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Mini Review

A Theory of Malignant Tumors Induced by Deficiency of Vitamin D1

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Abstract

The story of Vitamin D1 begins with the discovery of a new class of bipolar, partly water-soluble derivatives of polyhydroxylated 6-keto,7-dehydrocholesterol (ecdysone, ecdysteroids). The compounds were accidentally discovered in 1965 in the search for an insect moulting hormone. Soon after their discovery, these "insect hormones" were found widely distributed in multiple species of lower or higher plants, occasionally in enormously large amounts. We their action is to promote growth and cell proliferation in all organisms: plants, invertebrate or vertebtate animals, as well as in humans. Retrospective study revealed a broad spectrum of beneficial biological effects analogous to the effects of essential vitamins. Unlike the biologically inactive provitamins D2 and D3, the biological status of ecdysteroids can be traced down to the neglected vitamin D1, discovered 100 years ago as a special fraction of vitamin D, that was active without activation by UV-light. Our investigations on mitotic cell divisions and regeneration in insects revealed that the living cells of different tissues compose a mutually integrated system. Disturbance of the system by a natural cell death or artificial injury induces mitotic divisions in the neighboring cells. The divisions continue until the wound is replaced and tissue integration is again restored. According to our observations, the dividing cells require vitamin D1 (ecdysteroid) for successful construction and formation of cytolpasmic membranes. The healthy membranes are needed for restoration of the living cell integrity and termination of further divisions. The deficiency of vitamin D1 in insect haemolymph or human blood caused the formation of strange daughter cells with defective cytoplasmic membranes. The defective cells were not able to re-establish the integrity, stop further divisions and terminate the regeneraation process. The defective structures formed polynuclear syncytia of cells that are a characteristic of malignant tumors. Since the basic regulation of cell divisions and tissue regeneration are quite similar in plants, insects or mammals, a theory has been proposed that the pernicious, polynuclear tumors known in human medicine may also be produced by the deficiency of vitamin D1 in the blood. The vitamin is readily available from vegetable food and intestinal symbiotic flora. The theory also proposes a prediction of the risk of malignant tumor formation by comparing the blood content of vitamin D1 between the normal population and oncological patients.

Keywords: *Malignant Tumors; Deficiency; 7 Polar Hydroxylic; 7-Dehydrocholesterol; Hormones*

Outstanding German chemist P. Karlson accidentally discovered a new class of bipolar, partly water soluble derivatives of cholesterol. In the search for an insect moulting hormone, he extracted 500 kg of silkworm pupae and obtained 25 mg of a crystalline compound named ecdysone [1]. According to the current theory of Williams [2,3], the new compound was defined as an insect moulting hormone secreted by the prothoracic glands. The chemical structure of ecdysone and the related group of ecdysteroids was determined as the polyhydroxylated 6-keto, 7-dehydrocholesterol. In contrast to other derivatives of cholesterol, which are purely lipid soluble compounds occurring in animals (zoosterols), ecdysteroids are partly soluble in polar solvents, due to 6 or 7 polar hydroxylic groups displaced across the secondary or tertiary carbon atoms of the cholestane steroid template (Figure 1). Curiously enough, just several months after disclosure of ecdysone structure by Karlson, numerous phytochemists at different laboratories around the world reported finding these "insect moulting hormones" in a number of unrelated species of plants (see [4-6] for a review).

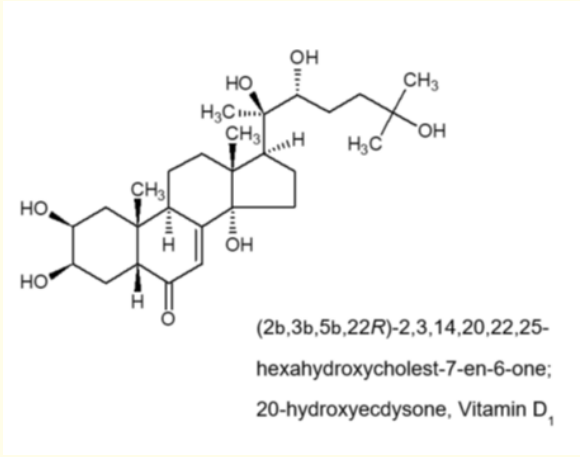

Figure 1: *Chemical structure of the polyhydroxylated 6-keto, 7-dehydrocholesterol (Vitamin D1, 20-hydroxyecdysone) which is widely distributed in insects and plants.*

