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UNRAVELING THE ENIGMA OF VITAMIN D

Most of us know that to maintain good health we need to eat a balanced diet that includes fruits, vegetables, grains, protein, and some fat. In this age of fast food and missed meals, however, many of us also take supplements to ensure that we're getting the minimum daily requirement of essential vitamins and minerals—nutrients necessary only in very small quantities to prevent disease and to keep us optimally healthy.

The first of these so-called micronutrients was discovered a little over a century ago, with investigations into the causes of such diseases as scurvy, beriberi, and rickets. The following article focuses on the twists and turns leading to the discovery and understanding of one such nutrient: vitamin D, a substance that occurs naturally in only a few foods and that is also manufactured in the skin when a precursor interacts with the short ultraviolet rays of the sun.

Without adequate levels of 1,25-dihydroxyvitamin D_3 —the active metabolite of vitamin D—in the blood, the body cannot absorb and use the dietary calcium essential for such vital functions as the electrochemical signaling between brain cells. When dietary calcium and the mineral phosphorus are not properly absorbed through the intestine, the body also cannot build strong bones. In children, vitamin D deficiency results in the once common disease known as rickets, which leaves its lifelong mark of bowed legs and deformed ribs. In adults, the result is the bone disease osteoporosis.

Today, as growing numbers of Baby

Boomers celebrate their fiftieth-plus birthdays, concerns about the brittle bones and fractures associated with advanced age are focusing renewed attention on vitamin D. Increasingly, researchers are learning that vitamin D is essential in maintaining health and preventing disease not just during the crucial growing years of childhood but throughout life. Recent studies show that vitamin D insufficiency may even be, in one researcher's words, "an unrecognized epidemic" among both women and men, who are middle aged and older. In addition to affecting bone growth, scientists are finding that vitamin D and calcium may affect diseases and disorders as disparate as colon cancer, multiple sclerosis, premenstrual syndrome, psoriasis, high blood pressure, and depression.



As seen in this X-ray image, the bones of a child with rickets, which prevents the conversion of soft cartilage to healthy bone, bow under the child's increasing weight. (Michael R. Richardson, University of Washington Department of Radiology)

A Case of Mistaken Identity

One of the reasons vitamin D was a puzzle to scientists for so many years was that it was initially misidentified as a true vitamin, that is an essential substance that our bodies cannot manufacture and which, therefore, can only be obtained from our food. But unlike essential dietary trace elements, such as vitamins A, B, and C, which humans must get directly from food, vitamin D can be produced in the body through a photosynthetic reaction when the skin is exposed to sunlight. The resulting substance is only a precursor, however, which must



then undergo two transformations—first in the liver and then in the kidney—to become the biologically active substance the body uses. This active form of vitamin D is a hormone, chemically akin to familiar steroid hormones, such as the sex regulators testosterone and estrogen and the stress regulator cortisol.

Arriving at a clear understanding of the multifaceted nature of vitamin D and its role in the body—especially its relationship to calcium—was the culmination of three different avenues of research. The earliest investigators were interested in the causes and prevention of particular diseases, such as scurvy, beriberi, and rickets. On a separate track, scientists were examining how the known primary constituents of food (proteins, fats, carbohydrates, salts, and water) affected health and growth. Work along these two fronts dovetailed to yield the concept of vitamins—an essential micronutrient in food—and to establish that vitamin deficiencies can lead to disease. This allowed a lack of vitamin D to be identified as the cause of rickets. But many aspects of this “vitamin” remained baffling, since it was actually a hormone whose active form is produced in our bodies in response to regulatory signals. An understanding of the vitamin D hormone and its roles in human physiology would require the knowledge and tools of a third line of research that had been developed by organic chemists studying sterols—the steroid alcohols (such as cholesterol) that occur in both animal and plant fats. Just as a tapestry image emerges from the weaving of many threads, clues from each line of inquiry eventually formed a pattern that solved the enigma of vitamin D.

Tracing the Cause of Disease

The first solid hint that a specific dietary deficiency could lead to disease came in 1754. In that year the Scottish naval surgeon James Lind showed that scurvy—the painful and sometimes fatal bane of mariners on long ocean voyages—could not only be cured but also prevented with the juice of oranges, lemons, and limes. By the late eighteenth century, British sailors (soon nicknamed “Limeys”) were reaping the benefit of Lind’s discovery.

