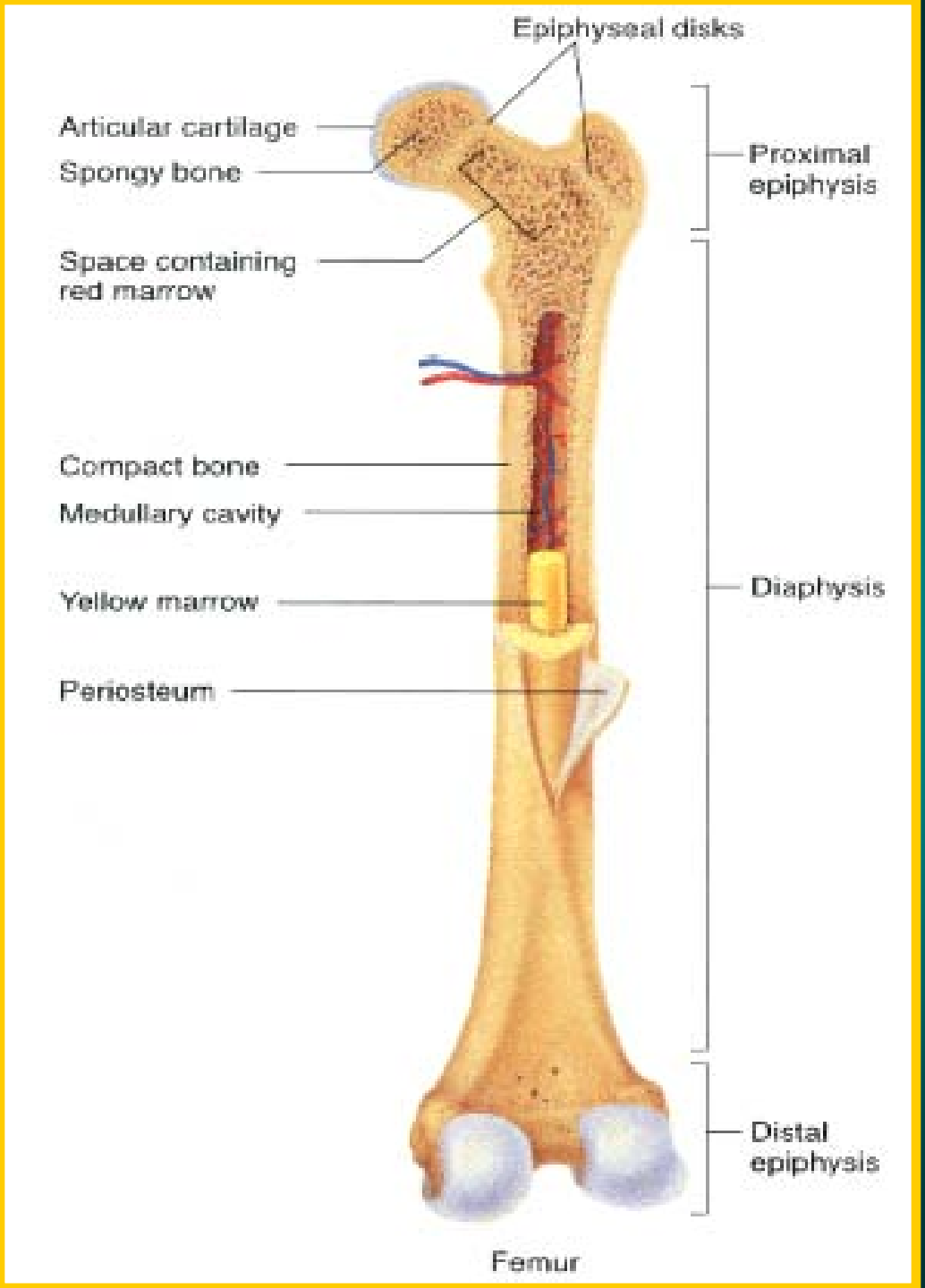
VDR:

