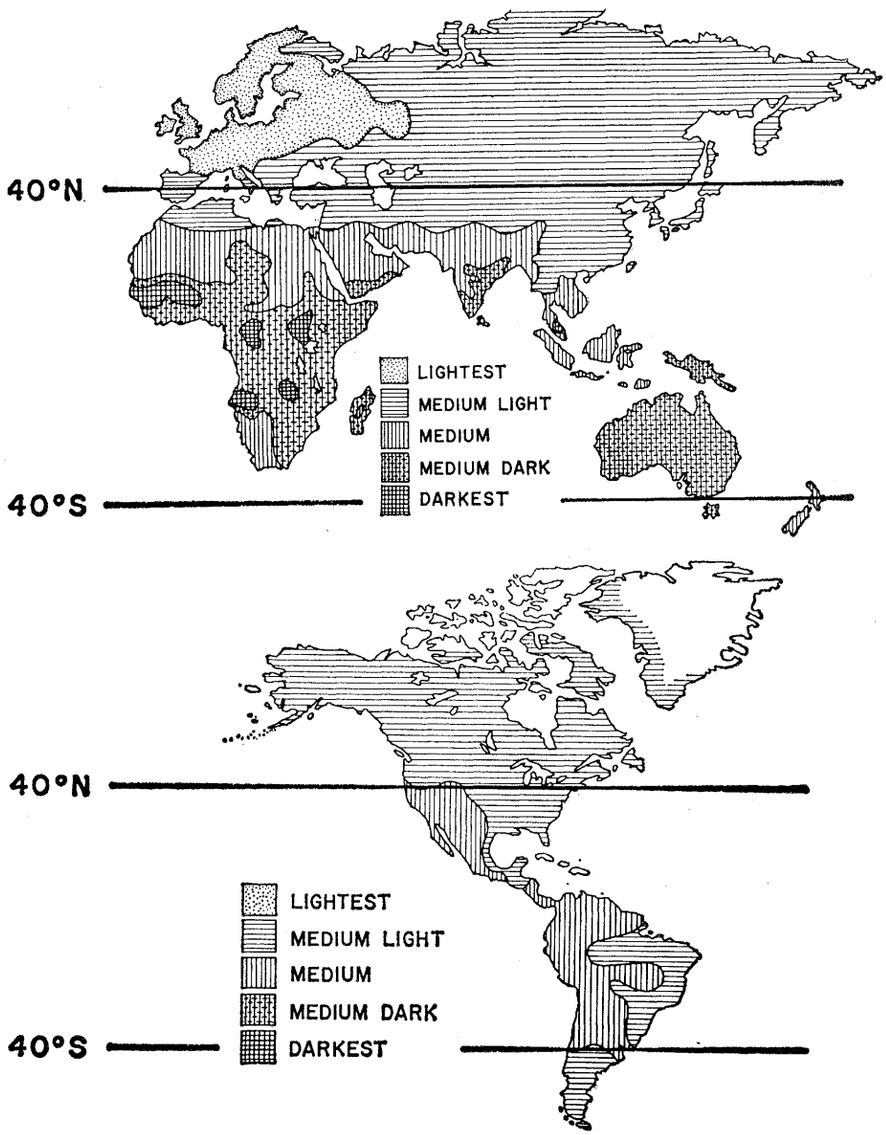

Fig. 2. Distribution of human skin color before 1492. [Adapted from Brace and Montague, *Man's Evolution* (Macmillan, New York, 1965), p. 272]

experimental proof of a relationship between skin pigmentation and rickets, he took six white and six black rats and placed them on a rachitogenic diet containing low amounts of phosphorus. Exposing both groups to a critical amount of ultraviolet light, he found that all the white rats remained healthy while all the black rats developed rickets. He concluded (*9*), "It is manifest that the protective rays were rendered inert by the integumentary pigment."