Meanwhile, the advent of the Industrial Revolution in Britain in the late 1700s brought with it a different scourge: rickets. The disease itself had first been described by physicians in the mid 1600s, but it was then relatively rare. By the nineteenth century, however, as more and more families left the

outdoor life of the farm for factory work in the smoggy air of industrial cities, rickets had become a plague all over Europe. Symptoms of the disease were unmistakable. The bones of afflicted infants remained soft, like cartilage, and the babies were slow to sit, crawl, and walk. As the children grew, their soft bones bent under the additional weight, leaving the children with rickets’ telltale pigeon breast, bowed legs, or knock-knees. Rachitic children (that is, children with rickets) also suffered from tetany: painful spasms of the hands, feet, and larynx, along with difficulty in breathing, nausea, and convulsions. This condition, later found to be symptomatic of insufficient calcium, was often so severe that children died.

Throughout the nineteenth century, sporadic reports of cures for rickets surfaced, but with little effect. In 1822, for example, a Polish physician observed that children in Warsaw suffered severely from rickets, whereas the disease was virtually unknown in the city’s rural outskirts. After experimenting with the two groups, he concluded that sunbathing cured rickets. Five years later, a French researcher reported cures among those given the home remedy cod-liver oil. Neither treatment gained widespread attention, in part because the prevailing medical wisdom was that people needed only to get adequate amounts of the so-called macronutrients—proteins, fats, and carbohydrates—in order to maintain health. However, researchers looking into the causes of such diseases as pellagra and beriberi began to suspect that the macronutrients might not be the whole story—that, in fact, there was more to ordinary food than met the eye.

“. . . a substance different from protein and salts . . .”

In the late 1880s Dutch physician Christiaan Eijkman was sent to the East Indies (now Indonesia) to investigate why beriberi was so widespread in the region. Eijkman observed that hens in his Jakarta laboratory suffered symptoms of nerve disease (polyneuritis) that were strikingly similar to those for beriberi—including muscle weakness, nerve degeneration, and paralysis. He then began a series of experiments to try to find a culprit organism, which he assumed was the cause. (Like most of his contemporaries, Eijkman was influenced by the work of Louis Pasteur and believed that a bacterium caused beriberi.)



Eijkman failed in this effort, but in 1897 he did succeed in establishing something more significant. He showed that the hens contracted the beriberilike polyneuritis soon after their feed was changed to polished rice—that is, rice whose outer husk had been removed. He also proved that by adding rice bran (the parts removed in polishing) to the hens' food, the disease could be cured.

Eijkman and his successor, Gerrit Grijns, later used water or ethanol to extract the mysterious antineuritic factor from rice hulls. "There is present in rice polishings a substance different from protein and salts," the two researchers wrote in 1906, "which is indispensable to health and the lack of which causes nutritional polyneuritis."



Dutch physician Christiaan Eijkman demonstrated the relationship between nutritional deficiency and disease through his studies of beriberi in Indonesia during the late nineteenth century—work that earned him the 1929 Nobel Prize for Physiology or Medicine. (The Nobel Foundation)

In 1926 B. C. P. Jansen and W. Donath, two Dutch chemists working in Eijkman's old laboratory in Jakarta, crystallized the water-soluble antineuritic factor—now called vitamin B₁, or thiamin—from rice bran.

Another researcher soon after the turn of the century also came to believe in the existence of certain "accessory food factors." English biologist Sir Frederick Gowland Hopkins developed this concept in the course of work that began with his discovery in 1901 of the amino acid tryptophan. Building on techniques developed in this research, Hopkins went on to perform a series of now classic experiments demonstrating that whole foods (as opposed to purified forms of proteins, fats, and carbohydrates) contain certain unknown constituents essential to health and growth.

Biochemist Casimir Funk, whose own work led him to believe these factors were amines (compounds derived from ammonia), suggested they be called "vital amines" or "vitamines" for short. The "e" was later dropped when scientists realized that these various nutrients have different chemical properties and functions and that many contain no amines at all.

Hopkins and Christiaan Eijkman—in belated recognition of his seminal work with beriberi—would later share the 1929 Nobel Prize for Physiology or Medicine for the discovery of essential nutrient factors.

At about the same time that Hopkins was demonstrating the existence of vitamins, other researchers were investigating the effects of different diets on the health of experimental animals. Over the next two decades, they would identify a number of vitamins, demonstrating again and again that these essential nutrients are not equally distributed in the foods we eat.