The indicated, 60-year-old concept of ecdysteroid-insect hormones has been conservatively used until the recent time [7,8]. Our investigations on the mode of action of insect hormones revealed, however, that ecdysteroids could not be regarded as insect hormones because they breached the definition of an animal hormone. In addition, ecdysone cannot be regarded as the prothoracic gland hormone. The gland exhibits distinctive cycles of growth and development when endogenous concentration of ecdysteroids is extremely low. Alternatively, there are large peaks of endogenous ecdysteroid at the time of complete disintergration of the prothoracic gland [9-12]. According to the reutilisation theory proposed by Sláma [13], ecdysteroid incorporated into tissue and organs vanish from the pool of soluble ecdysteroid. They appear as soluble ecdysteroids in haemolymph after the disintegration of the old outlived tissue being reutilized for simultaneous growth of tissues of the next developmental stage [12].

"Insect hormones" in plants

After recognition that ecdysteroids were not insect hormones, we investigated the true biological status of these generally important sterolic compounds. Due to their enormous accumulation in the reserve organs of plants, sometimes in 100,000-fold higher amounts compared to the insect body [4], the first alternative results proposed in 1979 that ecdysteroids were the reserve growth factors of plants [5]. The proposition that an insect moulting hormone could be reserve material for plant growth annoyed the conservative chemical community (ecdysonists). Further studies in plant physiology showed that ecdysteroids were reserve substances although it did not exert the activity of phytohormones [14].

Most of the currently known literature data on ecdysteroids have been provided by professional phytochemists. The findings of ecdysteroid presence includes mostly sources from the plant kingdom, like microorganisms, yeasts, mushrooms, and several species of lower and higher plants [4-8]. The biosynthetic capacity of animal tissues for ecdysteroids has not been established so clearly. Ecdysone was first isolated from insects. However, according to some earlier reports from literature, insects and presumably other animals do not synthesize the triterpenoid sterol nucleus *de novo* from acetate. It is rather difficult to elucidate whether ecdysteroids found in the insect body originated by the insect´s own biosynthetic capacity or whether they came into insects from their diet [16]. This shows that it is not fully justified to distinguish between phyto- and zoo-ecdysteroids [8].

Insect hormones, reserve materials of plants or human medicine?

When it became clear that ecdysteroids were neither insect hormones [9-13] , nor did they stimulate insect ecdysis [9,12] and also that they had nothing in common with the regulatory functions of the prothoracic glands [10,12,13,17], there appeared serious confusion with respect to the actual biological status of these unique, bipolar, derivatives of 7-dehydrocholesterol. The first discussion on this subject appeared in a publication entitled: "What are ecdysteroids? Insect hormones, plant defensive factors or human medicine?" [18, 19]. The discussions about the concept of insect hormones or essential vitamins increased with the appearance of numerous reports on strong anabolic, growth stimulating effects of dietary ecdysteroids in domestic animals and also in human patients. The most important data in this respect were obtained by researchers in the former Soviet Union in 1970 - 1995 (Abubakirov [19], Syrov [20], review by Koolman [21], Sláma and Lafont [22] and Dinan and Lafont [23]. The extensive research performed mainly in the republics of Ukraine, Belorussia and Uzhbekistan revealed strong anabolic effects of ecdysteroids in animals and revealed also a plethora of beneficial pharmacological health effects, including stimulation in the growth of flesh and bones, stimulation of muscular performance of sport athletes, immunogenic, beneficial neurogenic, tonic, antifatigue, adaptogenic, anti-stress and anti-inflammatory effects [22]. The Soviet Union registered the first ecdysteroid-based pharmacological patent application already in 1980 under the name ECDISTEN. It recommended the use of 5mg pills of ecdysterone per day [22]. The material was prepared from extracted roots of the plant *Leuzea carthamoides* and other Asiatic plants [23-25].

