

Vitamin D – the Sun Hormone. Life in Environmental Mismatch

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Abstract—While some representatives of the animal kingdom were improving their biological mechanisms and properties for adapting to ever-changing life conditions, the genus *Homo* was developing backward: human individuals were losing their adaptation to life areas conquered earlier. Losing step-by-step their useful traits including the body hair cover, the primitive genus *Homo* retained his viability only under very favorable conditions of the equatorial Africa. Protection from UV radiation danger was provided only by pigmentation of skin, hair, and eyes. However, “impoverished” individuals of this genus gained the ability to walk upright. Their hands became free from participation in movement and became fine tools for producing useful instruments, from the stone knife to the computer. The major consequence of upright movement and hand development became the powerful development of the brain. A modern human, *Homo sapiens*, appeared capable of conquering very diverse new habitats. The human’s expansion on the Earth occurred somewhat limited by his dependence on vitamin D. His expansion into new areas with lower Sun activity was partially associated with the loss of skin pigmentation. But there is an open question, whether under these new conditions he is satisfactorily provided with vitamin D. This paper discusses the following problems: how can we ensure a sufficient intake of vitamin D, how much does an individual require for his existence and optimal life, what will be consequences of vitamin D deficiency, and what are the prospects for better provision with vitamin D?

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VITAMIN D – EVOLUTIONARY BACKGROUND

No life can exist on the Earth without the Sun. Everything on the Earth, from favorable temperature conditions to creation of bioorganic mass and free oxygen in the atmosphere is created only due to the rays of the Sun. In the living world, a number of systems have been created that are capable of using solar radiation, such as photosynthesis in cyanobacteria and plants, regulation of diurnal rhythms by melatonin, etc.

The *photoisomerization* of some biologically important compounds such as sterols, cholesterol, and ergosterol plays a special role. These molecules can be synthesized only in living cells. However, their photoisomerization can occur not only in living cells, but also in organic remains and even simply in a test tube (*in vitro*) at temperatures above 25°C [1, 2].

The ability to synthesize sterols is thought to be a very ancient property of living organisms because these substances are indispensable components of biological

membranes. Sterols and products of their photoisomerization are widely distributed in algae. Microalgae are an important part of the phytoplankton that is the first link in the food chain for the majority of aquatic animals [3]. Therefore, sterols are likely to be found everywhere. There is an impression that vitamin D precursors, cholesterol and ergosterol, also existed in Nature from very ancient times. For formation of vitamin D, only two additional factors are needed: UV radiation for photoisomerization of 7-dehydroxycholesterol to previtamin D, and temperature above 25°C for thermoisomerization of previtamin D to vitamin D.

In 1989, M. Holick wrote [4] that vitamin D seemed to be one of the first hormones, or even the very first hormone existing on Earth. The phytoplankton species *Emiliania huxleyi*, which has existed without change in the Sargasso Sea for more than 750 million years, produces ergosterol (provitamin D₂) to ~0.1% of its dry matter. On irradiation of this organism with artificial solar light, ergosterol converts to previtamin D₂, which rapidly turns to vitamin D₂ [4]. Although it was unknown why these early life forms accumulated such a huge amount of provitamin D₂, it was supposed that ergosterol could pro-

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tect the organisms against UVB- and UVC-radiation. Holick also referred to this idea in his later works published in 2003 and 2007 [5, 6].

Certainly, vitamin D₂ did not play this role. Most likely, it was its precursor ergosterol, which could not be dissolved in cells in such amount, because it is a fat-soluble substance. In the cells, it can be present mainly as a component of cell membranes. In the membranes, molecules of this sterol are strictly oriented and subjected to photoisomerization under the influence of UV radiation. However, the further thermoisomerization to vitamin D does not occur because the ocean water has a low temperature. The photoisomerization of both ergosterol and cholesterol is reversible, and therefore these sterols are powerful absorbers of UV radiation at temperatures below 25°C.

Thus, in phytoplankton organisms, as in many similar organisms, ergosterol and cholesterol do not function as a provitamin or even a hormone. Photosensitive molecules of ergosterol or cholesterol, together with their s-cis, s-cis-isomers, at temperatures below 25°C can serve as powerful systems protecting bioorganic molecules against the damaging effect of UV radiation.

Perhaps both cholecalciferol and ergocalciferol could occur in very early stages of evolution. What functions could they execute in aquatic organisms before their coming onto land? It was unlikely that it was associated with providing their cells with calcium ions because the average Ca²⁺ concentration in seawater varies near 1.2%. This means that sea organisms live in a medium enriched with calcium ions. Moreover, calcium became the most important element of their outer and inner skeletons. The development and solidity of the skeleton became decisive evolutionary traits and simply the most important prerequisite for coming on land of aquatic organisms. Moreover, fresh water and food found by the neophytes on dry land were essentially poorer in calcium. Therefore, new regulatory mechanisms had to appear to provide a sufficient amount of this cation in blood vessels of these organisms. It is vitamin D that fulfilled this function.

There is clear evidence that for the majority of animals living under conditions of the atmosphere, from amphibians to primates, a vitally indispensable photo-dependent mechanism of vitamin D synthesis has been elaborated [4].