In 1913, for example, Wisconsin researchers Elmer McCollum and Marguerite Davis discovered a fat-soluble accessory substance. By feeding rats diets of different foods and observing the effects on the animals' growth and health, McCollum and Davis found that the new substance is present in egg yolk and butter fat but absent from lard and other fats. They called the nutrient "fat-soluble vitamin A." These scientists were further able to show that vitamin A in the diet prevents night blindness and the eye disease xerophthalmia. The team of L. B. Mendel and T. B. Osborne independently published similar results within weeks.

Closing in on Rickets

By this time, a number of studies had focused attention again on rickets, which was still a severe problem in Scotland and in parts of northern Europe. A few investigators approaching the question from another direction had picked up the nearly forgotten clue about the effectiveness of sunlight. In 1892, British scientist T. A. Palm found a relationship between the geographic distribution of rickets and the amount of sunlight in the region. In 1913, University of Wisconsin's H. Steenbock and E. B. Hart made a more direct link, showing that lactating goats kept indoors lose a great deal of their skeletal calcium, whereas those kept outdoors do not. Six years later, in 1919, the German researcher K. Huldshinsky carried out a remarkably innovative experiment and cured children of rickets using artificially-produced ultraviolet light. Two years after that, researchers Alfred F. Hess and L. F. Unger of Columbia University showed that by simply exposing rachitic children to sunlight, they were able to cure them of the disease.

On the nutritional front, in the meantime, British physician Sir Edward Mellanby, still searching for a dietary deficiency as the cause of rickets, decided in



1918 to test porridge, the staple food of Scotland, by feeding dogs exclusively on oats. Inadvertently, he also kept the animals indoors throughout the experiment, thereby inducing rickets. When he cured the dogs of the disease by feeding them cod-liver oil, Mellanby naturally credited the oil's recently identified vitamin A with the cure.

On learning of Mellanby's experiments, McCollum, who had since moved from Wisconsin to Johns Hopkins University in Baltimore, decided to pursue them further. From his own work on isolating vitamin A, McCollum had found that certain foods may contain more than one accessory food substance. He thus designed a series of ingenious experiments to follow up on Mellanby's findings and discover what else, if anything, cod-liver oil might have to offer. He began by heating and aerating the oil to destroy its vitamin A. As expected, the treated oil no longer cured night blindness. But, to everyone's surprise, it did remain effective against rickets. Clearly, an unknown essential nutrient was responsible. In his 1922 publication of these experiments, McCollum followed the designations of vitamins in alphabetic order; since vitamins B and C had recently been named, he dubbed the new miracle worker "vitamin D."

By the early 1920s, then, it appeared that the world had two cures for rickets: cod-liver oil and irradiation—that is, exposure to sunlight or ultraviolet light. Despite this promise, the disease remained



First at the University of Wisconsin, and later at Johns Hopkins University, Elmer V. McCollum carried out seminal research establishing the existence of the vitamin B complex, vitamin A, and vitamin D. (The National Academy of Sciences)

intractable. Although physicians knew that sunlight was essential for young bones, the streets of industrial cities were as smoky and sunless as ever. And changing people's dietary habits to include prescriptive doses of cod-liver oil was no easy matter.

Then came a series of experiments that tied together the nutritional research and the findings concerning irradiation, offering a solution to this critical piece of the vitamin D puzzle and paving the way for a widely available cure for rickets. During the course of extensive nutritional research, Harry Goldblatt and Katherine Soames, working in London, discovered that the livers from irradiated rats, when fed to other rats were growth promoting, whereas the

Timeline

This timeline shows the chain of research and events that led to an understanding of vitamin D in biological systems and to the development of some of its medical uses.

Early 1900s

Sir Frederick Gowland Hopkins demonstrates that whole foods (as opposed to purified proteins, fats, and carbohydrates) contain certain unknown constituents essential to health and growth.

1918

Sir Edward Mellanby induces rickets in dogs and then cures the disease by feeding the animals cod-liver oil.

Early 1920s

Harry Goldblatt and Katherine Soames, H. Steenbock and A. Black, and Alfred Hess and Mildred Weinstock independently discover that irradiating certain foodstuffs with ultraviolet light renders those foods antirachitic.

1927

Adolf Windaus, O. Rosenheim, and T. A. Webster deduce that ergosterol is the likely parent substance of vitamin D in food.

Mid 1600s

Rickets is first described.

