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MEDICAL PROGRESS

THE ROLE OF THE VITAMIN D ENDOCRINE SYSTEM IN HEALTH AND DISEASE

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THE secosteroid hormone 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is the major biologically active metabolite of vitamin D_3. (Secosteroids are those in which one of the rings has undergone fission; in vitamin D, this is ring B.) $1,25(OH)_2D_3$ is recognized as the principal mediator within the sphere of action of vitamin D in the regulation of bone and mineral metabolism in humans.[1-3] Recent evidence has suggested a wider biologic role of $1,25(OH)_2D_3$ in tissues not primarily related to mineral metabolism.

VITAMIN D METABOLISM

Metabolic Activation

An overview of vitamin D metabolism is given in Figure 1. Vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol in a reaction catalyzed by ultraviolet light.[4] Alternatively, vitamin D_3 from dietary sources is taken up into the bloodstream from the intestine. Vitamin D_2, which behaves metabolically like vitamin D_3, is provided only by dietary sources. The transport of vitamin D metabolites in the blood is achieved mostly through noncovalent binding to vitamin D–binding protein; this protein was originally termed "group-specific component," or "Gc protein," by human geneticists.[5] Vitamin D–binding protein is structurally homologous to two other blood proteins, albumin and α-fetoprotein,[6] at both the protein level and the genomic DNA level.

Further processing occurs in the liver, which is the major site of the hydroxylation of vitamin D_3 at carbon 25 to yield 25-hydroxyvitamin D_3 ($25(OH)D_3$). This metabolic step is not believed to be subject to particularly tight regulation. Accordingly, circulating $25(OH)D_3$ concentrations are considered to be a reflection of the availability of vitamin D_3 and are thought to be the best indicator of vitamin D levels. A recent study has suggested that the 25-hydroxylation of vitamin D is governed to some degree by $1,25(OH)_2D_3$. In that study, the ingestion of large quantities of vitamin D led to a clear increase in the serum levels of $25(OH)D_3$, but the concomitant administration of $1,25(OH)_2D_3$ with vitamin D prevented this increase.[7] Other investigators have demonstrated that hypocalcemia and the ensuing rise in the serum concentrations of $1,25(OH)_2D_3$ result in accelerated degradation and biliary excretion of $25(OH)D_3$, thus reducing to some extent the quantities of $25(OH)D_3$ available for activation in the kidney.[8]

The second important site of the transformation of vitamin D is the kidney, where the enzyme 25(OH) D_3-1α-hydroxylase introduces a hydroxyl group at the α-position of carbon 1 of the A ring. The activity of the 1α-hydroxylase, which is a classic mixed-function cytochrome P-450 steroid hydroxylase,[9] occurs in the proximal convoluted and straight tubules of the kidney nephron. The reaction yields the active metabolite $1\alpha,25(OH)_2D_3$, whose biologic activity is 500-fold to 1000-fold higher than that of the precursor $25(OH)D_3$.

The kidney can also produce a second dihydroxylated metabolite from $25(OH)D_3$ — 24(R),25-dihydroxyvitamin D_3 ($24(R),25(OH)_2D_3$). $1,25(OH)_2D_3$ is known to initiate the synthesis of $24(R),25(OH)_2D_3$ by activating $25(OH)D_3$-24(R)-hydroxylase. Under circumstances of relative vitamin D deprivation, the kidney produces only $1,25(OH)_2D_3$; however, if the supply of vitamin D is adequate, the kidney produces both $1,25(OH)_2D_3$ and $24(R),25(OH)_2D_3$. Controversy exists about whether $24(R),25(OH)_2D_3$ has a unique biologic activity.[2] The $1,25(OH)_2D_3$-induced activation of $25(OH)D_3$-24-hydroxylase is

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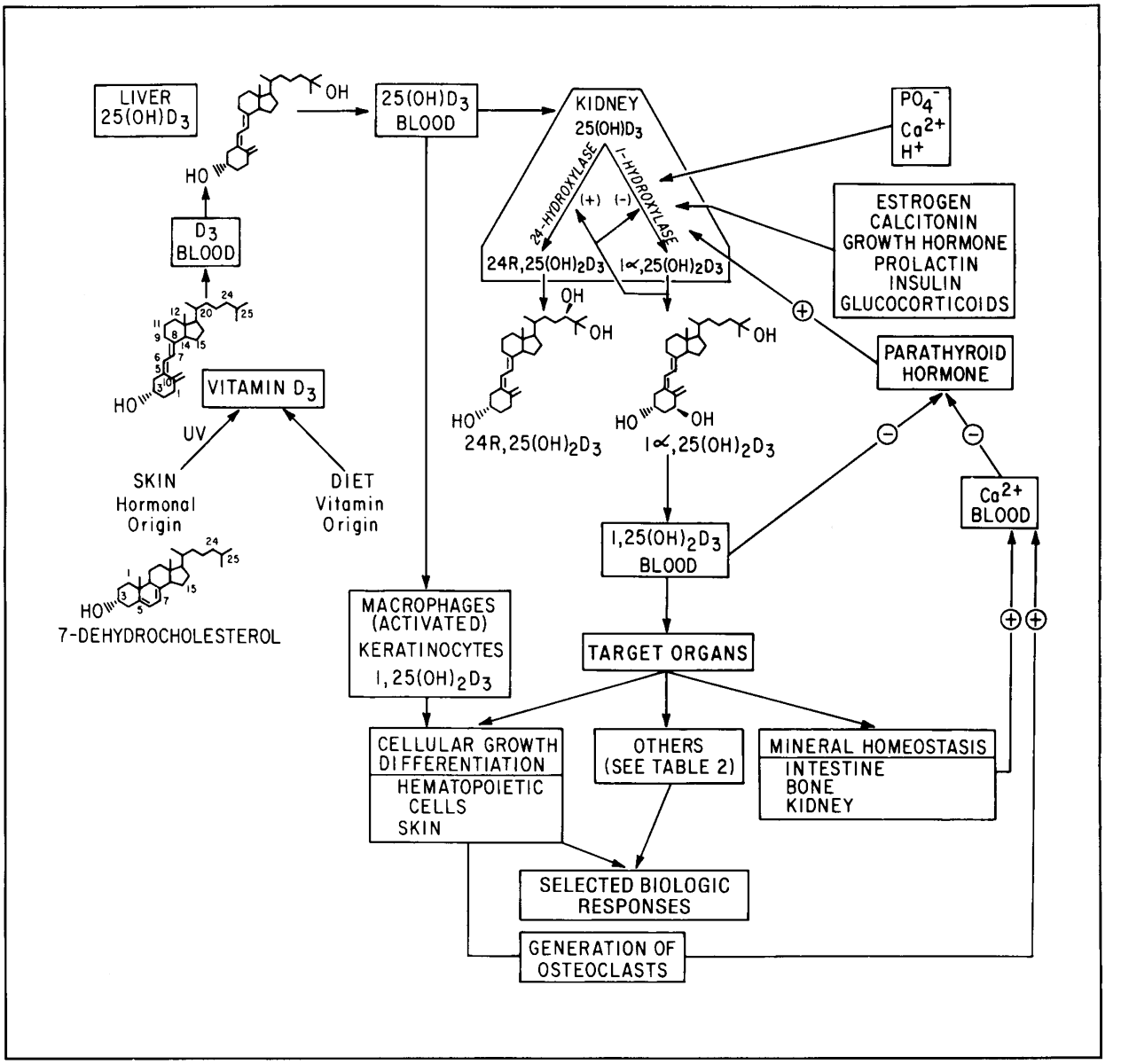