not bones only



Bones

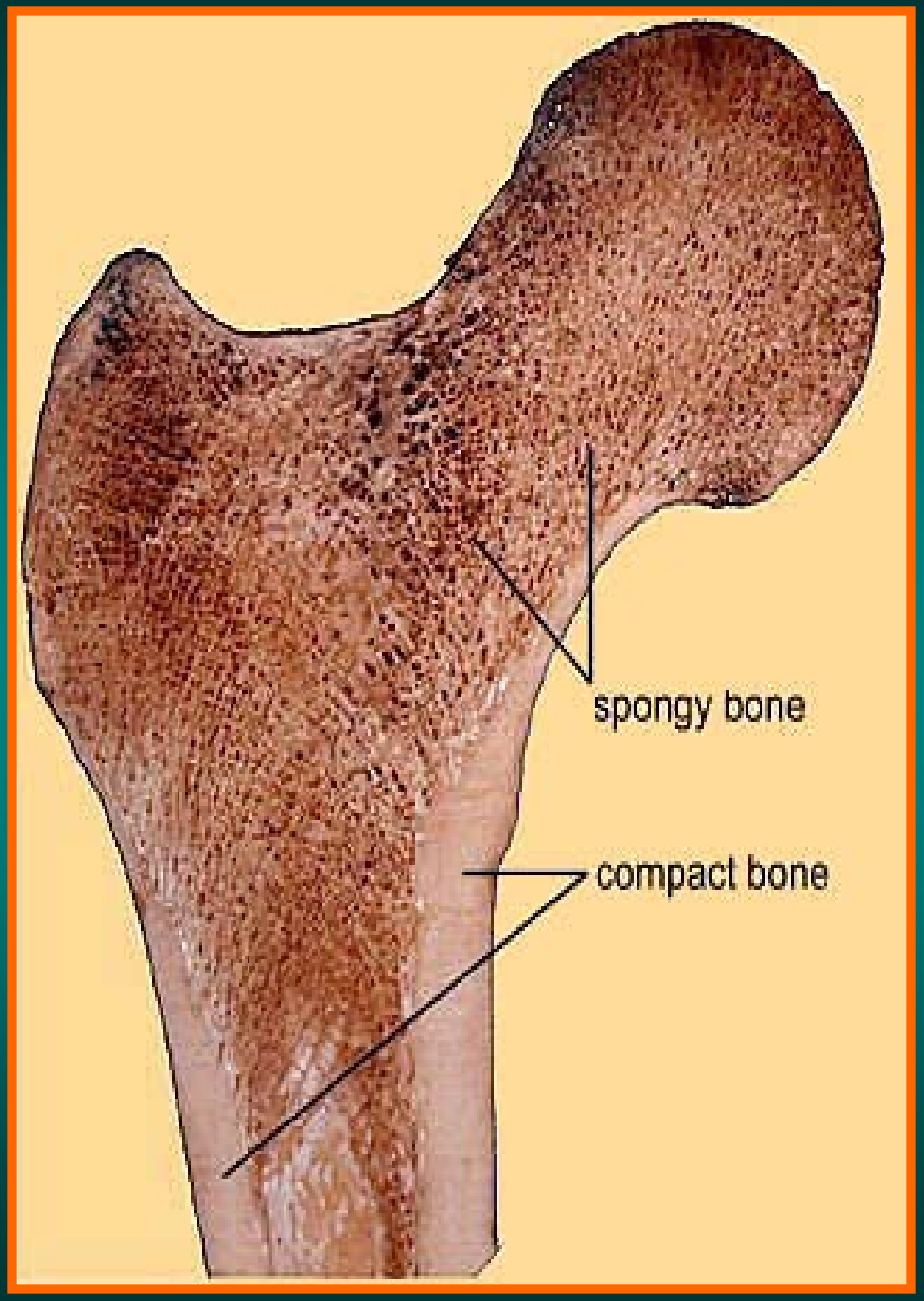
- During embryogenesis development of bones is a late event – it is the last stage of skeleton formation.