HUMAN EVOLUTION AND VITAMIN D

During evolution, all organisms acquired some features that promoted their survival in one or another environment, i.e. they adapted to conditions of their existence. However, every new adaptive trait to certain specific conditions automatically limited adaptations to other conditions. That is why every species occupies a strictly determined limited areal on Earth. Consideration of

human evolution shows that at a certain stage they began to lose step-by-step various specific adaptations of their ancestors, and, finally, they converted to a “naked ape”! They occurred biologically adapted only to the most favorable life conditions in equatorial regions of Africa and became really “*Homo imperfectum*”. Let us see if for humans anything occurred from the standpoint of evolution.

The loss by humans of specificity was associated, first, with gaining upright posture for walking that made hands free from participation in movement and provided a unique possibility for development of the brain. This finally created the conditions for converting the hands to a universal organ for making various tools. In turn, this promoted further development of the brain. Humans became “Homo sapiens”.

Using brain and hands, humans gradually conquered all regions of the Earth, lifted into the air, and realized the first steps in mastering space. All they needed humans created themselves! However, for *Homo sapiens* one limitation remained that made essentially more difficult progress into new regions of the Earth. This limitation was dependence on provision with UV radiation-dependent vitamin D, although they could more or less get this substance with food products. May be just because of this, humans spent nearly one million years to overcome the distance from the Equator to the Mediterranean Sea shore [7].

In the regions of the human origin, solar radiation seemed to be too aggressive for their naked body. But the human ancestors had strongly pigmented skin, hair, and eyes. It is not surprising that our ancestors were black! With expansion into new habitats where the Sun even in summer never rises to the zenith, a significantly less UV radiation reaches the Earth’s surface, especially in winter, and the capability of our ancestors of synthesizing vitamin D decreased significantly. Humans more or less succeeded in adaptation to these new conditions by a decrease in the pigmentation of their skin.

Loomis [8] supposed that the melanin pigmentation was developing under the influence of the solar radiation as a protection against “intoxication” with too high concentration of vitamin D. Later it has been shown that the Sun itself regulates the level of vitamin D that is produced under the influence of solar radiation (see below). Pigmentation prevents the production of vitamin D. The level of vitamin D in blood of white-skinned humans becomes balanced already in 20 min of exposure to UV radiation, whereas in dark-skinned humans the same state is reached after three-six times longer [9, 10].

This is the evidence that human pigmentation is protection against the deleterious effect of UV radiation. When humans had advanced into regions where the Sun did not provide the needed amount of vitamin D, they began also to lose step-by-step this protective function. As a result, they became more sensitive to the damaging effect of UV

radiation. In the new habitats, the UV radiation intensity was much lower than in regions near the Equator. This resulted in a kind of compromise: *the provision with vitamin D was improved at the cost of worsening skin protection against UV radiation*. (This situation has had far-reaching consequences for human life under new conditions, see below).

BRIEFLY ABOUT THE HISTORY OF VITAMIN D

Substances that are now called vitamins usually became known from the consequences of their insufficient supply. The same was in the case of vitamin D. In 1822, Sniadecki [11] noted that children living in Warsaw became ill with rickets more frequently than children living in the countryside did. He concluded logically that they simply had a shortage of Sun. In 1824, Schuette [12] treated children suffering with rickets with cod-liver oil. Both these publications as well as some later ones were not noticed.

The situation changed sharply when in 1918 Mellanby published results of his experiments on dog puppies [13]. He kept them in the dark and gave them different food. It appeared that the addition to the food of cod-liver oil protected the puppies against the development of rickets. Initially, the curative effect was ascribed to vitamin A. However, in contrast to vitamin A, the curative component of cod-liver oil was thermoresistant. This new substance was termed vitamin D [14]. In experiments of Huldschinsky, children with rickets were irradiated by mercury lamps [15], and after four months, these children became healthy. Moreover, the functions of both hands improved even if only one hand was irradiated.

Results of these studies, as well as using rats as new model experimental animals for treatment of rickets, induced a new wave of investigations in this field. Rats were easily treated for rickets using UV radiation. It was surprising that they became healthy even when they were taken from their cages and the cages were irradiated. Rats with rickets (non-irradiated!) were placed into the irradiated cages and they recovered [16]. Initially the authors thought that a component of the air in the cages was an acting factor. However, later it was found that the recovery of the rats was due to their eating their own excrements and the bedding that were not removed from the cages before the irradiation. Cholesterol and ergosterol of the excrements and bedding under the influence of UV radiation were converted to cholecalciferol and ergocalciferol, i.e. vitamins D₃ and D₂. This is how the rats overcame the vitamin D shortage and recovered [17].

Further studies on vitamin D were characterized by both increase and decrease in interest from time to time. Thus, interest in studies on the role of vitamin D in human life sharply increased after a patent was obtained on its enrichment in irradiated food products [18]. Upon the development of a method for production of a large

amount of inexpensive vitamin D₂ from yeast cultures, this vitamin began to be added directly into milk (423 IU/liter) [6]. For a long time, food products, especially milk, were widely enriched with vitamin D₂.

Unexpectedly in the 1950s in Great Britain, cases of neonatal hypercalcemia were recorded (British Pediatric Association, 1956 [19]). The situation suddenly changed sharply. Some rather authoritative specialists decided that this was due to overdosing vitamin D in milk. Governments of European countries urgently decided to forbid the enrichment of food products with vitamin D. Since this time, physicians are strongly prejudiced against using vitamin D. However, note that there was no direct proof that these clinical cases were caused only by intoxication with high doses of vitamin D. Symptoms of the illness determined as vitamin D₃ hypervitaminosis more likely indicated development of Williams syndrome. This syndrome is characterized by increased sensitivity to vitamin D and is observed very rarely in humans [6].