Figure 1. Overview of the Vitamin D Endocrine System.
UV denotes ultraviolet.

also found in virtually all other tissues that have $1,25(OH)_2D_3$ receptors,[2] and an assessment of the $24(R),25(OH)_2D_3$-synthesizing capacity probably gives a good measurement of the responsiveness of a given tissue to $1,25(OH)_2D_3$.

Regulation of $1,25(OH)_2D_3$ Production

The conversion of $25(OH)D_3$ to the active hormone $1,25(OH)_2D_3$ is under stringent control, so that the renal output of $1,25(OH)_2D_3$ is related to a person's calcium needs.[9,10] The principal regulators of $1,25(OH)_2D_3$ production are parathyroid hormone and $1,25(OH)_2D_3$. Parathyroid hormone stimulates 1α-hydroxylase activity through a direct effect on the kidney cell, whereas $1,25(OH)_2D_3$ mediates the inhibition of this enzyme. The feedback inhibition by $1,25(OH)_2D_3$ is also exerted directly on the kidney (Fig. 1).[9,10] Another important determinant of $1,25(OH)_2D_3$ production is the dietary intake of phosphorus. Phosphate restriction and hypophosphatemia produce an increase in $1,25(OH)_2D_3$ serum concentrations within several days, whereas a high intake of phosphate decreases serum levels of $1,25(OH)_2D$.[11] The alterations during phosphorus deprivation are due to an enhanced rate of production of $1,25(OH)_2D_3$ and are not associated with accelerated metabolic clearance of $1,25(OH)_2D_3$. Although phosphorus probably has a direct effect on the kidney cell,

the elevation of $1,25(OH)_2D$ levels in serum that is associated with hypocalcemia is probably mediated through the increased secretion of parathyroid hormone.

Alterations of serum $1,25(OH)_2D$ concentrations have also been found in hyperthyroidism, a condition in which abnormal calcium metabolism is characterized by osteopenia, low levels of parathyroid hormone, hyperphosphatemia, and a tendency toward hypercalcemia. Accordingly, a secondary decrease in the circulating levels of $1,25(OH)_2D_3$ with normal levels of vitamin D–binding protein has been described.[12] In contrast, hypothyroidism is associated with an elevation in $1,25(OH)_2D$ levels.[12] Although estradiol does not act directly on renal $25(OH)D_3$-1α-hydroxylase, an excess of estrogen in vivo leads to increased serum levels of $1,25(OH)_2D_3$.[13] This has been attributed to the stimulation of the hepatic synthesis of vitamin D–binding protein, resulting in a selective increase of protein-bound $1,25(OH)_2D_3$ and no change in the levels of physiologically active free $1,25(OH)_2D_3$.[14] Unlike estrogens, testosterone does not cause a change in the serum levels of vitamin D metabolites in boys at puberty, a stage at which the maximal increases in serum testosterone levels occur.[15] Other ionic and endocrine modulators that have been implicated in the regulation of renal $1,25(OH)_2D_3$ synthesis are shown in Figure 1.[9,10]

The recognition of vitamin D_3 activation by the liver and kidney and the understanding of the regulation of the renal synthesis of $1,25(OH)_2D_3$ resulted in the introduction of $1,25(OH)_2D_3$ for substitution therapy in chronic renal failure. Likewise, $1,25(OH)_2D_3$ is now used in the treatment of hypoparathyroidism, in which low levels of parathyroid hormone and hyperphosphatemia lead to a decline in the serum levels of $1,25(OH)_2D$. The synthetic analogue 1α-hydroxyvitamin D_3 ($1\alpha(OH)D_3$), which is known to undergo rapid hepatic conversion to $1,25(OH)_2D_3$,[16] can be used as an alternative pharmacologic agent.

Extrarenal $1,25(OH)_2D_3$ Production

Originally, the synthesis of $1,25(OH)_2D_3$ was postulated to occur exclusively in the kidney.[1-3] New data now demonstrate ectopic $1,25(OH)_2D_3$ production in humans under certain circumstances. The best evidence is in reports of several patients with hypercalcemia who had either sarcoidosis or tuberculosis and were anephric or had end-stage renal disease. The hypercalcemia in these patients was associated with elevated serum levels of $1,25(OH)_2D_3$.[17-20] Ectopic synthesis of $1,25(OH)_2D_3$ also takes place during pregnancy, when placental and decidual cells synthesize the hormone. This process probably contributes to the increased levels of circulating $1,25(OH)_2D_3$ during pregnancy.[21] However, the importance of $1,25(OH)_2D_3$ derived from the placenta and decidua in the maternal–fetal exchange of calcium is not known.