To return now to Thomson's results and consider their bearing on hypervitaminosis, they explain why deeply pigmented Africans living near the equator and exposing almost all their body surface to the ultraviolet of the tropical sun do not suffer from kidney stones and other evidences of hypervitaminosis. Under conditions where untanned Europeans would synthesize up to 800,000 I.U. per day, deeply pigmented Africans would synthesize 5 to 10 percent as much; thus their daily production would fall within the acceptable range.

In this connection it is significant that Reinertson and Wheatley (*10*) found that the 7-dehydrocholesterol content of human skin does not vary significantly between Negroes and Whites. Skin from the back, abdomen, and thigh of adults of both races averaged 3.8 percent (standard deviation, 0.8 percent), the lowest result in their series being obtained in a specimen of the epidermis of the sole, an area that receives no radiation at all, while the highest result among adults was from a Negro. The highest content of all was found in a specimen from a 2-week-old infant that showed 8.8 percent of the provitamin, a fact that correlates well with the especially high need for vitamin D during the first 2 years of life.

In their paper and ensuing discussion, the above workers emphasize that 7-dehydrocholesterol is found almost entirely beneath the stratum corneum, thus establishing the fact that in man it is not present in the secretions of the sebaceous glands as it is in birds and some northern fur-covered animals which, respectively, obtain their vitamin D by preening or by licking their fur after the provitamin has been converted into the vitamin on the surface of the body. It would appear that vitamin D is made in man solely by the irradiation of the provitamin in the layers underneath the stratum corneum, a mechanism that would allow efficient regulation of the biosynthesis of this essential factor by varying the degree of ultraviolet penetration through differing amounts of pigmentation in the overlying stratum corneum.

Origin of White Skin

Having originated in the tropics where too much sunlight rather than too little was the danger, the first hominids had no difficulty in obtaining sufficient amounts of vitamin D until they extended their range north of the Mediterranean Sea and latitude 40°N (Fig. 2), where the winter sun is less than 20 degrees above the horizon (*11*) and most of the needed ultraviolet is removed from the sun's rays by the powerful filtering action of the atmosphere through which the slanting rays have to pass. Before the present century, for example, there was a very high incidence of rickets among infants in London and Glasgow, because in these latitudes the midday sun is less than 35 degrees from the horizon for 5 and 6 months, respectively, of the year; in Jamaica and other southern localities, on the other hand, the sun's midday altitude is never less than 50 degrees and rickets is almost unknown (*2*). The farther north one goes, the more severe becomes this effect of latitude on the availability of winter ultraviolet radiation, an effect compounded by cloudy winter skies.

Table 1. Vitamin-D content of two fish-liver oils and of the only foodstuffs known to contain vitamin D. [From K. H. Coward, *The Biological Standardization of the Vitamins* (Wood, Baltimore, 1938), p. 223]

Fish-liver oil or foodstuff	Vitamin-D content (I.U./gram)
Halibut-liver oil	2000–4000
Cod-liver oil	60–300
Milk	0.1
Butter	0.0–4.0
Cream	0.5
Egg yolk	1.5–5.0
Calf liver	0.0
Olive oil	0.0

Having evolved in the tropics, early hominids were probably deeply pigmented and covered with fur, as are most other tropical primates. The first adaptation one might expect therefore to lowered availability of ultraviolet light as they moved north of the Mediterranean would be a reduction of fur, for Cruikshank and Kodicek have shown (*12*) that shaved rats synthesize four times more vitamin D than normal rats do.

As early hominids moved farther and farther north, their more deeply pigmented infants must have been especially likely to develop the grossly bent legs and twisted spines characteristic of rickets, deformities which