VITAMINS D ARE UNIQUE COMPOUNDS

Living beings can synthesize all needed organic compounds, but this concerns only the living world as a whole. Humans and other animals cannot produce some compounds and get them only with food, i.e. they utilize products of other organisms. Undoubtedly, such compounds for humans are vitamins. The exception is group D vitamins. *Without the UV part of the solar radiation spectrum, no vitamin D would be present on the Earth at all!*

If vitamin D precursors, *cholesterol* (7-dehydrocholesterol) and *ergosterol*, appear somewhere on Earth, the B ring of these molecules is broken under the influence of solar UV radiation (290-310 nm), previtamin D is produced, and then through thermoisomerization it is converted to cholecalciferol and ergocalciferol, i.e. vitamins D₃ and D₂, respectively.

Photoisomerization of the 7-dehydrocholesterol molecule dissolved in hexane or other solvents occurs relatively slowly because its intermediate product *s-cis,s-cis-previtamin D₃* changes to *s-trans,s-cis-previtamin D₃*, and the equilibrium of this reaction is shifted to the latter isomer. In living cells, provitamin D₃ is strictly oriented in the membrane, which results in instant conversion of *s-cis,s-cis-previtamin D₃* to vitamin D₃ at sufficiently high temperature [9]. The formation of vitamin D₃ is associated with breaking of hydrophilic and hydrophobic interactions with phospholipid compounds of the membranes, and it is released into the intercellular space. Then it is transferred into blood vessels where it is bound to a specific D₃-binding protein. Thus, vitamin D₃ is constantly removed from the intercellular space, and this maintains a gradient of its concentration [20, 21].

Already at the erythematous dose of solar radiation (slight reddening of the skin 24 h after irradiation), vita-

min D₃ is synthesized in the skin in the amount equivalent to its taking *per os* in dose 10,000–25,000 IU [22]. Such powerful production of vitamin D₃ would seem to result in its accumulation in the organism in toxic concentrations, but this does not occur. In a human with white skin, level of vitamin D₃ reaches a balance already upon 20–30 min of exposure to UV radiation. Vitamin D₃ synthesized above this level is not accumulated, but destroyed [23]. These data show that there is *a system responsible for regulation of vitamin D₃ level in blood directly by UV radiation*. Under the influence of UV radiation, previtamin D₃ can revert to provitamin D₃ or other isomers – lumisterol₃ and tachisterol₃. During the next stage, already vitamin D₃ is converted to other photoisomers – supersterol I, supersterol II, and 5,6-transvitamin D₃. Thus, intoxication of humans with increased dose of vitamin D₃ resulting from UV irradiation is completely excluded [24].

The unique properties of vitamins D₃ and D₂ depend on those of their precursors. For a long time, it was believed that cholesterol was synthesized in animals, and ergosterol in fungi and plants. It seems that ergosterol can be found in plants because of their contamination with fungi or fungal remains. Until now, there is no reliable proof that ergosterol can be synthesized by plants [25]. Sterols play a significant role in both the structure of cell membranes and regulation of their permeability and some other features. Sterols are also precursors of many steroid hormones [26]. Thus, their large amount in Nature is not surprising. Jaepelt and Jacobsen [3] supposed that plant sterols could be synthesized through cycloartenol and cholesterol (in animals) and ergosterol (in fungi) through lanosterol. It is reasonable to think that lanosterol might be a precursor of cholesterol also in plants.

If we admit that cholesterol in plants is not a unique compound but is rather widely distributed, we can expect also the presence of cholecalciferol, i.e. vitamin D₃. In fact, the existence of vitamin D₃ and its metabolites was discovered because of a disease of herbivorous animals, enzootic calcinosis. This disease is observed in cows, sheep, horses, goats, pigs, and other animals. Animals became ill in both Alpine meadows and South America pastures. This disease was shown to be hypercalcemia because the animals eat plants rich in vitamin D₃ and its activated form – *calcitriol*. In Europe, this disease is caused by the cereal *Trisetum flavescens*, which is a typical species for the European Alps and Caucasus [27–30]. The toxic effect of this plant is maintained and seems even to increase after drying by sunlight [31].

In South America, toxic effect to some animals is caused by *Solanum glaucophyllum*. Experiments were performed with rats [32] and rabbits [33, 34]. In the USA another plant from the Solanaceae family, *Cestrum diurnum*, is dangerous for animals [35]. A hydroxylated form of vitamin D₃, 1,25(OH)₂D₃, is found in both *T. flavescens* and *S. glaucophyllum*. The active form of vita-

min D₃ is often found in these plants at a relatively high concentration. High concentrations of 25(OH)D₃ and 1,25(OH)₂D₃ were found *in vitro* in *S. glaucophyllum* cell culture [36].

A question arises whether these three plant species (perhaps their number will be higher if searches are extended or the sensitivity of D₃ determination methods is increased) have any evolutionary advantage compared to other species. The situation became still more puzzling after a pathway of vitamin D synthesis was found in an *in vitro* culture without the influence of UV radiation. In other words, *S. glaucophyllum* cells in tissue culture and in cell suspension could open ring “B” of 7-dehydrocholesterol in the dark without UV radiation [37]. If this is true, it is sensational! However, no new data have been published from this laboratory and from others for more than 10 years.