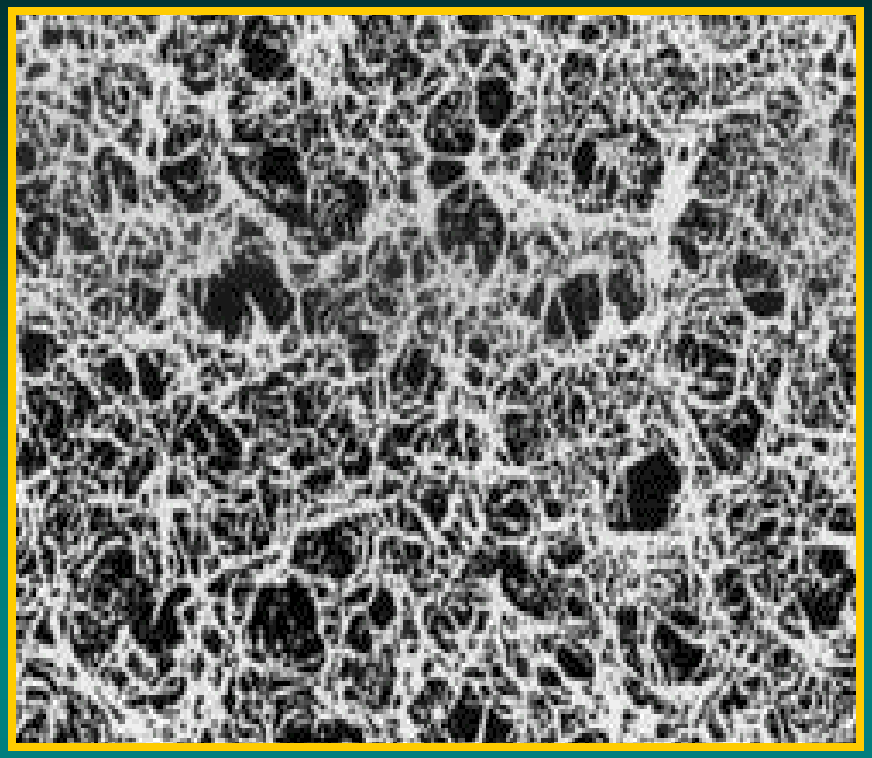
- Bone is a strongly metabolizing tissue, regulating the calcium storage and release.

- Its balance depends on equilibrated action of osteoblasts and osteoclasts during whole life.

Bone turnover

- Bone is renewed by continuous remodeling
- Bone is resorbed by osteoclasts
- Resorption releases calcium and collagen metabolites
- Bone is formed by osteoblasts
- Resorption and formation are normally in balance
- Uncoupling of bone turnover leads to bone loss



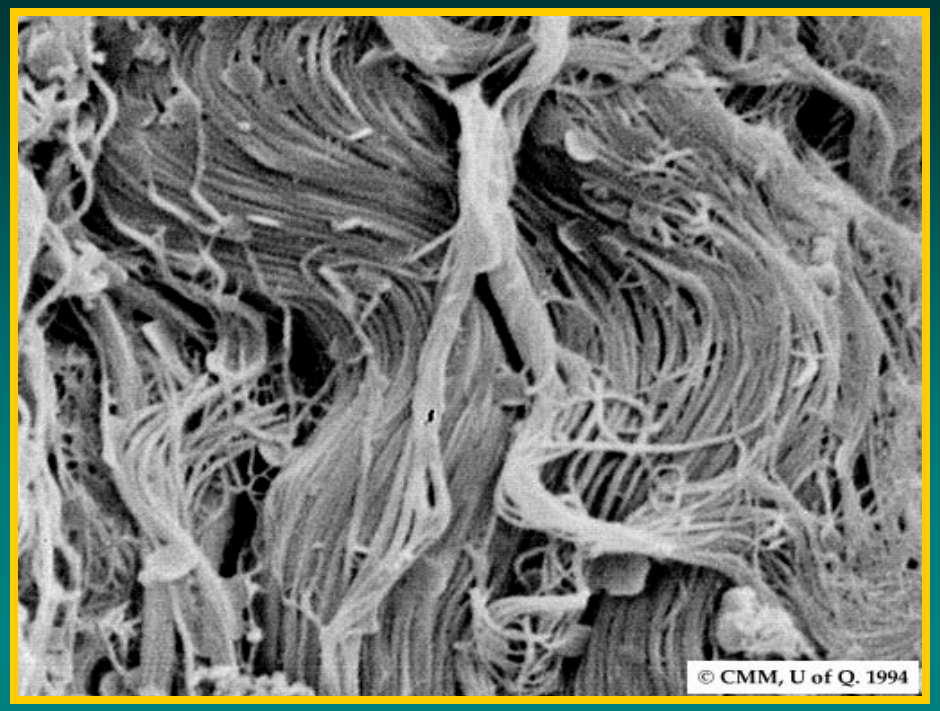


Calcium in bones

- Bones can be described as inorganic mineral deposited on an organic framework.
- The mineral portion of bones is composed largely of calcium phosphate in the form of hydroxyapatite crystals ($Ca_{10}(PO_4)_6(OH)_2$.