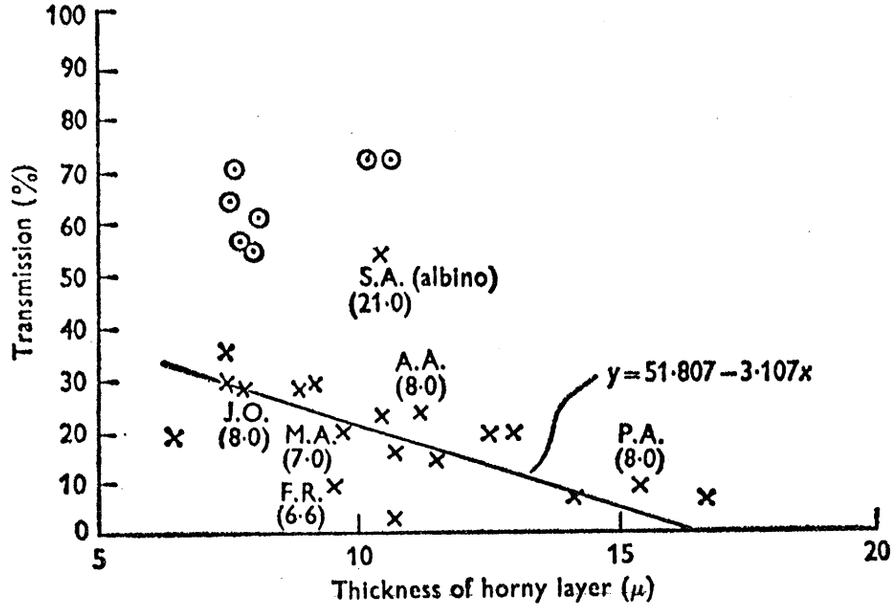

Fig. 3. Variation of transmission of solar ultraviolet light (3000 to 4000 angstroms) through the stratum corneum, plotted against thickness of this layer. ⊙, Europeans; ×, Africans. The numbers in parentheses after initials are percentages for reflectance of blue light on the forearm. [From M. L. Thomson (*6*)]

would cripple their ability to hunt game when they were adults. In this connection, Carleton Coon has written (*13*), "Up to the present century, if black skinned people were incorporated into any population living either north or south of the fortieth degree of latitude, their descendants would eventually have been selected for skin color on the basis of this vitamin factor alone." Howells agrees (*14*): "This variety of outer color has all the earmarks of an adaptation, of a trait responding to the force of sunlight by natural selection." The skin, he continues "admits limited amounts of ultraviolet, which is needed to form vitamin D, but presumably diminishes or diffuses dangerous doses by a screen of pigment granules."

Even in 1934 Murray clearly recognized the implications of these facts (*15*): "As primordial man proceeded northwards into less sunlit regions, a disease, rickets, accomplished the extinction of the darker, more pigmented elements of the population as parents and preserved the whiter, less pigmented to reproduce their kind and by progressive selection through prehistoric times, developed and established the white race in far northern Europe as it appears in historic times; its most extreme blond types inhabiting the interior of the northern-most Scandinavian peninsula."

It is a curious fact that Murray's thesis is almost unknown to the general public, including physiologists, biochemists, and physicians, and that it is not generally accepted by anthropologists, with the exception of Coon and Howells, quoted above, even though it fits the facts of Fig. 2. Both in Europe and China, skin pigmentation becomes lighter as one goes north, and it is lighter in young children; in almost all races the skin is lighter in the newborn infant (*16*) and gradually darkens as the individual matures, a change that parallels the declining need for vitamin D.

When Did European Hominids Begin To Turn White?

On the basis of the conclusion that white skin is an adaptation to northern latitudes because of the lowered availability of winter ultraviolet radiation, it appears probable that the early hominids inhabiting western Europe had lost much of their body hair and skin pigmentation even half a million years ago. Anthropological evidence indicates that early hominids such as the Heidelberg, Swanscomb, Steinheim, Fontechevade, and Neanderthal men lived north of the Mediterranean Sea—particularly during warm interglacial periods (*17*). It is important to recognize that the effect of latitude on the availability of ultraviolet light in winter is not related to climate but operates steadily and at all times, through glacial and interglacial periods alike.

Fig. 4. Distribution of early stone tools throughout the tropics of the Old World and in Europe as far north as 50°N. [From Brace and Montague, *Man's Evolution* (Macmillan, New York, 1965), p. 231]

Hand axes and other early stone tools have been found throughout the tropics of the Old World and also in Europe as far north as the 50th degree of latitude (Fig. 4). The presence of such stone tools as far north as England and France shows that some early hominids must already have adapted to the lowered level of ultraviolet radiation and consequent danger of rickets by partial loss of body hair and skin pigmentation, for without such adaptation they would have probably been unable to survive this far north.

