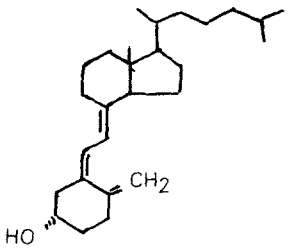
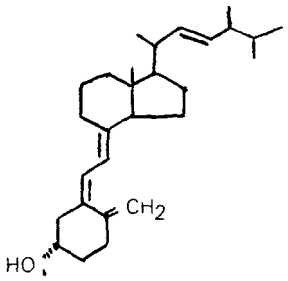


CHOLECALCIFEROL
(Vitamin D_3)



EROGOCALCIFEROL
("Vitamin D_2")

The Vitamin D-Problem

An Important Lesson in

Orthomolecular Medicine

J.Y. Moon, B.S.,[1] and CJ. Reich, M.D.[2]

Orthomolecular Medicine Defined

The prefix "ortho," from the Greek "orthos," meaning straight or correct, in the term "Orthomolecular therapy" indicates that the therapy is of substances which are the same as those that are naturally present in the human body.

The original definition of this term, in which inference to the correction of deficiency is made, is contained in the following statements by Linus Pauling: "Orthomolecular therapy is the treatment of disease by the provision of the optimal molecular constitution of the body, especially the optimum concentration of substances that are usually present in the human body" (1967) and "The word Orthomolecular may be criticized as the Greek-Latin hybrid. I have not, however, found any other word that expresses the idea of the right molecules in the right amount" (1968).

1 12701 S.E. King Road, Happy Valley, Oregon 97236.

2 205 A-906 8th Ave. S.W., Calgary, Alta., T2P 1H9, Co-Chairmen, International Committee for Re-Eval uation of Irradiated Ergosterol in Human Pathology.

These definitions seem relatively straightforward and simple, but in application they may be extremely complex. The all-too-complex "vitamin D-problem" is an excellent example of the extreme importance of accuracy in interpreting and applying the important principles of Orthomolecular medicine. Hopefully, a solution to the vitamin D-problem is close at hand, and will help to give direction to the developing young science of Orthomolecular medicine.

Fish Liver Oil: An Early Example of Orthomolecular Medicine

In historical perspective, the evolution of the "Orthomolecular concept" is closely interwoven with the development of the nutritional sciences. In his book, **Vitamin C and the Common Cold,** Pauling (1971) has traced the history of the development of the "vitamin hypothesis" with special emphasis on vitamin C in prophylactic levels for the prevention of scurvy and in "megavitamin" levels for the prevention of the common cold and related illnesses. Since rickets is

one of the four classical diseases suggested by Funk in his 1911 publication of the "vitamine hypothesis" to be due to faulty nutrition, a similar historical review of fish liver oil and the subsequent development of the vitamin D-problem should have great relevance in the theory and practice of Orthomolecular medicine.

Long before vitamin D was known to exist, the healing qualities of fish liver oil were well known. In his classical text, **Rickets, Osteomalacia, and Tetany,** Dr. A. F. Hess provides us with the most accurate historical account of fish liver oil therapy (1929):

"...The *history of cod-liver oil is especially instructive and may well serve as a lesson to the medical profession in regard to the attitude toward popular remedies.*

"It is usually impossible to ascertain just when and where a remedy not elaborated by man, such as cod-liver oil or fish oil, was first used as a therapeutic agent. There are indications that it was employed by the peoples who lived along the shores of the Baltic and North Sea, as well as by those on the coast of Scotland, many years before attention of physicians was directed toward its virtues. The earliest reference to its medicinal use, which we have been able to find, does not emanate from a district bordering on the sea but from the inland city of Manchester, England. The introduction of cod-liver oil into medicine must always be associated pre-eminently with Manchester. Although we are not informed as to the year in which it was first prescribed for patients of the Manchester Infirmary, we learn from a letter written in 1782 by Dr. Robert Darby, the house surgeon and apothecary, that the annual consumption of this oil, soon after its introduction in 1766, was from 50 to 60 gallons."

This early application of fish liver oil was in the treatment of rheumatism, arthritis, and related diseases, where fish liver oil both topically applied and orally ingested was reported to be effective. The first definite account of the employment of cod liver oil in a case of rickets was given by the German physician, D. Schuette, in 1824 (Schuette, 1824). Schuette published case histories of adults and of children whom he had cured with cod liver oil and remarked that he had used this remedy for 25 years and found it "as specific and reliable as the use of mercury in syphilis."