1906

Christiaan Eijkman and Gerrit Grijns extract the antineuritic factor from rice hulls, later shown to be vitamin B₁.

1919

K. Huldshinsky cures children of rickets using artificially produced ultraviolet light.

1922

Elmer V. McCollum destroys vitamin A in cod-liver oil and shows that the separate antirachitic substance remains. He calls the newly identified substance "vitamin D."

1931

F. A. Askew defines the chemical makeup of the form of vitamin D found in irradiated foods (now called ergocalciferol), derived from the precursor molecule ergosterol.



livers from unirradiated rats were not. In the early 1920s, two teams of researchers—H. Steenbock and A. Black, and Alfred Hess and Mildred Weinstock—followed up on this strand of research, as well as Huldshinsky’s lead, by further experimenting with the effect of ultraviolet light on foods fed to rats.

Independently, the two teams of researchers irradiated excised skin as well as such food substances as vegetable oils, egg yolk, milk, lettuce, or rat chow and found that irradiation produced a substance that seemed to work on rickets much as the vitamin D in cod-liver oil did. Rats that were fed irradiated foods or irradiated skin were protected against rickets, whereas those fed unirradiated foods or skin were not. Recognizing that simply irradiating certain foods that were common in most people’s diets could spare large numbers of children from the bone disease, Steenbock patented the food irradiation process using ultraviolet light in 1924, donating all future proceeds to support research at the University of Wisconsin.

Animal, Vegetable, or Mineral?

By 1924, the practical side of the battle against rickets had been won. Across the United States, chil-

dren began consuming irradiated milk and bread and, seemingly overnight, the imminent threat of epidemic disease dwindled to a half-forgotten historical event. But the quest to understand vitamin D was only just beginning, for scientists still knew almost nothing of what it was or how it worked.

The search continued for the exact substance in food and skin that was activated by ultraviolet irradiation. Several teams of researchers—Wisconsin’s Steenbock and Black; Columbia University’s Hess, Weinstock, and F. Dorothy Helman; and O. Rosenheim and T. A. Webster of the National Institute for Medical Research in London—confirmed that the substance is present in animal and vegetable fats. Moreover, they proved that it is localized in the fraction of fats known to contain sterol molecules. The researchers found that purified cholesterol (a major animal sterol) and phytosterols (vegetable sterols), both of which otherwise have no antirachitic properties, are rendered antirachitic by ultraviolet irradiation.

Up to this point, researchers investigating vitamin D had to be content with characterizing the elusive substance on the basis of its physiological effects. As it happened, however, the work of organic chemist Adolf Windaus, in Göttingen, Germany, would produce chemical tools that would finally help pinpoint the molecular identity of vitamin D. Early in the century, Windaus had embarked on his study of cholesterol and related sterols, about which virtually noth-

1936

Windaus deduces the chemical structure of vitamin D₃ produced in the skin (now known as cholecalciferol) and identifies the structure of its parent molecule, 7-dehydrocholesterol.

1968–1970

The existence of a second active metabolite produced from 25-hydroxyvitamin D₃ is reported by Anthony W. Norman, Mark R. Haussler, and J. F. Myrtle; by E. Kodicek, D. E. M. Lawson, and P. W. Wilson; and by DeLuca and coworkers.

1975

Haussler confirms the discovery of a protein receptor that binds the active vitamin D metabolite to the nucleus of cells in the intestine.

1980s

A Japanese research team and, independently, Michael F. Holick and coworkers show that vitamin D hormone inhibits skin cell growth. Holick and colleagues demonstrate that topical applications of the vitamin D hormone are a remarkably effective treatment of psoriasis.

1994

The U.S. Food and Drug Administration approves a vitamin D–based topical treatment for psoriasis, called calcipotriol.

1968

Hector F. DeLuca and colleagues isolate an active vitamin D metabolite and identify it as 25-hydroxyvitamin D₃. They later prove that the substance is produced in the liver.

1971

Three research groups identify the chemical/molecular structure of the final active form of vitamin D as 1,25-dihydroxyvitamin D₃, which is soon reclassified as a hormone controlling calcium metabolism.

1970s

Researchers discover the relationship of vitamin D to the body’s endocrine system and calcium regulation.

Mid 1980s

Researchers find that vitamin D hormone seems to play a part in modulating the immune system.



ing was known at the time. From the very start, he believed that sterols, which occur in every cell, must be considered as the parent substance of other groups of natural substances, and he was convinced that investigations into the structure of these molecules would yield unexpected results.