The question whether extrarenal $1,25(OH)_2D_3$ production occurs in anephric patients who are not pregnant and who are free of secondary disease has been addressed in several studies. In experiments in rats, extrarenal production of $1,25(OH)_2D_3$ in vivo could not be demonstrated within 24 hours after nephrectomy.[22] However, nephrectomized pigs, which were maintained on dialysis for several days and were given large amounts of vitamin D, had clearly detectable levels of $1,25(OH)_2D$ in the serum.[23] Controversy exists about whether anephric but otherwise normal humans have detectable levels of circulating $1,25(OH)_2D$. Most earlier studies have suggested that they do not. Recent studies, however, have reported low circulating concentrations of $1,25(OH)_2D$ (4 to 16 pg per milliliter) in the majority of anephric patients who either were untreated or were treated with vitamin D. The levels of $1,25(OH)_2D$ were measured by radioreceptor assay and bioassay[24] or by radioimmunoassay.[25] Improved assay methods or the examination of larger serum samples may resolve this issue.

Extrarenal 1-hydroxylases have been identified in vitro in a variety of tissues. Granulomatous tissue including the macrophage may be the source of the excess $1,25(OH)_2D_3$ that is found in sarcoidosis. A homogenate from a lymph node containing a granuloma synthesized a compound indistinguishable from $1,25(OH)_2D_3$,[26] and cultured pulmonary alveolar macrophages from patients with pulmonary sarcoidosis constitutively synthesized $1,25(OH)_2D_3$ from the substrate $25(OH)D_3$.[27,28] Cultured pulmonary alveolar macrophages from normal subjects required activation in vitro by interferon-γ or bacterial lipopolysaccharide to synthesize the hormone.[29,30] Macrophages derived from human bone marrow stimulated by interferon-γ[30] and peritoneal macrophages from patients undergoing peritoneal dialysis who had a history of peritonitis also produced $1,25(OH)_2D_3$.[31] Similarly, $1,25(OH)_2D_3$ synthesis by cultured embryonic calvarial cells from the chicken[32] and by cultured keratinocytes from neonatal human foreskin[33] has been conclusively demonstrated.

Inactivation of Vitamin D_3 Metabolites

In addition to the parent vitamin D and its metabolites $25(OH)D_3$, $1,25(OH)_2D_3$, and $24,25(OH)_2D_3$, approximately 30 other metabolites have been isolated and characterized from humans and animals.[9] To date, these other metabolites have not been shown to possess any unique biologic properties. For the most part, they involve metabolic transformations (hydroxylation followed by oxidation) that focus on the side chain and appear to be associated with the inactivation or breakdown of the parental metabolites.

Mode of Action of $1,25(OH)_2D_3$

Substantial evidence has accumulated that the mechanism of action of $1,25(OH)_2D_3$ is similar to that of other steroid hormones. $1,25(OH)_2D_3$ is known to interact noncovalently but stereospecifically with an

intracellular receptor protein. This steroid–receptor complex is then associated with DNA in the nucleus of target cells, either to initiate the synthesis of specific RNA encoding proteins that mediate a spectrum of biologic responses (Fig. 2) or to mediate a selective repression of gene transcription. The genes that are known to be regulated by $1,25(OH)_2D_3$ at the level of messenger RNA (mRNA) accumulation are listed in Table 1.[34-48]

The $1,25(OH)_2D_3$ receptors from several species have been characterized biochemically as DNA-binding proteins of 50,000 to 60,000 daltons that bind $1,25(OH)_2D_3$ with high affinity (dissociation constant = 1 to 50×10^{-11} M).[49] The ligand affinity of the receptor protein for vitamin D_3 metabolites is usually correlated with their biologic potencies. Recently, the primary amino acid structure of a major portion of the chicken intestinal $1,25(OH)_2D_3$ receptors[45] as well as the entire sequence of the human intestinal receptors[50] has been deduced from appropriate complementary DNA clones. Strong homologies occur in the putative DNA-binding region of the receptor with the DNA-binding domains of all the other steroid hormone receptors and with the v-*erb*A oncogene.[45] This suggests that the $1,25(OH)_2D_3$ receptor belongs to the same supergene family as all the other classic steroid-hormone receptors. The $1,25(OH)_2D_3$-receptor protein is expressed in almost every tissue that has been examined thus far (Table 2).

Some investigators have reported that $1,25(OH)_2D_3$ has very rapid effects (within 1 to 15 minutes), which therefore cannot be explained by genomic actions. These effects include the stimulation of the intestinal transport of calcium in the perfused chicken intestine[51] and the elevation of cyclic guanosine monophosphate levels in human fibroblasts.[52] Clear evidence exists that the very rapid effect of $1,25(OH)_2D_3$ on fibroblasts is receptor mediated, since fibroblasts from patients with defective $1,25(OH)_2D_3$-receptor proteins did not respond to the hormone.[52]

$1,25(OH)_2D_3$ and Mineral Metabolism

The importance of $1,25(OH)_2D_3$ for the maintenance of mineral homeostasis is apparent during states of either deficiency or resistance to vitamin D, in which disorders of mineral and bone metabolism dominate the clinical picture. With respect to calcium metabolism, $1,25(OH)_2D_3$ in concert with parathyroid hormone and calcitonin exerts actions on the classic target tissues: bone, parathyroid glands, kidney, and intestine.

Bone

Bone tissue undergoes constant remodeling, in that under normal conditions the osteoclast-mediated resorption of bone is in approximate equilibrium with the osteoblast-mediated formation of new bone material. A variety of local and systemic hormonal modulators have been implicated in the short-term and long-term regulation of these dual processes.[53,54] $1,25(OH)_2D_3$ is well characterized as an essential hormone for the regular mineralization of new bone and as a potent bone-resorptive agent.[55]

The $1,25(OH)_2D_3$-induced stimulation of bone growth and mineralization probably is not mediated through a direct effect on osteoblasts. Evidence suggests that $1,25(OH)_2D_3$ stimulates bone mineralization indirectly by providing minerals for incorporation into bone matrix through increased intestinal absorption of calcium and phosphorus.[56] On the other hand, osteoblasts, which possess $1,25(OH)_2D_3$ receptors, are probably the primary target cells for $1,25(OH)_2D_3$ in bone. Accordingly, a spectrum of osteoblast-related functions has been shown to be influenced by $1,25(OH)_2D_3$. For example, $1,25(OH)_2D_3$ modulated the proliferation of and alkaline phosphatase production in cultured osteoblasts,[57] increased the synthesis of osteoblast-derived bone γ-carboxyglutamic acid protein (osteocalcin)[58] and of matrix γ-carboxyglutamic acid protein,[38] and down-regulated the production of type I collagen by fetal rat calvaria.[36] Recently, investigators have demonstrated a $1,25(OH)_2D_3$-mediated increase of receptors for epidermal growth factor and of transforming growth factor β–like activity of osteoblasts.[59] Thus, $1,25(OH)_2D_3$ seems to play a part in the regulation of osteoblast function; however, the physiologic relevance of such interactions (e.g., for osteoblast-mediated processes of bone remodeling) must be defined more precisely.