England is at the same latitude as the Aleutian Islands, and no stone tools such as those found in southern England and France have ever been found in other areas at this latitude—for example, Mongolia and Manchuria. The unique combination of temperate climate and low levels of winter ultraviolet radiation in England and France is due to the powerful warming effect of the Gulf Stream on this particular northern area, which is unique in the world in this respect, for the Japan current in the Pacific is not as powerful as the Gulf Stream and warms only the Aleutian Islands, where no hominids existed until very recently.

Occupation of northern Europe and even Scandinavia up to the Arctic Circle seems to have taken place during the Upper Paleolithic, when presumably partially depigmented men already adapted to latitude 50°N lost nearly all their ability to synthesize melanin and so produced the blond-haired, blue-eyed, fair-skinned peoples who inhabit the interior of the northernmost part of the Scandinavian peninsula.

It has been held that the abundant appearance of stone scrapers in the Upper Paleolithic indicates that this far-northern extension of man's habitat followed his use of animal skins for clothing, a change that would select powerfully for infants with nearly transparent skin on their cheeks, who were thus still able to synthesize a minimum antirachitic dose of vitamin D even when fully clothed during the Scandinavian winter. Certainly the pink-to-red cheeks of northern European children are uniquely transparent; their color is due to the high visibility of the blood that circulates in the subepidermal region.

The one exception to the correlation between latitude and skin color in the Old World is the Eskimo; his skin is medium dark and yet he remains completely free of rickets (*18*) during the long dark arctic winters. Murray noted long ago that the Eskimo's diet of fish oil and meat contains several times the minimum preventive dose of vitamin D, concluding (*15*), "Because of his diet of antirachitic fats, it has been unnecessary for the Eskimo to evolve a white skin in the sunless frigid zone. He has not needed to have his skin bleached by centuries of evolution to admit more antirachitic sunlight. He probably has the same pigmented skin with which he arrived in the far north ages ago." Similar considerations would apply in the case of any coastal peoples of Europe and Asia, who would have been able to expand northward without depigmentation as long as they obtained sufficient vitamin D from a diet of fish; only when they ventured into the interior would antirachitic selection for blond types, as in Scandinavia, presumably have taken place.

Yellow, Brown, and Black Adaptation

Human skin has two adaptive mechanisms for resisting the penetration of solar ultraviolet: melanin-granule production in the Malpighian layer and keratohyaline-granule production in

the stratum granulosum. Melanin granules are black, whereas the keratohyaline granules produce keratin (from which nails, claws, horns, and hoofs are formed), which has a yellowish tinge. Particles of both types migrate toward the horny external layer, where they impart a black (melanin), yellow (keratin), or brown (melanin and keratin) tinge to the skin.

Thomson has shown (*6*) that, in Negroes, melanization of the stratum corneum plays the major role in filtering out excessive ultraviolet radiation, keratinization of the horny layer playing only a minor part. Mongoloids on the other hand have yellowish skin, since their stratum corneum is packed with disks of keratin (*13*) that allow them to live within 20 degrees of the equator even though their skin contains only small amounts of melanin (Fig. 2). On the equator itself, however, even Mongoloid-derived peoples acquire pigmentation—for example, the previously medium-light-skinned Mongoloids who entered the Americas over the Bering Straits at latitude 66°N as recently as 20,000 to 10,000 years ago (Fig. 2).