We performed experiments using a strictly defined pharmacological criteria for investigations of the daily peritoneal injections of pure 20-hydroxyecdysone [25]. The animals were juvenile and adult mice [25]. The injections induced strong anabolic effects in female juvenile mice and in the adults of both sexes. The results confirmed the existence of general similarities between the effects of ecdysteroids caused by peritoneal injections and oral applications. The experiments on mice showed considerable similarities between the effects of phytoestrogens and vitamins D and E [26]. The majority of previous reports on the anabolic action of ecdysteroids in vertebrates was made on domestic animals, predominantly mammals [22]. We explored a possibility of ecdysteroid effects on birds, using Japanese quails as the assay animals [26-27]. Curiously enough, the effects on quails were even more pronounced than in mice. The addition of graded amounts of pure 20-hysroxyecdysone (Vitamin D_1) to a standardized diet increased the growth rate of the juvenile quails more than did the commercial food additives [26]. In addition, measurement of ecdysteroid content in the blood of the investigated quails, determined by susceptible RIA methods, revealed the retention and storage of these vitamin-like sterolic compounds in the blood serum of the experimental animals. The blood concentration of ecdysteroid was directly proportional to the amounts added to the diet [27].

Storage of vitamin D_1 in blood of Japanese quails

Recognition that animals retain and store the dietry ecdysteroid in blood is biologically very important, especially with respect to retention and urinary excretion of the dietary vitamins. Recent reports show [28], that ecdysteroids are frequently consumed with food (spinach, Quinoa, Corn). Moreover, large amounts of the dietary ecdysteroid are rapidly excreted in the human urine [29]. It is a common physiological feedback mechanism preventing hypervitaminosis. These new facts show many features in common with the above described, 30-year old observations on storage and retention of ecdysteroid in the blood of Japanese quails [26-27]. In order to prove the validity of the old data, we have recently repeated experiments with commercial chicken broilers. The results shown in Figure 2 are quite consistent with the data obtained in Japanese quails. A graded addition of up to 0.05 % of pure 20-hydroxcdysone (vitamin D_1) into a standardized diet produced a proportional increase of chicken body mass, similarly to the case of the Japanese quails [27-28]. It is more important, however, that the data in Figure 2 also reveals the proportional retention of the dietary vitamin D_1 from 0.5 to 2 and 5,5 ng/100µl of blood serum (Figure 2).