The bone-resorbing effects of $1,25(OH)_2D_3$ probably can be divided into short-term and long-term actions. There is evidence that neither effect is exerted directly on the mature osteoclast. With respect to long-term effects, investigators have shown that the administration of $1,25(OH)_2D_3$ to rats results in an increased formation of osteoclasts in vivo over a period of several days.[60] Studies in vitro have indicated that the number of osteoclast-like cells increased in long-term cultures of primate bone marrow cells after exposure to $1,25(OH)_2D_3$ for 14 to 21 days.[61] Most of the available data suggest that the osteoclast originates from a hematopoietic cell of early macrophage lineage.[62] Therefore, the increase in osteoclasts induced by $1,25(OH)_2D_3$ may indicate a maturational effect of the hormone on myeloid hematopoietic precursor cells, in that these cells are prompted to differentiate toward functional osteoclasts. Consistent with the postulate that $1,25(OH)_2D_3$ alters the number but not the function of osteoclasts, chicken osteoclasts have been reported not to contain $1,25(OH)_2D_3$ receptors.[63] These findings may represent a case in which the ability of $1,25(OH)_2D_3$ to induce cellular differentiation is closely linked to its effects on mineral metabolism.

The short-term effects of $1,25(OH)_2D_3$ on bone resorption have been demonstrated in organ cultures of bone; the $1,25(OH)_2D_3$-mediated release of calcium from bone was demonstrable after several hours.[64]

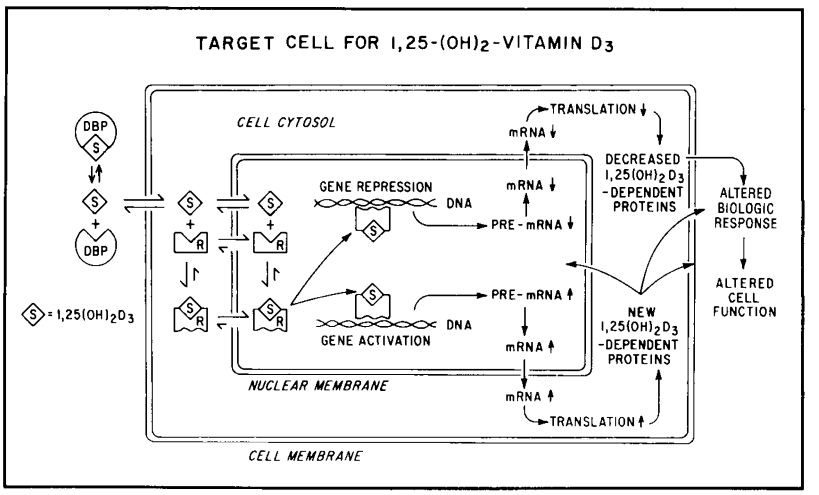

Figure 2. Proposed Genomic Mode of Action of $1,25(OH)_2D_3$.
Target organs and cells for $1,25(OH)_2D_3$ by definition contain receptors for this secosteroid that enable them to modulate genomic events. The interaction of $1,25(OH)_2D_3$ with genomic material is thought to be analogous to the mode of action of other steroid hormones. S denotes steroid hormone, R receptor protein, DBP vitamin D–serum binding protein, and P RNA polymerase.

This effect was too rapid to be explained by the ability of the hormone to increase the pool of osteoclasts. The exact mechanism of this short-term mobilization of calcium from bone is not known, but evidence suggests that $1,25(OH)_2D_3$ induces the release of osteoblast-derived resorption factors that stimulate osteoclast activity.[65]

Parathyroid Glands

Parathyroid hormone is an important tropic stimulator of the renal synthesis of $1,25(OH)_2D_3$. Conversely, the resulting elevated serum levels of $1,25(OH)_2D_3$ are known to lead to a decrease in the release of parathyroid hormone through two different mechanisms. A long feedback loop is established by means of increased serum concentrations of ionized calcium, which represent an inhibitory signal for the secretion and production of parathyroid hormone. In a short feedback loop, $1,25(OH)_2D_3$ directly inhibits the synthesis of parathyroid hormone through an interaction with the preproparathyroid hormone gene.[34] The expression of $1,25(OH)_2D_3$ receptors in parathyroid glands is reduced in chronic renal failure,[66] and the resulting impaired feedback inhibition of the synthesis of parathyroid hormone by $1,25(OH)_2D_3$ may contribute to the secondary hyperparathyroidism characteristic of this disorder.

Kidney

Probably the most important effect of $1,25(OH)_2D_3$ on the kidney is the inhibition of $25(OH)D_3$-1α-hydroxylase activity,[9,10] which results in a decrease of $1,25(OH)_2D_3$ biosynthesis. This effect is accompanied by a stimulation of $25(OH)D_3$-24-hydroxylase. The hormone has also been implicated in the regulation of renal calcium and phosphate excretion. There is controversy, however, about the direction (increased excretion vs. increased resorption) of a possible $1,25(OH)_2D_3$-mediated effect and on the conditions in which the hormone interferes with renal calcium and phosphate transport.[67] Clearly, more research is needed to determine the effects of $1,25(OH)_2D_3$ on the kidney in addition to its modulation of the $25(OH)D_3$-hydroxylases.