Even white-skinned peoples have to protect themselves against excessive doses of solar ultraviolet radiation in summer, for, as Blum has pointed out (*19*), on 21 June the solar ultraviolet is as intense in Newfoundland as it is at the equator, since at that time the two regions are at the same distance from the Tropic of Cancer (at 23°27′N). (At the equator, the solar ultraviolet is never less than on this date, while in Newfoundland it is never more.) In other words, adaptation to the variable intensities of solar ultraviolet in the north requires not only winter depigmentation but also the evolution of a reversible mechanism of summer repigmentation to keep the rate of vitamin-D synthesis constant throughout the year. It is significant that both the keratinization and melanization components of suntan are initiated by the same wavelengths which synthesize vitamin D, for it would be difficult to design a more perfect defense against excessive doses of vitamin D than this reversible response to ultraviolet light of these particular wavelengths—a pigmentation response that is further protected by the painful alarm bell of sunburn, which guarantees extreme caution against overexposure to solar ultraviolet in untanned individuals suddenly encountering a tropical sun.

Defenses against production of too much vitamin D therefore range from (i) reversible suntanning, as in Europeans, through (ii) constitutive keratinization, as in the Mongoloids of Asia and the Americas, to (iii) constitutive melanization, as in African and other truly equatorial peoples. The physiological superiority of melanization as a means of protection against ultraviolet was demonstrated by the ability, historically documented, of imported Nigerian slaves to outwork the recently adapted American Indians in the sun-drenched cane fields and plantations of the Caribbean and related tropical areas.

Additional evidence for the view that melanization of the stratum corneum is primarily a defense against the oversynthesis of vitamin D from solar ultraviolet is provided by the fact that the palms and soles of Negroes are as white as those of Europeans; *only* the palms and soles possess a thickly keratinized stratum lucidum (Fig. 5) under the external stratum corneum, which renders melanization of the latter unnecessary. The same reasoning explains the failure of the palms and soles of whites to sunburn during the summer.

Coon has written (*13*), "We cannot yet demonstrate why natural selection favors the prevalence of very dark skins among otherwise unrelated populations living in the wet tropics, but the answer may not be far away." Since overdoses of vitamin D administered orally are known to result in prompt and serious consequences, such as calcifications in the aorta and other soft tissues of the body, kidney stones, secondary renal disease, and death, it would appear that oversynthesis of vitamin D is sufficiently detrimental in young and old to favor the gradual selection for deeply pigmented skin near the equator, as seen, for example, in the repigmentation that has taken place among the equatorial American Indians during the last 10,000 years (Fig. 2).