Thus, vitamin D precursors are widely distributed throughout the world. Only sunlight is required to break ring “B” in them. The photoisomer previtamin D is produced not only in living cells, but also in their dead remains, anywhere, even in a drop from a pool, especially because living matter dying off is accompanied by releasing cholesterol molecules from membranes. The data indicated that animals including humans usually have two or more chances for obtaining vitamin D. This gives great advantages for conquering new territories.

HOW DO ANIMALS PROVIDE THEMSELVES WITH VITAMIN D?

In the first part of this paper, we mentioned that when animals came onto the land vitamin D began to play an important role in the regulation of blood level of calcium ions. Sources of vitamin D seemed to be UV radiation and food. Five pathways can principally exist for gaining this.

Application of biological products treated by UV radiation. Under the influence of UV radiation, cholesterol and ergosterol are converted into the corresponding previtamins D₃ and D₂. Photoisomerization beyond the organism was used in many model experiments conducted *in vitro* [10, 23]. This reaction can be widely distributed in Nature that shown by experiments on rats when UV irradiation even of their excrements and beddings in cages was sufficient to cure the animals from rickets [38, 39].

It was thought for a long time that only products of animal origin and fungi could be sources of vitamin D, but later it was found that plants also contain vitamin D (see [3] for a review). Some plants (*Trisetum flavescens*, *Solanum glaucophyllum*, *Cestrum diurnum*) contain vitamin D₃. By the way, nearly 100 years ago rats were treated against rickets by feeding them with UV irradiated grass and hay [40]. Very interesting experiments were performed on the medic *Medicago sativa*. Long-term treat-

ment of this plant with UV radiation significantly increased level of vitamin D₂ in it [2, 40]. Old leaves of adult plants were especially rich in vitamin D₂, and with plant aging, the amount of vitamin D₂ increased by an order of magnitude [41]. This was due to infection of the plants with fungi.

Thus, wide distribution of various fungi in the plant world is obviously useful for herbivorous animals. It is especially clear after the death of fungi that is associated with releasing a large amount of cholesterol from the cellular membranes. Under the influence of UV radiation, ergosterol is easily converted to vitamin D₂.

Coprophagous animals. We already mentioned that rats were easily cured from rickets due to eating their own excrements that had been treated with UV radiation. In Nature, rats mainly eat small animals, and this can fully satisfy their need in vitamin D. Coprophagy is widely distributed among animals. This type of nutrition has been observed in rats, mice, guinea pigs, rabbits, hares, wolves, dogs, horses, elephants, gorillas, etc. It is thought that this provides more complete use of partially digested food (caecotrophy in rabbits) along with assimilation of necessary intestinal bacteria, mineral substances, vitamins, etc. (e.g. a foal eats excrements of its mother). This perhaps provides the organisms with previtamin D and vitamin D₃. Whether coprophagy in Nature is significant for providing animals with vitamin D is still unclear.

Carnivorous animals. It is well known that carnivorous animals satisfy their need in vitamin D with meat of their prey because it contains vitamin D₃. Though data on vitamin D₃ content in different publications vary greatly, they allow us to see that meat is a reliable source of vitamin D₃. Especially rich are pluck. The liver and kidneys are places of synthesis of important metabolites of vitamin D₃ [42, 43]. Therefore, nutrition with meat products supplies carnivorous animals with a sufficient amount of vitamin D₃.

Excretion of cholesterol with fat onto hair coat surface. It is well known that cholesterol is excreted through adipose glands on the hair surface in animals possessing a fell with thick wool. When the animals are warming themselves in the Sun, cholesterol on their wool is converted through photo- and thermoisomerization to vitamin D₃, which is licked from the wool and thus enters the gastrointestinal tract and then into blood vessels [44]. In this respect, observations on primates are especially interesting [45]. It is known that they lick not only their own wool, but also the wool of their relatives. This is associated with absorption of vitamin D₃ produced from cholesterol and accumulated on the hair coats under the influence of UV radiation [46]. However, perhaps some vitamin D₃ can be absorbed directly by the skin [47]. Nevertheless, a significant fraction of vitamin D enters the organism of primates *per os*. It is interesting that vitamin D₃ has been detected also in the sweat of modern humans [46]. Based on these data, Vieth [45] concluded

that in the early stages of development humans could also gain vitamin D₃ through licking it from their skin. Some animals lick their wool very intensively, which leads to its full disappearance in some places on the body and even to skin inflammation, which is a pathological consequence. However, this can be associated only with insufficient provision of the organism with vitamin D₃ (hypovitaminosis, disorders in formation of vitamin D₃ receptors), and attempts of the animals to compensate for the shortage of vitamin D [48].

Skin upper layer cells as producers of vitamin D₃. We are speaking about the epidermal layers of skin cells. These covering layers do not have blood vessels, but they consist of living cells from which their dying remains are constantly desquamating outwards. Cholesterol is released just into this layer, *stratum spinosum*, in the neighborhood of melanocytes accumulating a protective pigment. Here, on the outer edge of a living organism, at the very skin surface in its external cells, photo- and thermoisomerization of cholesterol occur. Note that here cholesterol is not dissolved but is in cellular membranes [24].

The calculation per surface unit shows that ~65% of the total cholesterol is located just in the skin epidermis and only 35% in the dermis. More than 95% of previtamin D₃ is synthesized just in the skin epidermis [20, 49]. In a white human being (European skin type II), the skin epidermis passes about 20-30% of radiation with wavelength of 295 nm [50, 51]. A significantly lesser amount, 2-5% of this radiation, penetrates through the epidermis of a black human's skin (skin type V).