Intestine

The maintenance of serum calcium and phosphate levels as well as the provision of minerals for bone formation by $1,25(OH)_2D_3$ is largely mediated by the hormone's intestinal activities. One of the best-defined effects of $1,25(OH)_2D_3$ is the stimulation of the intestinal lumen–plasma flux of calcium and phosphate.[1-3] Extensive evidence exists for an interaction of $1,25(OH)_2D_3$ with an intestinal receptor and for genome-mediated up-regulation of a calcium-binding protein, known as calbindin-D.[46,47] The amounts of calbindin-D in the intestinal mucosa in both humans and animals are positively correlated with the rate of calcium transport or absorption; however, studies have not yet defined the exact role of calbindin-D in this process. In addition to the genomic actions of the hormone, emerging evidence supports the existence of a nongenomic stimulation of intestinal calcium transport by $1,25(OH)_2D_3$ that is very rapid.[51]

Role of $1,25(OH)_2D_3$ in Involutional Osteoporosis

Two distinct syndromes of involutional osteoporosis have been postulated: postmenopausal osteoporosis and senile osteoporosis.[68] Both forms have been linked to disturbances of vitamin D metabolism. The latter has been associated with a primary decrease in the levels of $25(OH)D_3$-1α-hydroxylase (as a result of aging), whereas the former is thought to be associated with a secondary decrease in 1α-hydroxylase levels. This decrease seen in postmenopausal osteoporosis has been ascribed to an enhanced release of calcium from bone, which lowers levels of serum parathyroid hormone.[68] Some investigators have found that patients with postmenopausal osteoporosis have moderately reduced serum concentrations of $1,25(OH)_2D$ accompanied by impaired intestinal absorption of calcium.[69] However, there is disagreement about whether lower plasma levels of $1,25(OH)_2D$ are uniformly present in postmenopausal osteoporosis. Early postmenopausal bone loss in asymptomatic women was not associated with changes in $1,25(OH)_2D$ levels in plasma.[70] Likewise, other studies did not find differences in circulating levels of $1,25(OH)_2D$ between os-

Table 1. Genes Regulated by $1,25(OH)_2D_3$ at the Level of mRNA Accumulation.*

Gene	Tissue	Direction of Regulation	Reference
Preproparathyroid hormone	Rat parathyroid glands	↓	Russell et al.[34]
Calcitonin	Rat thyroid glands	↓	Naveh-Many and Silver[35]
Type I collagen	Rat fetal calvaria	↓	Rowe and Kream[36]
Fibronectin	Human fibroblast line	↑	Franceschi et al.[37]
Bone matrix γ-carboxyglutamic acid protein	Rat osteosarcoma cells	↑	Fraser et al.[38]
Interleukin-2	Activated human lymphocytes	↓	Rigby et al.[39]
Interferon-γ	Activated human lymphocytes	↓	Reichel et al.[40]
Granulocyte–macrophage colony-stimulating factor	Activated human lymphocytes	↓	Tobler et al.[41]
c-*myc*	Human HL-60 myeloid leukemia	↓	Simpson et al.[42]
c-*fos*	Human HL-60 myeloid leukemia	↑	Brelvi and Studzinski[43]
c-*fms*	Human HL-60 myeloid leukemia	↑	Scariban et al.[44]
$1,25(OH)_2D_3$ receptor	Mouse fibroblasts	↑	McDonnell et al.[45]
Calbindin-D_{28K}	Chick intestinal mucosa	↑	Theofan et al.[46]
Calbindin-D_{9K}	Rat intestinal mucosa	↑	Dupret et al.[47]
Prolactin	Rat pituitary cells	↑	Wark and Tashjian[48]

*An effect of $1,25(OH)_2D_3$ on transcription has thus far been demonstrated only for the genes encoding preproparathyroid hormone, calcitonin, c-*myc*, and calbindins D_{9K} and D_{28K}. $1,25(OH)_2D_3$ modifies granulocyte–macrophage colony-stimulating factor mRNA post-transcriptionally and also has post-transcriptional effects on the mRNA expression of both calbindins. For the other genes, it is not known whether $1,25(OH)_2D_3$ modulates gene transcription or induces the synthesis of other factors that alter the accumulation of mRNA after transcription.

teoporotic subjects and age-matched controls.[71] These controversial results probably indicate variations in the characteristics of the patients studied, dietary or geographic differences, or methodologic differences.

Similarly, there is controversy about the role of $1,25(OH)_2D_3$ in the prevention or treatment of involutional osteoporosis. On the one hand, the hormone has been reported to improve calcium balance, increase calcium absorption, increase trabecular bone volume, and reduce the rate of fractures among women with postmenopausal osteoporosis.[72] On the other hand, other studies, such as that by Christiansen et al.,[73] did not find that $1,25(OH)_2D_3$ was beneficial in postmenopausal osteoporosis. Certainly, further investigations are necessary to define the long-term effects of $1,25(OH)_2D_3$ in osteoporosis and to identify whether certain subgroups of patients with osteoporosis may benefit from $1,25(OH)_2D_3$ therapy.

Rickets

The importance of the $1,25(OH)_2D_3$ receptor in the mediation of hormone action becomes apparent in patients with the rare syndrome of vitamin D–resistant rickets or vitamin D–dependent rickets Type II. Affected patients have symptoms comparable to those of classic vitamin D–deficient rickets, despite an adequate intake of vitamin D and normal or elevated serum levels of $1,25(OH)_2D_3$.[74] Type II is an X-linked dominant inherited disorder that is heterogeneous and is apparently caused by defective $1,25(OH)_2D_3$ receptors. Studies in cultured fibroblasts from patients with vitamin D–dependent rickets Type II have revealed an absent or impaired nuclear uptake of $1,25(OH)_2D_3$, absent or impaired binding of the hormone to cytosolic extracts containing the receptor, or decreased affinity of the hormone–receptor complex for DNA.[75-77] The cloning and sequencing of the normal $1,25(OH)_2D_3$ receptor should allow the elucidation of the various molecular defects underlying this disease.[50]

Vitamin D–dependent rickets Type I, a rare autosomal-recessive $25(OH)D_3$-1α-hydroxylase deficiency, is distinguished from vitamin D–resistant states by low-to-undetectable levels of circulating $1,25(OH)_2D_3$.[78] Another disease with similar symptoms is renal X-linked hypophosphatemic rickets, or vitamin D–resistant rickets. The presumed defect is an abnormality of phosphate anion transport in the renal tubule, resulting in increased renal phosphate clearance and hypophosphatemia.[79] The $1,25(OH)_2D_3$ serum concentrations in vitamin D–resistant rickets are inappropriately low for the accompanying hypophosphatemia, so that a defect in the production of the hormone has been suggested as an additional mechanism for the disease.[80] Similar biochemical findings are present in hypophosphatemic oncogenic rickets, or familial hypophosphatemic osteomalacia. The disease is almost always associated with a tumor of mesenchymal origin. The removal of the tumor usually resolves the symptoms.[67]

$1,25(OH)_2D_3$ and Cellular Growth and Differentiation

Data gathered in the past five years suggest additional activities of $1,25(OH)_2D_3$ in tissues not primarily related to mineral homeostasis. Like the vitamin A metabolite retinoic acid, $1,25(OH)_2D_3$ may influence the proliferation and differentiation of several tissues, and like the glucocorticosteroids and estrogens, $1,25(OH)_2D_3$ may have immunoregulatory properties. The effects of the hormone on hematopoietic cells, cancer cells, and the epidermis are discussed in more detail in the following sections.