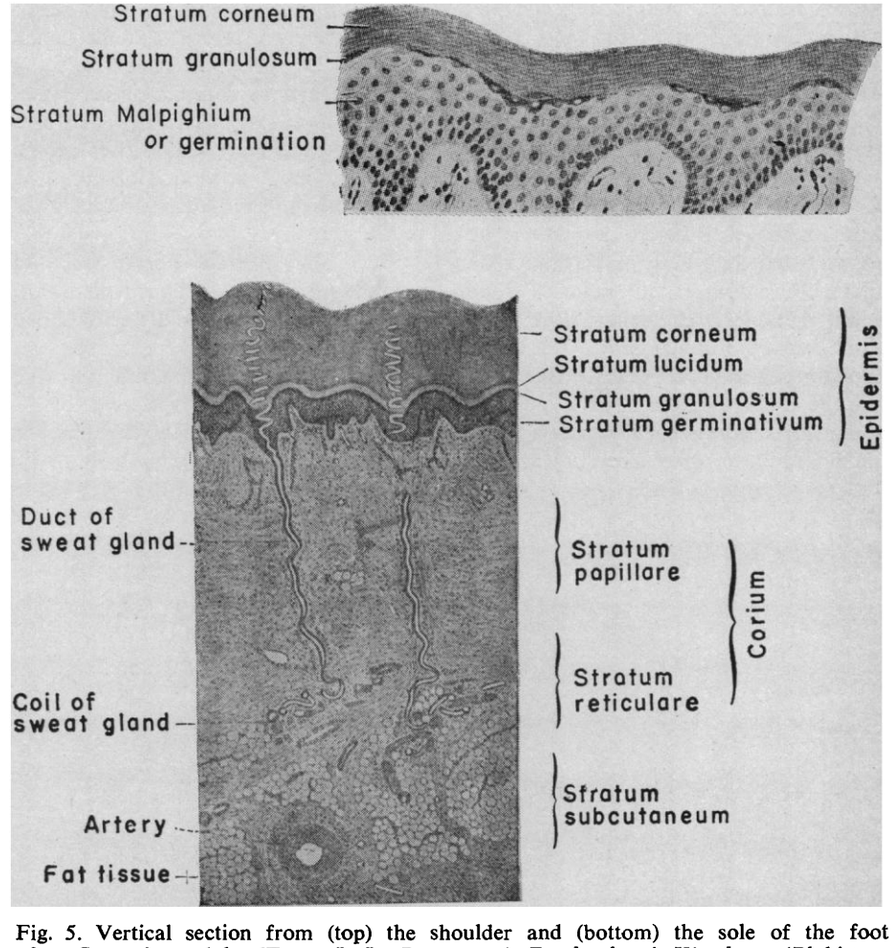

Fig. 5. Vertical section from (top) the shoulder and (bottom) the sole of the foot of a Caucasian adult. [From J. L. Bremer, *A Textbook of Histology* (Blakiston, Philadelphia, 1936)]

Secondary Results of Pigmentation and Depigmentation

It is known that black skin absorbs more heat than white skin; the studies of Weiner and his associates (*20*) show that black Yoruba skin reflects only 24 percent of incident light whereas untanned European skin reflects as much as 64 percent. Of themselves, these facts would lead one to expect that reflective white skin would be found near the equator while heat-absorbing black skin would be found in cold northern climate.

Since the exact opposite is true around the world, it seems clear that man has adapted his epidermis in response to varying levels of ultraviolet radiation despite the price he has had to pay in being badly adapted from the standpoint of heat absorbance and reflectance of visible and near-infrared wavelengths. Similar considerations naturally apply to summer pigmentation due to suntan; ultraviolet regulation rather than heat regulation explains why Caucasians are white in the winter but pigmented in the summer.

In addition to being badly adapted for maximum heat absorbance, white-skinned northern peoples are known to be particularly susceptible to skin cancer (*21*) and such skin diseases as psoriasis and acne. Therefore, only some powerful other advantage, such as relative freedom from rickets, would explain the worldwide correlation between high latitudes and white skin, for without some such factor it would seem that black or yellow skin would be the superior integument.

From this and other evidence, such as the fact that lion cubs and the young of other tropical animals develop rickets in northern zoos unless given cod-liver oil (*2*), it appears probable that depigmentation occurred north of latitude 40°N (a line marked by the Mediterranean Sea, the Great Wall of China, and the Mason-Dixon line) as an adaptation that allowed an increased penetration of winter ultraviolet radiation and consequent freedom from rickets. Certainly no other essential function of solar ultraviolet is known for man besides the synthesis of vitamin D.

Summary

The known correlation between the color of human skin and latitude (Fig. 2) is explainable in terms of two opposing positive adaptations to solar ultraviolet radiation, weak in northern latitudes in winter yet powerful the year around near the equator. In northern latitudes there is selection for white skins that allow maximum photoactivation of 7-dehydrocholesterol into vitamin D at low intensities of ultraviolet radiation. In southern latitudes, on the other hand, there is selection for black skins able to prevent up to 95 percent of the incident ultraviolet from reaching the deeper layers of the skin where vitamin D is synthesized. Selection against the twin dangers of rickets on the one hand and toxic doses of vitamin D on the other would thus explain the world-wide correlation observed between skin pigmentation and nearness to the equator.

Since intermediate degrees of pigmentation occur at intermediate latitudes, as well as seasonal fluctuation in pigmentation (through reversible suntanning), it appears that different skin colors in man are adaptations of the stratum corneum which regulate the transmission of solar ultraviolet to the underlying stratum granulosum, so that vitamin-D photosynthesis is maintained within physiological limits throughout the year at all latitudes.

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22. The work discussed here was partially supported by grant E-443 of the American Cancer Society to Brandeis University, Waltham, Massachusetts. This article is Graduate Department of Biochemistry Publication No. 505.