PROVISION OF HUMANS WITH VITAMIN D

It was already shown that in the region of their origin humans were fully provided with vitamin D, but on their movement northward they occurred in new regions where the UV radiation level was much lower than in their historical motherland. When humans remained as hunters, they gained some amount of vitamin D as a carnivorous being. However, in regions with another climate they were forced to cover their bodies to protect against cold. Their life mode changed sharply. They began to spend more time in closed places and under shelters built by themselves. Moreover, cultural, social, and religious traditions required them to use clothes. Under new environmental conditions, the humans began to suffer from vitamin D shortage. This was manifested, first, by rickets in children that, by Professor Holick expressed, is only "the top of the iceberg".

The following questions arise. 1) What is the degree of human provision with vitamin D under current conditions? 2) What amount of vitamin D do humans need for existence at the minimal level and for full-valued life? 3) Under what conditions is vitamin D toxic for humans? 4)

What are the consequences of vitamin D shortage? 5) What must be done to provide humans with vitamin D at the optimal level?

Are humans sufficiently provided with vitamin D? Let us proceed from the environmental conditions during the emergence of humans. If we consider now living primates to be somehow related to our ancient ancestors, it is interesting to know their blood level of vitamin D₃, especially taking into account that nearly all of them remained in warm Equatorial regions. Unfortunately, these data include those obtained on primates living in zoos: 134 and 33 ng/ml [52], 200 ng/ml [53], 129 ng/ml [54] vitamin D₃. For people living under approximately similar geographical conditions and working mainly outdoors, the following data are obtained: 42 ng/ml in medical persons and 54 ng/ml in farmers in Puerto-Rico [55], 65 ng/ml in lifeguards in St.-Louis [56], 59 ng/ml in lifeguards in Israel [57]. Most likely, 55-100 ng/ml is the etalon level for many inhabitants of sunny countries and the aboriginal population of tropical countries [58]. On the other hand, there are many literature data on very low blood level of vitamin D in populations of England, Canada, and other countries. Even in regions with low latitudes, i.e. not far from the Equator, many people suffer from insufficiency of vitamin D and have children with rickets. Materials concerning this problem are discussed in detail in a two-volume edition about vitamin D [59].

Consider data on this problem for Germany as a country with relatively high levels of life and medical care. The provision of the German population with vitamin D is officially represented by data obtained by the Robert Koch Institute in Berlin (the central institution of the federal government for disease prevention). The data were published by the German Society on Nutrition (DGE) based on the decision of the German Bundestag [60]. Altogether, 11,721 persons were examined. The blood level of vitamin D was >30 ng/ml in only 20% of men and women of ages from 18 to 79 years old. In half of this age group, the blood level of vitamin D was lower than 20 ng/ml. In children and young people, the situation was still worse – a level lower than 20 ng/ml was found in 86%. These data reveal a very strong insufficiency of vitamin D in the young people of Germany. It is especially dangerous that in 4% of German children and young people the blood level of vitamin D is lower than 5 ng/ml. These data characterize changes in the human life nowadays that have been spoken about above. Before considering health problems related with these data, it is necessary to elucidate what blood level of vitamin D₃ is *needed* for humans.

What amount of vitamin D is necessary for humans?

There is no generally adapted opinion about this question among physicians and scientists. The official opinion is that humans gain vitamin D mainly when under the Sun as well as from food products. The lacking part of vitamin

D has to be compensated by food supplementation. For a long time it was thought in Germany that it was sufficiently to take 200 IU vitamin D daily, then this dose was increased to 400 IU. In 2013, an official institution increased the recommendation up to 800 IU [61]. This official institution soothes the people by the statement that frequently being under the Sun can provide an acceptable blood level of vitamin D without additional supplements. It is important to note that according to this document, the “desired” blood level of vitamin D is only 20 ng/ml. Obviously, the authors think that the normal level of vitamin D in the organism is such that is not associated with a development of rickets and osteomalacia. There are similar statements about the provision of people with vitamin D in the USA and many other countries.

Certainly, to proceed from the *desired blood level of vitamin D₃* would be the best, but what is this level? Remember that in people working every day outdoors under the Sun the blood level of vitamin D₃ is 54-65 ng/ml, and in populations of sunny countries its level is 55-100 ng/ml (see above). The physician von Helden presented a scale of vitamin D₃ blood level [62]: <12 ng/ml – extreme shortage (risk of rickets and osteomalacia), <20 ng/ml – significant shortage (risk of osteoporosis, disorders in the vegetative nervous system), <30 ng/ml – shortage (risk of osteoporosis in old age), >30 ng/ml – satisfactory provision (good absorption of Ca²⁺), >40 ng/ml – good provision (decreased risk of many diseases), 50-90 ng/ml – the level for regular insolation, the minimal risk of many diseases, 100 ng/ml – recommended upper limit of vitamin D₃ blood level, >150 ng/ml – risk of an increased blood level of Ca²⁺, >300 ng/ml – toxic effect.

Based on his own observations, von Helden concluded that therapy with increased doses of vitamin D₃ could cure or at least improve conditions by about 80% in the following states: weakness, chronic somnolence, disorders in blood circulation, insomnia, muscular convulsions, headache, aches in feet and back. Von Helden successfully used his “vitamin D therapy” also in the treatment of other diseases. However, these results cannot be considered reliable because of the limited number of observations.

Other specialists think that vitamin D blood level of 32-50 ng/ml is only satisfactory, of 20-31 ng/ml – insufficient, and <20 ng/ml – deficient [58].