Interaction of $1,25(OH)_2D_3$ with the Hematopoietic System

Several workers have found abnormalities of the immunohematopoietic system in children with rickets. Rickets caused by a deficiency of vitamin D was associated with an increased frequency of infections and impaired phagocytosis by neutrophils.[81] Anemia, decreased cellularity of bone marrow, and extramedullary hematopoiesis were observed.[82] The administra-

Table 2. Tissue Distribution of the $1,25(OH)_2D_3$ Receptor.*

Normal mammalian tissues or cell types
Intestine
Kidney (proximal and distal tubules)
Bone (osteoblasts)
Parathyroid glands
Skin (epidermal cells and fibroblasts)
Skeletal muscle (myoblasts)
Cardiac muscle
Mammary tissue
Testes
Ovary
Uterus
Placenta
Pituitary gland
Pancreas
Colon
Parotid gland
Thymus
Circulating lymphocytes (activated)
Circulating monocytes
Malignant tissues or cancer-cell lines
Osteosarcoma
Melanoma
Breast carcinoma
Colon carcinoma
Medullary thyroid carcinoma
Myeloid and lymphocytic leukemia
Pancreatic adenocarcinoma
Transitional-cell bladder carcinoma
Cervical carcinoma
Fibrosarcoma

*Additional studies in the chick have reported the presence of the $1,25(OH)_2D_3$ receptor in the avian ultimobranchial gland, oviduct, and egg shell gland.[2,10,49]

tion of vitamin D_3 corrected these irregularities. Another study, which used vitamin D–deficient mice, demonstrated reduced phagocytosis of peritoneal macrophages and an impaired inflammatory response, as determined by an examination of peritoneal-exudate cells.[83]

Nevertheless, vitamin D deficiency or $1,25(OH)_2D_3$ receptor defects do not cause clear deficiencies of the hematopoietic–immune system in vivo, suggesting that $1,25(OH)_2D_3$ probably is not absolutely necessary for the normal functioning of this system. This may reflect the presence of many other factors and hormones that regulate hematopoiesis.

Effects on Differentiation and Proliferation of Hematopoietic Cells

A possible role of $1,25(OH)_2D_3$ in the differentiation of hematopoietic stem cells was suggested in 1981 by Abe and coworkers.[84] Immature mouse myeloid leukemia cells differentiated to more mature macrophage-like cells on treatment with $1,25(OH)_2D_3$. The human promyelocytic leukemia cell line, designated HL-60, and the human monoblastic leukemia cell line, designated U937, were the models most frequently used to study the effects of $1,25(OH)_2D_3$ on hematopoietic differentiation. Exposure to $1,25(OH)_2D_3$ reduced the proliferation of these cells in liquid culture and decreased their clonal growth in soft agar. The expression of macrophage-related antigens and enzymes was increased, the production of lysozyme was increased, and phagocytic activity was enhanced; the cells also gained the ability to degrade bone matrix.[85-90] These alterations were preceded by modulations in the expression of growth-related proto-oncogenes: a rapid decline in the levels of c-*myc* mRNA,[42,43] the transient expression of c-*fos*[43] and the sustained expression of c-*fms*.[44] Thus far, there is no evidence that the variations in oncogene expression are necessary or sufficient for differentiation.

Further results were obtained with primary cultures of normal and abnormal human myeloid cells. Freshly harvested leukemic cells from patients with myeloid leukemias were exposed to $1,25(OH)_2D_3$. The antiproliferative and differentiation-inducing effects of the hormone were confirmed[90,91]; however, supraphysiologic doses of $1,25(OH)_2D_3$ (0.1 to 10 μM) were required for clear results. $1,25(OH)_2D_3$ increased the number of macrophages in liquid cultures of normal mononuclear cells from human bone marrow.[86] Colony-forming assays showed that $1,25(OH)_2D_3$ (1 to 10 nM) did not markedly alter the clonal growth of normal human myeloid precursors[90,92]; however, the formation of macrophage colonies was preferentially induced over the formation of granulocyte colonies.[92] Taken together, these results are consistent with the conclusion that $1,25(OH)_2D_3$ promotes the differentiation in vitro of myeloid precursor cells toward cells with the properties of mature macrophages.

The in vitro studies suggest that $1,25(OH)_2D_3$ may be useful in the treatment of myelodysplastic syndrome and, possibly, acute myeloid leukemia, since the hormone may induce the abnormal hematopoietic cells to differentiate into more mature, less aggressive cells. An observation by Honma et al.[93] suggested that the effect of $1,25(OH)_2D_3$ on differentiation indeed may be operative in vivo: the survival of mice that had been inoculated with immature mouse myeloid leukemia cells was prolonged significantly after the administration of $1\alpha(OH)D_3$. In contrast, the administration of $1,25(OH)_2D_3$ (2 μg per day) did not result in an apparent improvement of hematopoiesis in patients with myelodysplastic syndrome.[91] Since this dose could result in $1,25(OH)_2D_3$ serum levels of only approximately 100 pg per milliliter, the results seem to suggest that pharmacologic levels of $1,25(OH)_2D_3$ are required to achieve the theoretically required concentrations of the hormone in myelodysplastic syndrome and that the desired concentrations cannot be achieved in vivo because of the hypercalcemic side effects of the hormone. Therefore, attempts are currently being directed toward the identification of chemically modified vitamin D analogues that, like $1,25(OH)_2D_3$, can induce differentiation but do not have the ability to cause hypercalcemia through the stimulation of intestinal calcium absorption.[94-96]

Effects of $1,25(OH)_2D_3$ on Lymphocytes

Receptors for $1,25(OH)_2D_3$ are expressed in activated, proliferating human B lymphocytes and T lymphocytes, but they cannot be detected in quiescent lymphocytes. $1,25(OH)_2D_3$ receptors are also found in

cells from transformed lymphocyte lines. Research in the past three years has revealed a large spectrum of effects of $1,25(OH)_2D_3$ on lymphocytes.