The medical literature of Germany during the mid-1800's is replete with articles on the value of cod liver oil as an "analeptic" or reparative agent, especially in cases of rheumatism, scrofula, gout, etc. Cod liver oil was also used for "strumous ophthalmia" (xerophthalmia) in the children's wards of the Charite' Hospital in Berlin.

Like many household remedies, however, fish liver oil was soon to fall into disrepute and be virtually forgotten, only to be rediscovered at some later date. The healing qualities of fish liver oil began to be rediscovered in 1917 when Hess and Unger (1917) carried out a study of the "Prophylactic Therapy for Rickets in a Negro Community" and concluded that "cod-liver oil proved to be a more potent factor than breast-feeding in warding off rickets."

In 1919, Mellanby published radiographs which left no doubt of the specificity of cod liver oil in preventing and reversing experimental rickets in puppies, and in 1921 Park and Howland (1921) showed in a similar way that calcification of the epiphyses could be brought about in rachitic infants by giving this oil. Thus cod liver oil became universally acknowledged to be a specific for rickets—one of the few specific remedies with which medicine is blessed.

In 1922 McCollum (1922) demonstrated the presence of a fat-soluble antirachitic substance in fish liver oil, which he designated "vitamin D."

Sunlight: A Second Example of Orthomolecular Medicine

The earliest clear clinical description of rickets comes to us from early industrial England. As Loomis (1970) has observed, "In actual fact rickets was the first air-pollution disease. It was first described in England in about 1650, at the time of the introduction of soft coal, and it spread through Europe-with the

Industrial Revolution's pall of coal smoke and increasing concentration of poor people in the narrow, sunless alleys of factory towns and big-city slums."

Although rickets from its earliest inception has been clearly associated with smog, big-city shade, and lack of solar radiation, it was not until 1916 that Rollier published the first indication that solar radiation might be effective in the prevention of rickets (Rollier, 1916). He wrote, "the sun cure is without doubt the treatment of choice in rickets."

This early recommendation of heliotherapy has been completely lost sight of, and Dr. Kurt Huldschinsky (1919, 1925) is generally given credit for being the first to employ ultraviolet radiations in the treatment of rickets. Working in Berlin, Huldschinsky observed the greater incidence of rickets among infants born in the fall and winter months than in the spring and summer. He also recognized the protective effect of living in mountainous regions where the sun's ultraviolet radiations are strong. Since the climate afforded little opportunity for direct solar exposure during the winter months in Berlin, Huldschinsky employed the newly-marketed sun lamps to treat his rachitic infants. His results were remarkable, and, for this achievement, he is rightly recognized as the first to demonstrate the specificity of ultraviolet radiation in rickets prophylaxis.

With the publication of Huldschinsky's first report in 1919, and its subsequent verification by Hess (1922, 1923, 1924), Hess and Weinstock (1923, '1927), Kramer et al. (1922), Kramer et al. (1921), and others, two methods of rickets prophylaxis and cure (fish liver oil and ultraviolet radiation) were clearly documented.

Ultraviolet Radiation and Vitamin D: The Birth of Irradiated Ergosterol ("vitamin D_2")

In 1924, Hess (1924), Steenbock and Nelson (1924), independently and almost simultaneously reported that various foods, for example cottonseed and linseed oils, which were of no value in rickets, could be endowed with specific antirachitic properties by subjugation to the rays of the mercury-vapor lamp. The ultraviolet radiations responsible for this activation of oils and foods were of the same wave-length as those which would cure rickets, and it was therefore suggested that the antirachitic factor produced in these foods by artificial ultraviolet activation was also produced in humans when exposed to solar ultraviolet radiations. The fact that these foods in their natural state have no antirachitic potential was attributed to the low-intensity of the short ultraviolet radiations emanating from the sun.

Early in 1925, Hess and his collaborators (Hess et al., 1925) and Steenbock and Black (1925) found that although cholesterol possessed no antirachitic activity, it acquired marked antirachitic properties after it had been irradiated for a short time by means of a mercury-vapor lamp, and it seemed as if the origin of the antirachitic factor had been fathomed: cholesterol in the skin was activated by ultraviolet light to give rise to the antirachitic factor.

Soon, however, the accuracy of this conclusion was to be questioned when it was discovered by Rosenheim and Webster (1926) that cholesterol which had been treated with charcoal could not be activated, and it was concluded that ordinary cholesterol was contaminated with a substance which they termed "vitasterol", the true precursor of vitamin D. They also reported that ergosterol was one of the sterols which could be activated by means of irradiation.

With the successful synthesis of highly purified irradiated ergosterol in 1927 (Rosenheim and Webster, 1927, 1928), and demonstrations of potent antirachitic activity, it became accepted that ergosterol occurs naturally in humans and is the true antirachitic vitamin-precursor.