By 1925, Windaus was recognized as the leading expert on sterols, and Hess invited him to come to New York to work on antirachitic vitamins. Windaus also was collaborating with Rosenheim and Webster in London at the time, and in 1927 both teams, using a series of clever chemical transformations and comparisons with known compounds, deduced that ergosterol was the likely parent substance of vitamin D in food. Back in his own laboratory in Göttingen the following year, Windaus isolated three forms of the vitamin: two derived from irradiated plant sterols, which he called D_1 and D_2 , and one derived from irradiated skin, which he called D_3 . F. A. Askew's British team followed up in 1931, successfully defining the chemical makeup of D_2 —the form of vitamin D found in irradiated foods (now called ergocalciferol)—which was derived from the precursor molecule ergosterol. Five years later, in 1936, Windaus synthesized the molecule 7-dehydrocholesterol and then converted it by irradiation to vitamin D_3 , now known as cholecalciferol. Although it was assumed that vitamin D was photosynthesized in the skin from 7-dehydrocholesterol, the final proof did not emerge until more than three decades later. A Wisconsin team led by R. P. Esvelt and one led by Michael F. Holick at the Endocrine Unit of Massachusetts General Hospital then independently demonstrated that vitamin D_3 is, in fact, what is produced in the skin through irradiation.

Because of these discoveries, it became possible to synthesize the vitamin in large quantities. Synthesizing the vitamin costs a fraction of what it costs to irradiate foods and does not destroy or change food flavors, as irradiation sometimes does. Synthesized vitamin D provided the capstone of the public health campaign to eradicate rickets. For his “research into the constitution of the sterols and their connection with the vitamins,” Windaus was awarded the Nobel Prize for Chemistry in 1928.

Vitamin D's Connection to Calcium Control

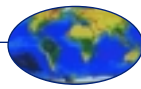
With rickets under control, scientists now concentrated on finding out how the miracle bone builder

worked. Over the next forty years, a number of research teams teased out vitamin D's metabolic pathway in the body. One of the confusing initial findings was that the metabolic by-products of vitamin D all seemed to be biologically inactive. How, then, did vitamin D build bone and cure rickets?

Scientists did not have the tools to follow this complicated process in living subjects until the advent, in the mid 1960s, of new techniques using radioactively labeled substances. Between 1968 and 1971, researchers made great progress in understanding the metabolic processing of vitamin D and its physiological activity. In 1968, a team headed by Hector F. DeLuca at the University of Wisconsin isolated an active substance identified as 25-hydroxyvitamin D_3 , which the team later proved to be produced in the liver. During the next two years, the Wisconsin team, Anthony W. Norman and colleagues at the University of California-Riverside, and E. Kodicek and coworkers at Cambridge University in England independently reported the existence of a second active metabolite. Kodicek and David R. Fraser showed that this second metabolite is produced in the kidney. Finally, in 1971 all three research groups published papers in which they reported the chemical/molecular structure of this metabolite, which was identified as 1,25-dihydroxyvitamin D_3 . It was now clear that the liver changes vitamin D_3 to 25-hydroxyvitamin D_3 , the major circulating form of the vitamin. The kidneys then convert 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 , the active form of the vitamin.

But how does all of this affect calcium deposition to build strong bones? Since the 1950s, scientists had been puzzling over the implications of two findings related to this question. In the early part of that decade, the Swedish researcher Arvid Carlsson made the startling discovery that vitamin D can actually remove calcium from bones when it is needed by the body. At about the same time, the Norwegian biochemist R. Nicolaysen, who had been testing different diets on animals for years, concluded that the uptake of calcium from food is guided by some unknown “endogenous factor” that alerts the intestines to the body's calcium needs. Answers began to emerge with the experiments tracing the activation of vitamin D.