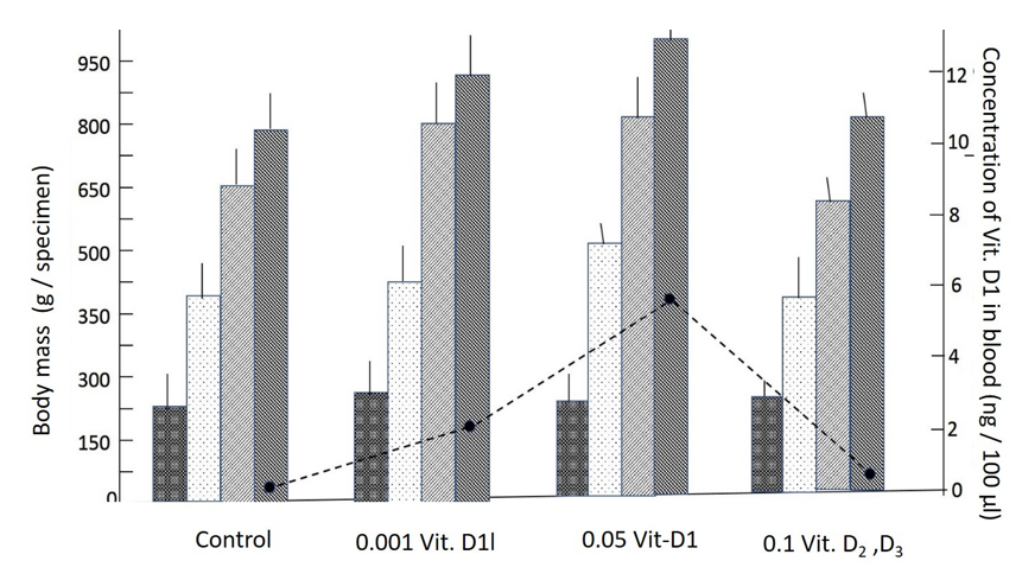

Figure 2: *Effect of the dietary addition of 0.001 to 0.05 % of pure vitamin D1 (20-hydroxyecdysone) on growth of tbody mass in chickens kept on sdtasndard diet for broilers. The columns show age (control, 10-, 20-, 30-days-old xhicken). The RIA method used for determinaation of vitamin D1 in chicken blood has been previously described [26, 27].*

Due to the rapid urinary excretion of exogenously applied vitamin D_1 [29], there is no danger of hypervitaminosis in people. Theoretically, this could appear as hypoglycemia, due to increased incorporation of glucose into glycogen, which is deposited in muscle fibres. In insects, on the other hand, ecdysteroid hypervitaminosis is a common feature. It results in developmental disturbances, when exogenous ecdysteroid has been applied out of the strictly delimited endogenous ecdysteroid peaks. The phenomenon was first described by C. M. Williams using the first sample of ecdysone received from P. Karlson. The phenomenon was described as "hyperecdysonism." Similarly, to the human body, injections of large amounts (up to 1 mg) of ecdysteroid into the feeding caterpillars of *Manduca sexta* were rapidly disposed of in the form of excrements. By contrast, a 1000-fold smaller dosage injected into the nonfeeding pepal stages produced large developmental, hyperecdysonic deviations [31]. The adverse hypervitaminosis effects were experimentally avoided by synthetic preparation of bulky ecdysteroid-porphyrine complexes. They slowly released the biologically active, free ecdysteroid by metabolic hydrolysis of the complex [30].

The recent phytochemists still make a distinction between the class of phytoecdysteroids and zooecdysteroids [8,28]. Nobody knows, however, what is a true zooecdysteroid, because animal herbivores receive a lot of essential ecdysteroids from vegetable food. When Karlson isolated ecdysone from silkworm pupae, he did not know that this " insect hormone" was a widely distributed secondary substance in plant food [1].

The biologically inactive provitamins D_2 and D_3

With increasing data, it became obvious [22,27] that the biological status of ecdysteroids was a vitamin, not an Arthropod moulting hormone. The accumulated experimental results on the anabolic, growth promoting effects of ecdysteroids in invertebrate and vertebrate animals [review 22], suggested that the respective type of the vitamin should be closest to the antirachitic, anabolic and growth promoting

vitamin D. This vitamin and ecdysteroids share the common structural backbone represented by 7-dehydrocholesterol. In addition, these vitamins share the common, quantitatively dependent dose-response relationships (Figure 2). Alternatively, as in the case of insect juvenile hormone, a minimum physiologically active concentration as well as 5000-fold larger dosages produce a qualitatively identical, maximal biological effect [31]. According to these pharmacological differences, ecdysteroids, like toxins, drugs and other physiologically active compounds, should be classified among vitamins not hormones.