The hormone inhibited the synthesis of DNA and the proliferation of lectin-activated human lymphocytes.[97] These effects were probably mediated through a repression of interleukin-2 production.[97] This repression occurred at the mRNA level,[39] although $1,25(OH)_2D_3$ had no influence on the number of interleukin-2 receptors. The hormone also suppressed the production by lectin-activated lymphocytes of two other immunologically active lymphokines: granulocyte–macrophage colony-stimulating factor and interferon-γ.[40,41] This could be demonstrated at both the mRNA and the protein levels and was independent of DNA synthesis and interleukin-2 production rates. The $1,25(OH)_2D_3$-induced inhibition of the synthesis of granulocyte–macrophage colony-stimulating factor was at a post-transcriptional level.[40] Other studies have shown that $1,25(OH)_2D_3$ has inhibitory effects on the synthesis of immunoglobulins by B lymphocytes; these effects are either exerted directly on B lymphocytes[98] or mediated indirectly by T helper–cell activity.[99] The relevance of these new findings to osteoporosis is not clear; studies have shown that the ratio of helper cells to suppressor cells is increased in patients with spinal fracture and that administration of $1\alpha(OH)D_3$ corrects this irregularity.[100]

Interaction of $1,25(OH)_2D_3$ with Cancer Cells

Receptors for $1,25(OH)_2D_3$ are present in a variety of nonleukemia cancer cell lines, including melanomas and lung and colon cancer, and most primary breast cancer cells that have been examined (Table 2). A possible effect of $1,25(OH)_2D_3$ on the growth of cancer cells was assessed in several studies.

In a manner comparable to its antiproliferative activity in some leukemia cell lines,[84,86,87] $1,25(OH)_2D_3$ at high concentrations inhibited the proliferation of cell lines that had been established from solid tumors.[101,102] Inhibitory effects of the hormone on tumor growth were also found in investigations under in vivo conditions. The administration of $1\alpha(OH)D_3$ reduced the size of transplanted sarcoma cells in mice and reduced the number of lung metastases after implantation of Lewis lung carcinoma cells into mice.[103] The growth of human colon cancer and melanoma xenografts in mice was inhibited by high doses of $1,25(OH)_2D_3$.[104] In contrast, tumor growth was enhanced by the administration of $1,25(OH)_2D_3$ to mice that had been inoculated with rat osteosarcoma cells (17/2.8).[105] In one study, $1\alpha(OH)D_3$ (1 μg per day) was given to patients with low-grade non-Hodgkin's lymphoma.[106] Preliminary data suggested an antitumor activity of $1\alpha(OH)D_3$ in one lymphoma subtype (follicular small cleaved lymphoma).[106] Moreover, the $1,25(OH)_2D_3$-induced stimulation of fibronectin production by a variety of human cancer and transformed cell lines[37] was putatively implicated as a possible antimetastatic effect of the hormone.

Although the majority of findings suggest an inhibitory effect of $1,25(OH)_2D_3$ on tumor growth, divergent results have been reported,[105] indicating that the effects of the hormone may vary with the cell type. Again, additional studies are needed to establish whether $1,25(OH)_2D_3$ or suitable analogues have important chemopreventive or therapeutic potential in malignant diseases.

Role of $1,25(OH)_2D_3$ in the Differentiation of Epidermal Cells

Skin may be another tissue in which $1,25(OH)_2D_3$ exerts effects on cellular growth and differentiation. Nuclear $1,25(OH)_2D_3$ receptors are present in human and mouse skin. Studies of a possible functional effect of $1,25(OH)_2D_3$ on skin cells showed that the synthesis of DNA by mouse epidermal cells in primary culture was inhibited by $1,25(OH)_2D_3$.[107] The hormone-induced changes in cultured mouse and human keratinocytes were consistent with terminal differentiation toward nonadherent cornified squamous cells.[107,108] In addition, keratinocytes from neonatal human foreskin,[33] but not those obtained from adult donors,[108] were found to produce $1,25(OH)_2D_3$ from $25(OH)D_3$ in vitro. These results suggest that, under certain conditions, keratinocyte-derived $1,25(OH)_2D_3$ may influence epidermal differentiation locally.

In psoriasis, the normal maturation and proliferation of epidermal cells are disturbed, resulting in a hyperproliferative state. As in the case of leukemia, $1,25(OH)_2D_3$ is a possible treatment for psoriasis because of its ability to induce differentiation and to inhibit the proliferation of epithelial cells. Therefore, $1,25(OH)_2D_3$ treatment of patients with psoriasis has been initiated. Studies involving approximately 30 patients have indicated that the topical or oral administration of $1,25(OH)_2D_3$ improves the symptoms in the majority of patients.[109-111] However, these results are preliminary, and controlled studies are needed to dissociate the true activity of $1,25(OH)_2D_3$ from random alterations in disease activity.

Other Target Tissues

Recently, $1,25(OH)_2D_3$ has also been associated with the function of other tissues not primarily related to calcium metabolism. Some of these include the pancreas, with the stimulation of insulin secretion[112]; skeletal and cardiac muscle[113,114]; the pituitary gland, with the modulation of prolactin synthesis[48]; the thyroid gland[35]; and the gonads.[115] Space limitations preclude a more detailed discussion of these investigations.