Thus in the 1929 edition of **Rickets, Osteomalacia, and Tetany** (Hess, 1919), Hess wrote:

"The relationship of ergosterol to the etiology of rickets may be rationalized as

follows: Ergosterol is contained in the skin and probably in almost all animal tissues and cells, in combination with the omnipresent cholesterol. In order to be activated, it requires but a small intensity of ultra-violet radiations and the resulting product is needed in but a minute fraction of a milligram to bring about calcification of the bones. It is highly probable that the action of sunlight in protecting against rickets comes about through the mechanism of the activation of ergosterol in the skin and in its circulating blood."

We know today that this interpretation is not correct. It is specifically 7-dehy-drocholesterol which is activated by ultraviolet radiation to have antirachitic properties, and the plant steroid, ergosterol, does not occur naturally in humans or other animals. By the time this mistake was discovered in the mid-30's, it was too late to turn the tide and rather than recognize the nonidentity of irradiated ergosterol and the natural antirachitic factor, it was proposed that "vitamin D" is represented by a large number of activated sterols which constitute the "vitamin D-group."

Origin of the Vitamin D-Problem: Irradiated Ergosterol is Not Vitamin D

Prior to the advent of irradiated ergosterol there is a paucity of information regarding possible toxicity of cod liver oil vitamin D. In fact, to the best of my ability to determine there are only two published papers dealing with this subject (Agduhr, 1926) prior to irradiated ergosterol. Both reports are from the same physician and involve the use of very large amounts of fish liver oil.

Within months after the introduction of Vigantol—one of the first commercial preparations of irradiated ergosterol —reports of toxicity began to appear (Bamberger, 1929; Collazo et al., 1929; Fischl and Epstein, 1929; JAMA Editorial, 1928; JAMA Editorial, 1929; Lancet Editorial, 1928). From that time to now, these reports on the toxicity of the "vitamin D-group" have literally flowed from laboratories and clinics throughout the world at a phenomenal rate of more than one each month (Moon, 1974)!!

At first it was hypothesized that the irradiation of ergosterol was accompanied by the production of unwanted side-products, appropriately designated Toxisterol (Reed, 1939). Toxisterol was never isolated, but Vigantol was withdrawn from the market, the method of synthesis was altered many times, and each new product claimed freedom from toxisterol. Many expert physicians and careful clinicians warned that this extreme toxicity was directly attributable to the unnatural nature of irradiated ergosterol (Moon, 1974), but these many warnings went unheeded, and irradiated ergosterol virtually completely replaced the natural vitamin/hormone of fish liver oil, activated 7-dehydrocholesterol.

Although irradiated ergosterol ("vitamin D2," ergocalciferol) and activated 7-dehydrocholesterol (vitamin D3, cholecalciferol) are the best-known members of the "vitamin D-group," there is a large number of sterols which may be activated by ultraviolet radiations to have antirachitic properties.

Some of these are very toxic to humans, while others have very little antirachitic potency, or toxicity. Since these isomers may vary a hundred-fold or more in toxicity from one animal species to another, there was little way to assess potential toxicity of any particular isomer to humans, except by trial and error. Since it was believed that ergosterol might occur naturally in humans, and since relatively rich sources of ergosterol were readily available from yeast colonies, ergosterol, rather than the very scarce 7-dehydrocholesterol, was chosen for activation and general use as "vitamin D." "D2" is used in all D-fortified foods today (Committee on Nutrition, 1963) as well as in most multivitamin supplements.

Magnitude of the Vitamin D-Problem

Although it is commonly believed that chronic vitamin D3 deficiency only involves the metabolism of bone to cause rickets and osteomalacia, a more careful review of the published literature clearly

reveals that inadequate ultraviolet radiation, or chronic deficiency of its dietary equivalent, vitamin D3, alone or in some cases supported by a chronic vitamin A deficiency, may cause a wide spectrum of diseases involving smooth and skeletal muscle, conjunctivae, skin, and mucous membrane.

Reich (1971) has presented evidence that chronic asthma responds to vitamin D3, vitamin A, and bone meal therapy as if it were a deficiency disease. Moreover, he has suggested that this disease is but one of a genus of "spastic conduit diseases" all of which arise for reason of spasm of the smooth muscle of the muscle-walled conduits of the respective organs. Reich, moreover, suggests that spasm of this very functional muscle arises partially for reason of abnormal ionization, created by chronic mineral and vitamin D deficiency, and partially for reason of the manner in which these conduits are constricted in autonomically controlled adaptive function to attempt physiological compensation of the biochemical changes enforced by chronic deficiency. For these reasons, these and other diseases have been also defined as the "deficiency-maladaptive diseases."