Vitamin D stimulates the somatic growth in newly hatched or newborn animals. Deficiency of vitamin D causes retardation of growth known as the ratchet disease (rachitis) (review by Wolf , [32]. Structural identification of vitamin D some 100 years ago was very difficult. The assays indicated that it was somehow related to 7-dehydrocholesterol. At that time, derivatives of cholesterol were recognised as a purely lipid soluble, nonpolar moieties. Unlike all other vitamins they were recognised as zoosterols, that were absent in plants. The sources of vitamin D were thus compared to animal lipids, like lard, butter or fish oils. A. Windaus and his co-workers [33] identified in animaal skin seco-sterol compounds related to 7-dehydrocholesterol. They were called vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol). These vitamins were biologically inactive provitamins D_2 and D_3, which were activated in animal skin by UV-light. The idea about UV-radiation came from chemical laboratories where it was used for photochemical conversion of cholesterol into 7-dehydrocholesterol. The pioneers of vitamin D research, A. Windaus and his colleagues, irradiated vitamin D_3 by UV-light and obtained a biologically active fraction indicated as the vitamin D_1 [34]. Although they tried very hard, they failed to identify the biologically active D_1 fraction. According to old textbooks of isoprenoid chemistry, cholesterol derivatives were strictly apolar compounds and occurred only in animals. The partly polar, hydroxylated derivatives of 7-dehydrocholesterol were unknown at that time. For this reason, the chemists investigated only apolar fractions while polar fractions were discarded without being tested for antirachitic activity. Provided that the mysterious, active fraction D_1 contained a partly hydroxylated 7-dehydrocholesterol, it was undetected. The polyhydroxylated sterols became known to organic chemistry only some 30 years later, after the discovery of ecdysone [1]. Unfortunately, the biologically active vitamin D_1 of Windaus and his colleagues remained unidentified until this time [35].

The abundance of bipolar, partly water soluble, polyhydroxylated sterol (ecdysteroids) in microorganisms, mushrooms and various species of plants [6-8, 19, 21, 23, 28], challenged the view of isoprenoid chemists that cholesterol was exclusively a zoosterol. We found that certain plants contained 700-fold more of the polyhydroxylated 7-dechydrocholesterol in comparison with the true plant sterols, like ergosterol or β-sitosterol [36]. The absence of cholesterol in plants was explained by its preferential hydroxylation, which resulted in increased polarity and practical disappearance from the pool of purely apolar, free sterol fractions.

More recent pharmacological data on provitamin D_3 (calciferol) showed that it can be metabolically hydroxylated and converted in the liver or kidneys into the biologically active alciferyltriol. The biological activity of hydroxylated vitamin D_3 -triol (2, 25-dihydroxy, 7-dehydrocholesterol) without UV-light accentuated the importance of hydroxylated sterol for the acquired growth-stimulating properties of vitamin D. It has been reasonably concluded by Sláma [37-40] that ecdysteroids may actually represent the true, active antirachitic vitamin D. As in the case of other vitamins but unlike the provitamins D_2 and D_3, animals can get plenty of the dietary ecdysteroids (vitamin D_1) from a vegetable diet. Unlike the exclusive lipid solubility of vitamin D_3, the bipolar vitamin D_1 is bipolar, partly soluble in water and partly in lipid solvents. This property is due to the already built-in 6 or 7 polar hydroxylic groups. The greatest advantage of this bipolar vitamin, is the pronounced anabolic, growth promoting property in insects, birds or mammals, including humans [review 22-23]. For all of the above mentioned reasons and the lack of dependence on UV-light, it has been reasonably concluded that the neglected and unidentified vitamin D_1 should be the long known ecdysteroid [38].

Unfortunately, the recent pharmacological status of the biologically inactive provitamins D_2 and D_3 did not change too much from the definition created 100 years ago. The cumbersome theory of activation by UV-light, derived from a laboratory test-tube, has never been experimentaly reconfirmed. Nobody wants to accept that physicians have used a false vitamin D for 100 years. To get the effects of vitamin

D, doctors prescribe enormous daily dosages of the inactive vitamin D_3, in the hope of getting its metabolic conversion into the biologically active calciferyltriol.

Theoretically, the most important role of the antirachitic vitamin D can be expected during the period of embyroenesis and in newly born babies. In mammals, vitamin D should be urgently needed in milk. The content of provitamins D_2 and D_3 in commercial milk is rather low, not higher than in the other organs. During our investigations on the dietary effects of vitamin D_1 (20-hydroxyecdysone) in Japanese quails [26,27], we performed preliminary measurements of D_1 content in milk, using RIA immunological methods developed for insects. We obtained extraordinarily large readings for vitamin D_1 , which was in the range of 100 µg of D_1 per ml of milk. We assumed that the RIA method might be wrong and refrained from further measurements.