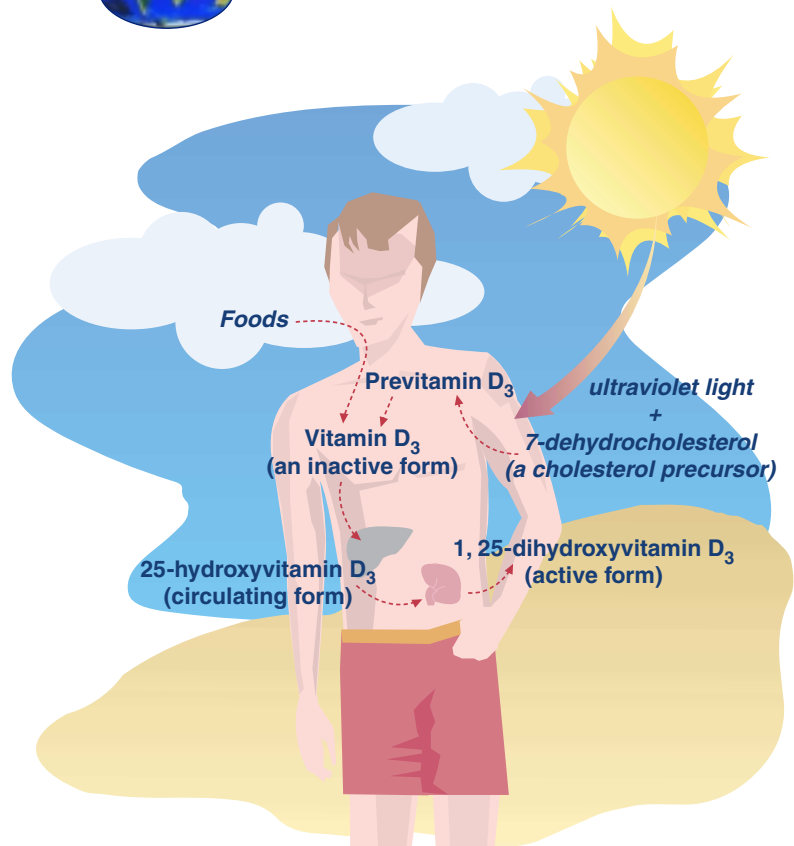
An important result of those experiments was that 1,25-dihydroxyvitamin D_3 , the active form of vitamin D, was reclassified as a hormone that controlled calcium metabolism. A hormone is a chemical substance produced by one organ and then transported in the bloodstream to a target organ, where it causes a specific biological action. Evidence for reclassifying the



active form of vitamin D came with the realization that 1,25-dihydroxyvitamin D₃ is produced by the kidneys and that its secretion by the kidneys is followed by its build up in cell nuclei of the intestine, where it regulates calcium metabolism. By 1975, Mark R. Haussler at the University of Arizona confirmed the discovery of a protein receptor that binds the active vitamin D metabolite to the nucleus of cells in the intestine.

With vitamin D now linked to the intestine, scientists were zeroing in on the mechanism of calcium control. Researchers noted that as the level of calcium in the diet rises, the amount of active vitamin D hormone in the body falls, and vice versa—a feedback-loop pattern that clearly pointed to the vitamin D hormone as Nicolaysen’s calcium-regulating “endogenous factor.” Many research teams, including those at the University of Wisconsin and Cambridge University, now focused on tracing the relationship of vitamin D hormone to the rest of the body’s endocrine system. They found that a hormone produced by the parathyroid gland is critical to maintaining adequate levels of vitamin D hormone in the blood. When calcium is needed, the parathyroid gland sends the parathyroid hormone to the kidneys to trigger production of vitamin D hormone. That hormone, in turn, prompts the intestines to transfer calcium from food to the blood. When calcium intake is too small to support normal functions, both vitamin D and the parathyroid hormone trigger a process in which stored calcium is mobilized from the bones (confirming the Swedish finding nearly twenty years earlier).

Regulating blood calcium levels is important. When there is too little calcium in the blood, soft-tissue cells—especially nerves and muscle—shut down, sending the body into convulsions; when there is too much calcium in the blood, organs calcify and eventually cease to work. For human patients who had lost their parathyroid glands or their kidneys and could no longer regulate the level of calcium in their blood, the newly synthesized vitamin D hormone, when given with plenty of calcium, had a dramatic effect, curing them of convulsions and chronic bone disease.



The Vitamin D cycle. As illustrated here, humans can get a precursor (inactive) form of vitamin D from food and also from the photosynthetic reaction that occurs when 7-dehydrocholesterol in skin cells is exposed to ultraviolet light. This inactive precursor travels to the liver, where it is changed to 25-hydroxyvitamin D₃, the major circulating form of vitamin D₃. The kidneys, in turn, convert this intermediate form of the vitamin to 1,25-dihydroxyvitamin D₃—a hormone that not only controls calcium metabolism by increasing intestinal calcium absorption and bone calcium mobilization, but also has many other effects throughout the body.