Increased irritability of skeletal muscle and heightened tendon reflexes, almost invariably found in association with these disease states, are considered as arising for reason of the same biochemical defect of the contractile mechanism of striated muscle.

Hess (1929) suggested that spasmophilia (infantile tetany) is also a D3 deficiency disease. Knapp (1974) has been studying the role of insufficient vitamin D3 in various eye afflictions for the past 40 years and is convinced that some of these diseases are also due to vitamin D deficiency.

Table 1 lists some of the illnesses which may result from chronic vitamin D3 deficiency.

On the other hand, Seelig (1969, 1970), Taussig (1966), Selye (1962), Taylor (1972), and many other respected physicians and clinicians (Moon, 1974) have

TABLE 1

Some Diseases Attributed to, or Associated with, Vitamin D3 Deficiency

A) Mineral Transfer Diseases
Rickets Osteomalacia Osteoporosis Rheumatoid Arthritis Presenile Osteoarthritis

B) Spastic Conduit Diseases*
Spasmophilia (Infantile Tetany) Bronchiolar Spasms (Asthma) Coronary Spasms (Coronary) Peripheral Artery Spasms (Hypertension) Gastrointestinal Spasms
-stomach (gastric spasm and gastric ulcer)
-duodenum (duodenal ulcer)
-ileum (ileitis)
-colon (colitis, constipation) Cerebral Spasm
-large temporal artery (migraine) Genitourinary Spasm
-bladder (enuresis)

C) Eye Afflictions
Keratoconus
Myopia
Allergic Conjunctivitis
Night Blindness * **The Spastic Conduit Diseases may be further classified as direct or indirect vitamin D3 and mineral deficiency diseases. The direct effect is mediated by ionic imbalances in the conduits themselves, while the indirect effect is mediated via the autonomic nervous system.**

clearly documented the possibility of widespread poisoning by "vitamin D." Often in the published literature no distinction is made between irradiated ergosterol ("D2") and vitamin D3, but in light of preponderant evidence that it is almost invariably "D2" which has been responsible for human poisoning, we have listed these in Table 2 as the "D2" Excess Diseases. In the accompanying figure, we have attempted to show diagrammatically the origin, classification, and control of the D3 Deficiency and "D2" Excess Diseases.

The past decade has witnessed remarkable advances in knowledge concerning the mode of activity and functions of vitamin D3 in human and animal physiology. Some of the presently known functions are listed in Table 3. Details regarding vitamin D3 activity have been summarized recently by Ohmdahl and

TABLE 2

Diseases which may be induced by "D2" Excess

A) Hypercholesterolemic Diseases
Atherosclerosis Rheumatoid Arthritis Peripheral Vascular Disease Idiopathic Hypercalcemia

B) Deposition of Calcium
-In Conduits Coronary Artery Disease Cerebral Sclerosis Peripheral Vascular Calcification -In Other Tissues
Kidneys (renal calculi) Eyes -Band Keratophathy -Cataracts -Macular Degeneration

C) Variation in Serum and Urine Calcium Levels
Urinary Stones
Renal Acid Phosphaturia
Magnesium Deficiency
Idiopathic Hypercalcemia of Infancy -Hypercalcemic Convulsions -Supravalvular Aortic Stenosis -Generalized Arteriosclerosis of Infancy -Infantile Iliac Artery Calcification -Infantile Carotid Artery Calcification