Vitamin D toxicity. The question of the toxicity of vitamin D is under consideration in discussions about its application. There is no publication concerning the application of vitamin D without a notice about its toxicity even in relatively moderate doses. This situation is mainly a consequence of the enrichment with vitamin D of milk and other food products in European countries.

Cases of vitamin D toxicity were observed on its application in pharmacological doses from 50,000 to 1,000,000 IU per day. This increased blood level of vita-

min D above 200 ng/ml [6]. The critical limit of high doses of vitamin D is usually determined by the stability of calcium ion content in blood. Taking vitamin D in the dose of 12,500 IU per day for eight weeks did not influence the blood level of Ca^{2+} [63]. Later it was shown that on taking vitamin D at the dose of 40,000 IU per day for one month, $[\text{Ca}^{2+}]$ in both blood and urine was unchanged [64]. This is in a good agreement with the above-presented classification of von Helden [62].

It is not quite clear why up to now many medical reports stubbornly warn about the threat of taking increased doses of vitamin D. There are warnings even against taking ≥ 4000 IU per day as if it is already a significant overdose accompanied by very dangerous consequences. However, there are many data indicating that these statements do not correspond to reality. From the abundance of literature data, we shall present only a few works that show the wrongness of these warnings and allow the reader to have a correct understanding.

VITAMIN D AND ENVIRONMENTAL MISMATCH

Are humans living in an adequate environment? From the evolutionary standpoint, we can boldly say *NO!* An adequate environment for *Homo sapiens* is Equatorial Africa. Here they find favorable life conditions if they retain their skin and hair pigmentation. All deviations are already an "environmental mismatch". Even the loss of the skin pigmentation could only partially improve human adaptation to new life conditions. Moreover, covering the body with clothes, preferential residence in closed rooms, changed food products, etc. — all this is an environmental mismatch from the standpoint of human evolution.

At present, it is aggravated by the development of transport that significantly simplifies human migration. On one hand, many people from Southern regions migrate or were forced earlier to resettle in northern regions: black Africans into America, Mexicans into USA, black Africans and residents of Mediterranean countries into Northern Europe, residents of Asia, Central Asia, and near East into countries of middle and Northern Europe. On the other hand, residents of European and North America countries migrate for a short time (leave, holidays, and temporal work) or even immigrate into countries with excess solar radiation. All this sharply enlarges the circle of people living in environmental mismatch. In the USA, medicine is dealing for long with this problem [65], but in Europe it is not studied enough in spite of its significance. Some results obtained in the USA are presented below. The blood level of vitamin D was determined in men and women of age ≥ 70 years for three ethnic groups: white Americans, Mexicans, and Blacks. The blood level of vitamin D < 15 ng/ml was found in 5, 13, and 33%, and > 30 ng/ml in 52,

27, and 11% of subjects of these ethnic groups, respectively. These data convincingly indicate that the shortage of vitamin D in blood is especially pronounced in the black population and the least expressed in white people [65]. Certainly, such data raise the question about the real consequences of insufficient provision of humans with vitamin D.

VITAMIN D SHORTAGE AND ITS CONSEQUENCES

Symptoms of rickets have been known for a rather long time. The situation is more difficult with many other diseases that can also be caused by insufficient supply of the organism with vitamin D.

It is reasonable to find out some general criteria that would allow systematizing different responses of the organism to shortage of vitamin D. The first group will include all diseases associated with disorders in homeostasis of Ca^{2+} in blood, i.e. diseases associated with disorders in the normal development of bones. Another group of diseases depending on vitamin D is associated with the immune response of the organism. Many problems in the human health that are also caused by insufficiency of vitamin D are associated with chronic inflammation of different organs. There are also diseases that some authors think to be associated with vitamin D insufficiency, but other authors think they are not.

Significance of vitamin D for development of bones.

Rickets. The appearance of this disease in children has been discussed above. Remember only that the blood level of vitamin D_3 above 20 ng/ml reliably protects children against this disease. Moreover, note that vitamin D acts on bone tissues not directly, but through homeostasis of Ca^{2+} in blood. This also refers to all other bone diseases.

Osteomalacia. There are data indicating that osteomalacia also develops because of vitamin D insufficiency [66-68].

Osteoporosis. About 95% of all cases are classified as primary osteoporosis. The optimal blood level of vitamin D is needed for generation of maximal bone mass beyond youth, and this, in turn, is a prerequisite for preventing primary osteoporosis [69-71].

Growing pains. Children, more frequently at the age of 4-6 and 8-12 years, complain (particularly at night) of bone aches, especially in the legs and sometimes in the arms [72]. In this case, pediatricians usually recommend that parents pay more attention to their children because these are only growth-associated pains, which will disappear soon, but these problems should not be ignored. It is proved that bone density in children suffering with night bone aches in legs is significantly lower than in other children [73]. However, referring to work [74], Evans [72] states that treatment of such children with vitamins C and D or calcium and magnesium ions is inefficient. In fact,

in the work of Uziel and Hashkes [74] only one sentence concerns vitamin D: they wrote that nutrition enriched with Ca ions and vitamin D was likely to influence bone conditions and pains, but this theory was not studied. In their recent work, which also considered the growing pain problem, vitamin D was not mentioned. Positive results were obtained from the treatment of two girls (3 and 5 years old) with 5000 IU of vitamin D₃ per day [62].