Granulomatous Disease and $1,25(OH)_2D_3$

Sarcoidosis

Hypercalcemia is a complication of sarcoidosis in 10 to 20 percent of cases; hypercalciuria occurs more frequently.[116] The increased sensitivity of patients with sarcoidosis to the hypercalcemic action of vitamin D[117] led to the early suggestion that vitamin D is involved in the disordered calcium metabolism in this disease. This hypersensitivity to vitamin D was again

demonstrated in a more recent study, in which administration of vitamin D to normocalcemic patients with sarcoidosis produced a several-fold increase in the serum $1,25(OH)_2D$ levels, whereas the same amount of vitamin D had no effect on normal control subjects.[118]

Elevated serum levels of $1,25(OH)_2D$ were noted in patients with sarcoidosis during hypercalcemic episodes.[119,120] The increase in $1,25(OH)_2D$ concentrations could be attributed to an enhanced rate of $1,25(OH)_2D$ production in sarcoidosis and was not due to impaired metabolic clearance of the hormone.[121] Thus, overproduction of $1,25(OH)_2D$ may account for the disturbances of calcium metabolism in sarcoidosis. A report of a hypoparathyroid patient with elevated serum levels of $1,25(OH)_2D$[122] suggested that the synthesis of $1,25(OH)_2D$ in sarcoidosis was not under the same degree of control by prevailing parathyroid hormone levels as is synthesis in normal persons. The presence of detectable and even elevated serum levels of $1,25(OH)_2D$ in patients with sarcoidosis who were anephric[17] or who had end-stage renal disease[18] indicated that the excess $1,25(OH)_2D$ in sarcoidosis may be of extrarenal origin.

The activated macrophage is the most likely source of the ectopic $1,25(OH)_2D$ found in patients with sarcoidosis.[27,28] In pulmonary sarcoidosis, the activation of alveolar macrophages occurs in vivo through the exposure of cells to interferon-γ from T lymphocytes. Possibly, the synthesis of $1,25(OH)_2D_3$ by sarcoid alveolar macrophages is due to stimulation by this lymphokine, since interferon-γ has profound stimulatory effects on the synthesis of $1,25(OH)_2D_3$ by cultured alveolar macrophages in vitro.[28] The function of the $1,25(OH)_2D_3$ produced by macrophages is not clear. We have postulated that $1,25(OH)_2D_3$ derived from activated macrophages may influence the activity of hormone-responsive cells locally. In particular, lymphocytes that are present at the site of an immune response could be considered the target cells for $1,25(OH)_2D_3$.[39-41,97-99]

Other in vitro data have shown that the synthesis of $1,25(OH)_2D_3$ by alveolar macrophages is clearly different from renal $1,25(OH)_2D_3$ synthesis, in that hormone production is largely independent of the presence of $1,25(OH)_2D_3$ and parathyroid hormone.[28,123] Glucocorticoids can correct abnormal vitamin D and calcium metabolism in sarcoidosis. Likewise, chloroquine has been shown to be of clinical value in normalizing disturbed calcium and vitamin D metabolism in patients with sarcoidosis who have severe side effects from cortisol treatment.[124] This therapeutic effect may be explained in part by an inhibition of the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ by sarcoid alveolar macrophages.[120,121]

Other Granulomatous Diseases

Reports in the literature suggest that abnormal vitamin D metabolism may also be present in several other granulomatous disorders. The clinical manifestations of this abnormality appear to be less frequent than in sarcoidosis, however. Extrarenal synthesis of $1,25(OH)_2D_3$ can occur in tuberculosis, as postulated from the description of two hypercalcemic patients with tuberculosis, end-stage renal disease, and elevated $1,25(OH)_2D$ serum levels.[19,20] Studies of the source of extrarenal $1,25(OH)_2D_3$ in patients with tuberculosis have not been performed. As in sarcoidosis, an abnormal increase in circulating $1,25(OH)_2D_3$ concentrations has been reported in normocalcemic patients with active pulmonary tuberculosis after the administration of vitamin D.[125] Hypercalcemia associated with elevated serum levels of $1,25(OH)_2D$ has also been described in patients with leprosy,[126] disseminated candidiasis,[127] silicone-induced granuloma,[128] and plasma-cell granuloma.[129] Although a homogenate of plasma-cell granuloma has been reported to synthesize $1,25(OH)_2D_3$ from $25(OH)D_3$,[129] the source of the additional $1,25(OH)_2D_3$ in the other disorders is unknown.

Lymphoma and $1,25(OH)_2D_3$

Research has been undertaken to evaluate the potential role of $1,25(OH)_2D_3$ in mediating the humoral hypercalcemia related to hematopoietic cancers. Several reports have demonstrated that the hypercalcemia that is sometimes observed in patients with Hodgkin's or non-Hodgkin's lymphoma may be associated with elevated serum levels of $1,25(OH)_2D$. The high concentrations of $1,25(OH)_2D$ have been regarded as the probable cause of the hypercalcemia.[130-132] Although the source of the excess $1,25(OH)_2D_3$ is unknown in most cases, ectopic production of $1,25(OH)_2D_3$ by a homogenate of a lymph node containing a B-cell lymphoma has been demonstrated.[132] This lymph node was resected from a patient with hypercalcemia and high serum concentrations of $1,25(OH)_2D_3$.

One patient with elevated serum levels of $1,25(OH)_2D_3$ had adult T-cell leukemia related to human T-lymphotropic virus Type I (HTLV-I).[130] Since hypercalcemia develops in approximately 50 percent of patients with adult T-cell leukemia, researchers investigated whether HTLV-I–transformed lymphocytes could produce $1,25(OH)_2D_3$. Indeed, two lymphocyte cell lines infected with HTLV-I were identified that were capable of synthesizing $1,25(OH)_2D_3$.[133,134] However, several other lymphocyte cell lines infected with HTLV-I did not produce $1,25(OH)_2D_3$,[134] and the serum levels of $1,25(OH)_2D_3$ in five patients with hypercalcemia and adult T-cell leukemia were found to be low to normal.[135] Thus, elevated serum levels of $1,25(OH)_2D_3$ probably are not the usual cause of hypercalcemia in adult T-cell leukemia. However, in some rare cases, excess production of $1,25(OH)_2D_3$, possibly by malignant lymphocytes, may occur and lead to hypercalcemia. The circumstances that result in this excess are not known.

Conclusions

In addition to its well-established effects on the

maintenance of mineral homeostasis, $1,25(OH)_2D_3$ may also be involved in the functioning of tissues not primarily related to mineral metabolism. Prime examples are hematopoietic cells, the skin, cancer cells of various origins, and the pancreatic B cells. Further studies of a possible physiologic role of $1,25(OH)_2D_3$ in noncalciotropic tissues are needed and may eventually lead to new clinical applications for this hormone.

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