D) Heavy Metal Poisoning
-Lead -Mercury -Strontium -Cadmium

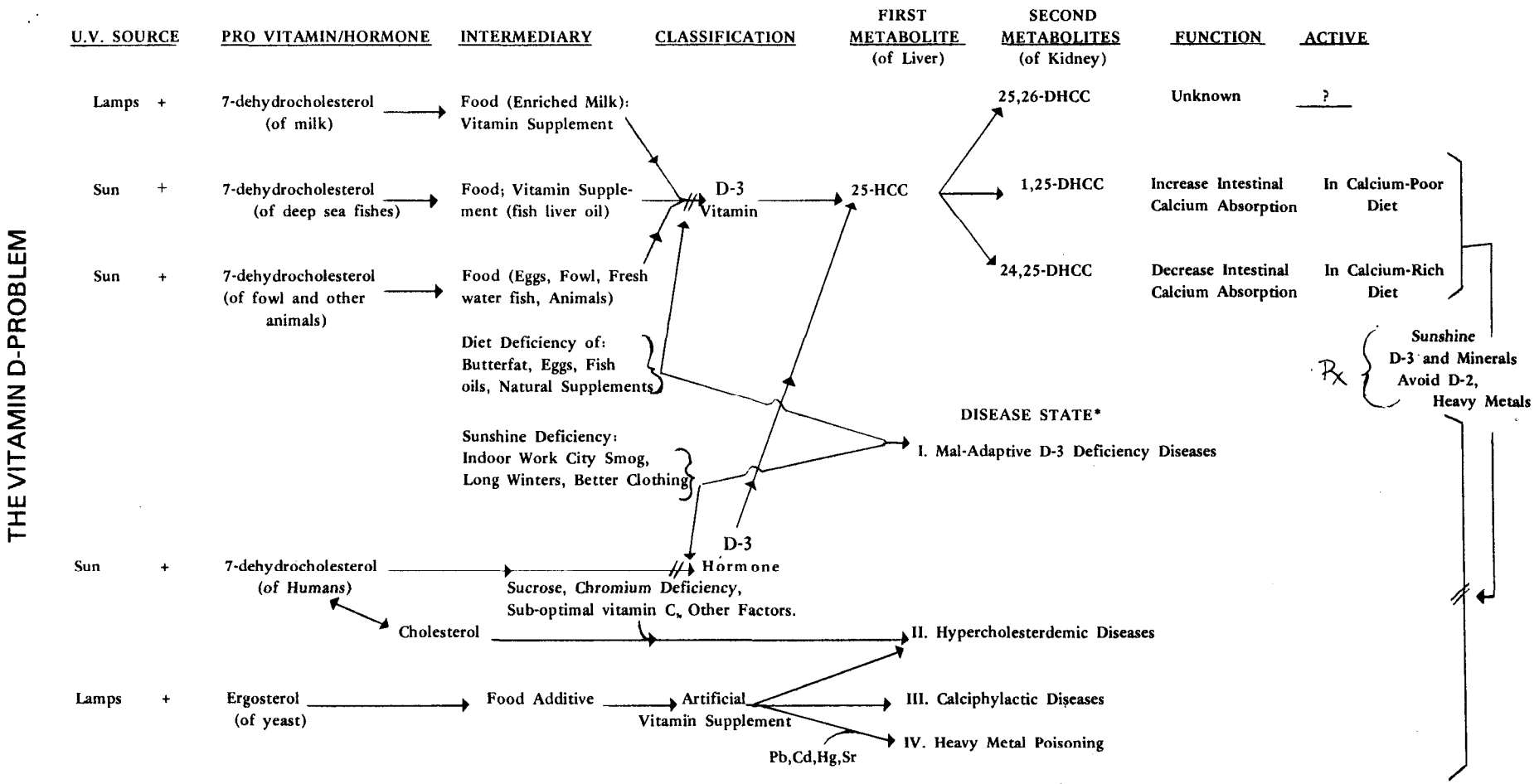
It is still uncertain how vitamin D3 metabolism is different from that of "D2," or why "D2" is apparently so much more toxic to humans than is the natural vitamin/hormone. For this reason, we wish to reiterate Reich's (1972) recommendations: "....until the possible existence of varying biological effectiveness and of toxicity in the human has been thoroughly investigated, I suggest that the profession and public be advised by labelling in an appropriate fashion when each of the D-vitamin substances is used as a food additive or is used in vitamin preparations. In this, I suggest the use of the following terms: 'D2 Synthetic,' 'D3 Semi-synthetic,' and D3 Natural.' "

TABLE 3 Some Functions o"f Vitamin D3

Regulates Ca + +/HPO4 = Homeostasis by:	a) Intestinal Calcium Absorption
	b) Bone Calcium Resorption
	c) Renal Calcium Re-absorption
Active in Synthesis of:	a) Brush border "calcium ATPase-alkaline phosphatase" enzyme complex
	b) Calcium-binding protein
	c) Vitamin D-binding protein (?)
Utilized in Formation of:	a) 25-hydroxycholecalciferol (25-HCC)
	b) 1, 25-dihydroxycholecalciferol (1, 25-DHCC)
	c) 24, 25-dihydroxycholecalciferol (24, 25-DHCC)
	d) 25, 26-dihydroxycholecalciferol (25, 26-DHCC)
	e) Others (?)
Regulates Function of:	a) Corticosteroid hormone homeostasis
	b) Calcitonin
Aids in Maintenance of:	a) Optimal Blood Cholesterol levels
	b) Integrity of cardiovascular, renal, striated and smooth muscle, nervous, and skeletal systems through maintenance of bone, nerve, blood, and muscle Ca+ +/HPO4 = homeostasis

c)

FIGURE 1



Origins and Classification of the D_3 Deficiency and "D_2" Excess Diseases.
*See Tables 1 and 2

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