Crooked teeth. It is believed that 70% of all children in Germany have crooked teeth. Crooked teeth in children are corrected with braces that are associated with discomfort, difficulties, and sometimes pain for children. This is a rather expensive treatment, and parents in many countries cannot treat their children because of financial problems. Crooked teeth are mainly a result of insufficient development of jawbones. Jawbones do not reach the necessary thickness, and therefore permanent teeth on their appearance do not find the due place for their orientation. Vitamin D was shown to be very important also for the development of alveolar bones [75, 76]. To realize that vitamin D (or UV radiation) plays a role in the correct development of teeth, one has only to look at smiling faces of African children.

Influence of vitamin D on development of immune reactions. The innate immune system reacts rapidly but not very specifically, whereas the acquired immune system reacts very specifically but is less active. Some studies have revealed the influence of vitamin D (1,25(OH)₂D) on the innate and acquired immune systems [19, 77, 78]. In work [79], vitamin D was shown to be a decisive factor for activation of immune protection. Below we present some examples to illustrate this statement.

Tuberculosis. The influence of vitamin D on the treatment of tuberculosis has been studied in many works [80]. A favorable role of Sun for recovery from tuberculosis has been known for a long time. This disease was widely distributed among poor urban populations. Prosperous people with tuberculosis went to Southern sunny regions, e.g. to Italy. One can see a kind of parallelism with rickets.

Influenza infections. An inverse correlation is shown between the distribution of influenza infections and the Sun's radiation intensity [81, 82]. In 2008-2009, school-children in Japan were given daily 1200 IU of vitamin D or a placebo during December-March; the morbidity from influenza in the experimental classes was 58% lower [83].

This list can be continued: pneumonia, sepsis, etc. Certainly, these diseases cannot be cured with vitamin D – it only improves the immune response against these infections.

Vitamin D and chronic inflammation. The organism reacts to infection (with bacteria, viruses, fungi, parasites) or to irritation of tissues (with UV radiation, chemical substances, wounds, etc.) by generating tissue hormones (histamine, serotonin, cytokines, prostaglandins, etc.).

The immune system is activated, and then the organism recovers, or an acute inflammation can become a secondary chronic one. As differentiated from secondary chronic inflammation, *primary chronic inflammation* develops as an autoimmune inflammation when the immune system attacks cells of its own organism, as is exemplified in cases of arthritis, ulcerative colitis, Crohn's disease, multiple sclerosis, rheumatoid arthritis, psoriasis, etc. Although patients with these diseases were shown to have a shortage of vitamin D, up to now there are no reliable data on the dependence of these diseases on the organism's supply with vitamin D [84].

Secondary chronic inflammations are very numerous: gum diseases (gingivitis, periodontitis, etc.), asthma, some forms of arthritis, Alzheimer's disease, cardiac diseases, atherosclerosis, type 2 diabetes, Parkinson's disease, some intestinal diseases, neurodermitis, etc. Sometimes secondary chronic inflammation occurs unrecorded (silent inflammation). Such chronic inflammation can develop for decades and lead to a latent damage to the brain, heart, and nervous system. Chronic inflammation can cause development of serious diseases [85].

During recent years, the number of works increased indicating that the development of these diseases can depend on vitamin D insufficiency or demonstrating the possibility to prevent these diseases with vitamin D. Examples of such diseases are gingivitis [86-88], periodontitis [89, 90], type 2 diabetes [91, 92], cardiovascular diseases [93], and arthritis [94].

A positive effect of vitamin D on the development of these diseases was shown in many works, but in other publications, no positive effect was demonstrated. For other diseases, e.g. for tumors, the results are even more contradictory. A recent review [95] presented results of 46 studies performed during the period from 1985 to 2012. Even first acquaintance with this review reveals that only in 11 of these works was vitamin D used at a dose ≥ 1000 IU. The observations in the majority of these works were for no longer than two years; therefore, one could not expect convincing results. Moreover, when cancer diseases were under consideration.

VITAMIN D IS NOT A DRUG, NOT A VITAMIN, IT IS A HORMON

It is unlikely that vitamin D can be considered a drug, a therapeutic agent. More likely, vitamin D as a hormone is a necessary compound for development of the immune system of the organism [96-98].

If so, it would be reasonable to take care of providing the normal status of vitamin D in all people. Physicians of the whole world try to maintain blood pressure and composition in certain limits, but why so little attention is paid to the status of the hormone "vitamin D"?

Even in such a developed country as Germany, nearly 80% of the population is not sufficiently provided with vitamin D. This means that all studies on various medical problems are performed on “sick people”, in any case on people “insufficiently provided with vitamin D”. Vitamin D insufficiency can cause fatigue, morning indisposition, and exhaustion [62]. These manifestations can be pronounced stronger or weaker depending on the vitamin D deficiency degree, individual features of the organism, etc. If so, what is the true value of chronobiological studies performed with such people?

Thus, many diseases are shown to depend on vitamin D level in the organism. Considering that in developed countries nearly 80% of the population is not sufficiently provided with vitamin D, it is surprising that the number of patients with one or another disease is even not higher than it is recorded presently. First, under relatively favorable conditions, humans are not inevitably ill with shortage of this hormone. The organism can adapt to an insufficient provision with various factors. Second, we do not know the number of people with so-called chronic inflammation. In humans of these two groups, any additional load (influenza, stress, etc.) can worsen their health suddenly and sharply. Moreover, many people are suffering from fatigue, nervousness, night sweating, dryness of skin and mucous membranes, neuropathic pains, joint pains, muscular-skeletal pains, paresthesia, absent-mindedness, insomnia, morning constraint, absence of motivation and enthusiasm, indifference, passivity, dissatisfaction, fear, depression, and food cravings. Very often, no organic causes of these states can be found.