More Than Just a Way to Regulate Calcium

Now that its role in calcium uptake had been sketched out, researchers in the 1970s began investigating vitamin D in greater detail—and with surprising results. Several groups managed to find the vitamin D hormone in the nucleus of cells that were not part of the classical calcium maintenance system including the brain, lymphocytes (infection fighting white blood cells), skin, and malignant tissues. What business would vitamin D have in these places?

In the early 1980s, Japanese researcher Tatsuo Suda made the exciting discovery that adding the hormone to immature malignant leukemia cells caused the cells to differentiate, mature, and stop growing. The amount of vitamin D hormone needed



to stop the runaway growth of tumors and cancers has so far proved too toxic for human use, but Suda's discovery suggested that this fascinating hormone had roles beyond the part it played in maintaining the body's calcium levels. This finding spurred on a new era in vitamin D research.

In the mid 1980s, a group of researchers led by S. C. Manolagas found that vitamin D hormone also seemed to play a part in modulating the immune system. In 1993, S. Yang and other researchers in DeLuca's laboratory found that rats given a large dose of vitamin D hormone were protected from the inflammation normally associated with wounds and chemical irritants. This unexpected immunosuppressant function for vitamin D hormone suggested a whole new range of possibilities—including its use in the control of autoimmune diseases.

More developed is vitamin D hormone's effect on psoriasis, a disfiguring skin disorder that affects some 50 million people worldwide. For reasons unknown, psoriasis causes skin cells to multiply uncontrollably. Failing to differentiate and develop normally, the skin cells clump in unsightly rashes, scales, and scars. In the 1980s, a Japanese research team demonstrated that 1,25-dihydroxyvitamin D₃ can inhibit skin cell growth. A team of scientists at Boston University School of Medicine, led by Michael F. Holick, investigated this

inhibition further and reasoned that it could be used for the treatment of psoriasis.

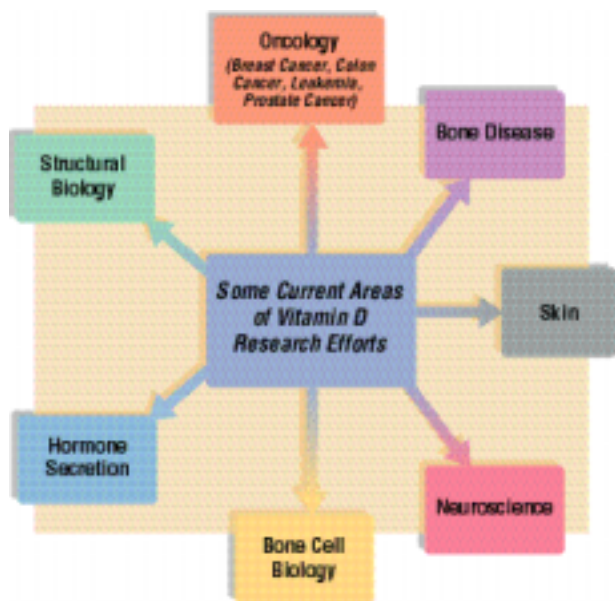
Initial experiments by Holick and coworkers with vitamin D hormone have shown that topical applications of the hormone are remarkably effective. After two months, the lesions of 96.5 percent of the patients treated with a topical calcitriol (vitamin D hormone) preparation had improved with no noticeable side effects, as compared with 15.5 percent of the controls treated with petroleum alone. In 1994, the U.S. Food and Drug Administration approved a vitamin D-based topical treatment for psoriasis, called calcipotriol.

As we enter the twenty-first century, we recognize that the basic scientific research done in the previous two centuries has not only untangled the workings of the elusive vitamin D hormone, but has also given us ways to protect the health of both adults and children. Researchers are pursuing many new applications for vitamin D, but its role in building and maintaining bone continues to be an important health issue, especially among middle-aged and older adults.

*This article, which was published in 2000 and has not been updated or revised, was written by science writers Roberta Conlan and Elizabeth Sherman, with the assistance of Drs. David R. Fraser, Mark R. Haussler, Michael F. Holick, Robert Neer, Anthony W. Norman, and Munro Peacock for **Beyond Discovery™: The Path from Research to Human Benefit**, a project of the National Academy of Sciences.*

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The discovery that Vitamin D is present in the nuclei of cells in many different tissues of the body has led scientists to begin exploring a variety of new applications, further revealing the potential benefits of this once enigmatic hormone.