In previous sections we could observe some differences between the currently used vitamins D_2 and D_3 and the biologically active, bipolar vitamin D_1. The brief recapitulation of the data can perhaps help to summarise some of the essential points: 1. The basic structural feature of all D-vitamins is the triterpenoid backbone of 7-dehydrocholesterol; 2. The biologically inactive provitamins D_2 and D_3 are expected to be purely lipid soluble compounds, activation of the biological activity requires exposure of animal skin to UV-light; 3. Vitamin D_1 (ecdysteroid) is biologically active without exposure to UV-light, it is partly soluble in lipid solvents as well as in polar water solvents; 4. A specific structural feature of D1 is the presence of 6 or 7 polar hydroxylic groups (paradoxically, a cholesterol sugar) ; 5. A further structural characteristic is the conjugated, 6-keto -7 dehydro unsaturation in the B ring of cholestane, with strong electron accepting ability, introducing hydroxylic functions into secondary and tertiary C-atoms; 6. Unlike other vitamins, D_2 and D_3 are thought to be manufactured within the animal body, not in the plant system; 7. The bipolar Vitamin D_1 is biosynthetised by microorganisms, yeasts, mushrooms and in a number of plant species, including common vegetable foods (spinach, quinoa, corn, [28]; 8. Animals which feed on a vitamin D_1 deficient diet (Termites, Cattle) receive vitamin D_1 from intestinal bacterial symbiotic flora; 9. Some plants synthesize vitamin D_1 in their green leaves during the season and store enormous quantities of the vitamin in seeds and roots for stimulation of growth in the next season; 10. The vitamin D_1 (ecdysterone) containing extracts from *Leuzea carhamoides* (ECDISTEN, root extracts, tablets), *Serratulaa coronata* (SERPISTEN), *Cyanotis arachnoide*a (98% pure ecdysterone by Alibaba, Amaon) have been commercially used by athletes for improving muscular activity); 11. As has been already mentioned, vitamin D_1 produces strong anabolic, growth stimulating effects in insects, mice, birds, domestic animals and in the human body [18, 19, 22, 29].

Vitamin D_1 deficiency theory of malignant tumors

The conclusions are based on the studies of mitotic cell divisions and regeneration of excised epidermal patches in insects [4, 8, 18, 30, 31, 40-43]. The most important vitamin that is required for growth and proliferation of cells in plants and animals, was originally discovered as an insect hormone (ecdysone). Recently it turns to be the previously neglected, polyhydroxylated, 6-keto, 7-dehydrocholesterol, or vitamin D_1 . This vitamin represents a special class of unusual, partly polar derivatives of cholesterol, which is used for the construction of structurally and physiologically compatible cytoplasmic membranes during the mitotic cell divisions. For a long time, the vitaminic properties have been camouflaged by the erroneous belief that it was an insect moulting hormone. During the work on isolation of vitamin D in 1930, the bipolar derivatives of 7-dehydrocholesterol were absolutely unknown. The structure of vitamin D was incorrectly assigned to exclusively lipid soluble, biologically inactive provitamins currently known as provitamins D_2 and D_3, which need to be tentatively activated by UV-light.

I found that ecdysone was not an insect hormone and it did not stimulate insect ecdysis. These suspicions brought me back to the conclusions of A. Windaus in 1930. He obtained the real biologically active fraction of vitamin D, after irradiation of vitamin D_3 by UV-light. The active principle was called vitamin D_1. Since that time, chemists of various laaboratories tried to identify the structure of the biologically active fraction of vitamin D, but the structure has never been resolved. I trust that the data presented in previous sections provides well based evidence that the neglected vitamin D_1 is ecdysteroid or ecdyson.