Von Helden [62] treated 228 patients suffering from one of the above-listed symptoms. Every patient was given initially 100,000 IU vitamin D₃ per day for some days and then 20,000 IU per week. Even in 17 days, positive results were observed in 78% of the patients, and 20% the results were estimated as very good and in 26% as good. The author thinks the states with such symptoms to be associated with a disease of the vegetative nervous system, i.e. to vegetative dystonia. In many cases, these symptoms coincided with symptoms of fibromyalgia. Studies on vitamin D status or its taking revealed the dependence on vitamin D in patients with fibromyalgia [99-101]. But in works [102, 103] the correlation between vitamin D and fibromyalgia was not confirmed. However, in these works the level of vitamin D was far from sufficient in both control and experimental groups.

Other aspects that are consequences of the wide distribution of the above-mentioned symptoms among the population are also interesting. On one hand, many of these symptoms frequently occur in *very old people* who also have extremely low level of vitamin D. When very old people visit a physician and complain of such symptoms, the physician often speaks that it is common for the patient's age, and even “if you are older than 65 years and you do not have an ache you are already dead”, but it is

possible to improve the state of many such people and sometimes even significantly. The level of vitamin D in these people is very likely to be in the limits of 5-10 ng/ml, and why not save them from this extremely strong deficiency. It is quite reasonable to expect an improvement of the symptoms in about 80% of the patients!

What is the situation with *children and teenagers*? They also have a very low level of vitamin D (5-20 ng/ml, see above), and it is striking that many of the above-mentioned symptoms are widely distributed among these age groups. It is very likely that their chronic fatigue, absence of motivation and purposefulness, tendency for food cravings and obesity, depressive mood, flight to the world of narcotics, uninhibited aggression, and inclination to violence cannot be explained only by social reasons. Maybe a biological component also plays a role, e.g. the shortage of vitamin D.

The discussion of different consequences of an increase in the blood level of vitamin D₃ leads to the question *how the same chemical compound can be involved in such different processes in our organism*. First, we are to understand that vitamin D is not a pharmaceutical preparation! Second, vitamin D is not a vitamin! This substance was termed vitamin only because it was found to be an active component of cod-liver oil, which was used for treatment of puppies against rickets [13]. In fact, the so-called vitamin D can be synthesized in our organism, but only under the influence of UV radiation. Chemically, vitamin D is a secosteroid and can be ascribed to steroid hormones based on its biological action. Its major action is mediated through activation of certain genes [96, 104-106, 135], but non-genomic reactions are also described [98, 107].

WHAT MUST BE DONE FOR OPTIMAL PROVISION OF HUMANS WITH VITAMIN D?

It has been said already that vitamin D is present in many *food products*. However, its concentration in them is rather low. Fatty fish, eggs, and meat are especially rich with vitamin D. Carnivorous animals eat meat in great amount (see above), but people usually can insufficiently satisfy their need for vitamin D with meat. The content of vitamin D in fish and eggs is higher, but it is still too low [59] that to satisfy the need for vitamin D; a human would have to eat daily dozens of eggs or up to 2.5 kg fish. It is necessary to take into consideration how the hens were maintained and fed and whether the fish was caught in the sea or grown in special farms. The level of vitamin D in fishes can vary 4-6-fold [108]. In the best case, on using for nutrition the best opportunities, e.g. buying fish just caught in the open sea, a person can obtain with food only to 20% of their need for vitamin D, but in fact, humans satisfy with food only about 10% of their need in vitamin D. Only people inhabiting the far North or South are exceptions [59]. They do not obtain UV radiation at all.

They really eat only fatty fish and other animals of the Arctic and Atlantic Oceans. The liver of the polar bear is especially rich in vitamin D.

Humans can also obtain vitamin D due to its synthesis in the skin under the influence of *UV radiation*. We have already considered in detail problems associated with this pathway for present day humans. The question is *whether we really want to subject our skin to the influence of UV radiation in the due dose*. Our skin is already not pigmented sufficiently to protect us against oncologic diseases. Regular visiting solariums is also not recommended because their sources of UV radiation are often even more oncologically dangerous for white peoples' skin than solar radiation [109]. However, not all specialists believe that UV radiation has such a great threat of melanoma for humans with white skin [110]. Daily irradiation for no more than 15 min is recommended.

Taking into considering specific conditions of our existence, we cannot satisfy the need in vitamin D with nutrients. Moreover, because for different reasons (religion, traditions, special way of life, cancerophobia, etc.), many people are also unable to synthesize it in the skin under the influence of UV radiation!

The only thing to be done is addition of vitamin D to food products, e.g. enrichment of milk and milk products with vitamin D₃ or D₂ as it is done already in many countries (USA, Iceland, Sweden, Finland, France) [111], using vitamin D capsules (each capsule contains from 3000 to 5000 IU) (USA, France, Netherlands, etc.), using pharmaceutical preparations such as Dekristol 20000, Drisdol 50000, Pro D3 30000, Vitamin D3 20000, Sterogyl 20000, Zymad 10000, etc.

It would be reasonable to create in the future new agricultural products with increased concentration of vitamin D [25]. New cultivars of rice, wheat, soya, and other plants, which are major agricultural food products, would be capable of satisfying the basic need of humans for vitamin D that would be especially important for inhabitants of the developing countries.

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