The accumulated data led me to assume that vitamin D_1 was absolutely essential for successful mitotic divisions and regeneration both in animals and plants. I have proposed a theory of tumor formation that stems from the following statements: 1. The living cells of an animal tissue represent a physiologically integrated unit, dependent on direct, cell-to-cell communication; 2. Disturbance of the system by a sudden cell death or artificial injury, induces mitotic divisions in the neighboring disconnected cells. 3. The mitotic divisions are immediately arrested when the cell-to-cell communicaton integrity become re-established. 4. The restoration of integrity in the daughter cells depends on the ability of the dividing cells to develop the structurally compatible cytoplasmic membranes. 5. In order to develop perfect structures, the mitotically dividing invertebrate or vertebrate cells require the presence of ecdysone (vitamin D_1, or polyhydroxylated 6-keto,7-dehydrocholesterol). 6. In the absence of vitamin D_1, the regenerating cells produced atypical, structurally defective, polynucleated syncytia with incompatible cytoplasmic membranes and endomitotically dividing cell nuclei. 7. The vitamin D_1-deficient, polynuclear metaplasia were not able to restore the tissue integrity and did not stop the endomitotic nuclear divisions. 8. The aberrant polynucleated syncytia assumed a structure similar to the malignant, polynuclear tumors.

A retrospective look at the antirachitic (against ratchet growth retardation) principle shows that the growth stimulating factor, vitamin D, shoud be present in the milk of newborn babies. As has been already mentioned, the provitamins D_2 nd D_3 are not present in milk in sufficient quantity. I can reasonably predict, however, that due to its large anabolic effects, the magic growth and immunity factor in milk is the vitamin D_1 . So far, nobody has invested large efforts into a search for "insect moulting hormone" in milk. Moreover, nobody dares to question the usefulness of the provitamins D_2 and D_3, which have been broadly used in medicine for almost 100 years. It may be relatively easy to prove or disprove the importance of vitamin D_1 in prevention of tumors or retarded growth by analysis of its concentration in the blood or milk. Unfortunately, these measurements were abandoned due to the belief in an insect hormone.

As it has been mentioned that vitamin D_1 is readily accessible from a vegetable diet or intestinal symbiotic flora. We know that the vitamin is stored in the blood stream (Figure 2). This content can (potentially?) be used for a simple prognosis of the risk of malignant tumor formation. At first, the concentration of vitamin D_1 is measured in the blood of the tested subject. Subsequently, the risk of malignant tumor is determined by comparison of the data with the level of vitamin D_1 in oncological patients [39,41]. The most susceptible tissue to a deficiency of vitamin D_1 are mainly tissues with the relatively large, acinose cells, which manufacture and release proteins (milk glands - casein; intestinal epithelium – trypsin; pancreas – insulin; prostate – sperm proteins; thyreoidea – thyreoglobulin;). Additional susceptibility includes the frequently injured or intoxicated cells from adverse chemicals (alcohol, smoke, drugs). The nerve cells, which do not undergo mitotic divisions, need the bipolar vitamin D_1 for the reconstitution of defective structural elements.

The last point to be mentioned is concerned with the temporary inhibition of all mitotic divisions, with chemotherapy. Due to the still unknown origin of malignant tumors, chemotherapy and surgical treatment became the best methods for saving the lives of onclogical patients. Provided that the proposed D_1 avitaminosis theory could be generally confirmed, the combinations of surgery, chemotherapy and a supply of vitamin D_1 could hopefully save the lives of many with a diagnosis of malignant tumors.

The content of vitamin D_1 in human blood, in the milk or vegetable food is almost unknown. Biological health effects of the vitamin have not been well investigated due to the notorious beliefs into an insect hormone. The potentially adverse effects of D_1 avitaminosis may not include only growth of the malignant tumors, but also a number of so far incurable diseases of unknown etiology. "If you do not know the vitamin, you cannot cure the avitaminosis". The miraculous beneficial health effects have been just described in the latest publication [39-41].

It may be useful to list the common synonyma of the neglected vitamin D_1: ecdysone, 20-hydroxyecdysone, ecdysterone, crustecfysone, ecdysteroid, phytoecdysteroi, insect hormone, prothoracic gland hormone, arthropod moulting hormone, root of the deer Maral.

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