- Approximately 99% of total body calcium is present in bone (1-2 kg in a normal adult)
- Mineral portion of bone typically comprises about 25% of its volume (but about half of weight).
- Bone also contains considerable amounts of carbonate, magnesium, and sodium.

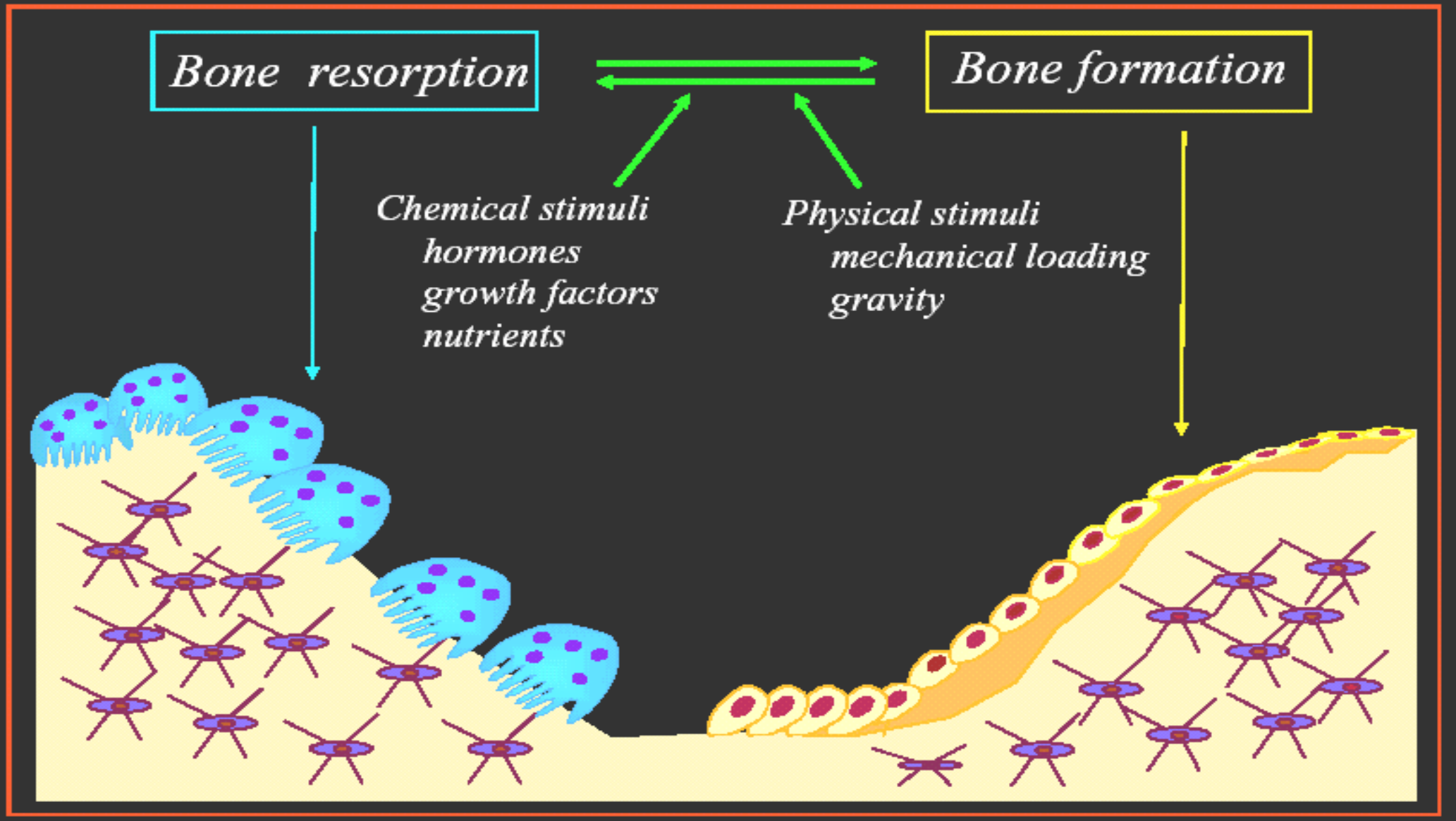
Collagen in bones



- The organic matrix of bone is called osteoid.
- Its primary constituent is type I collagen, comprising ~95% of osteoid mass.
- Needle-like hydroxyapatite crystals lay alongside collagen fibers and this orderly association is responsible for the strength and hardness of bone:

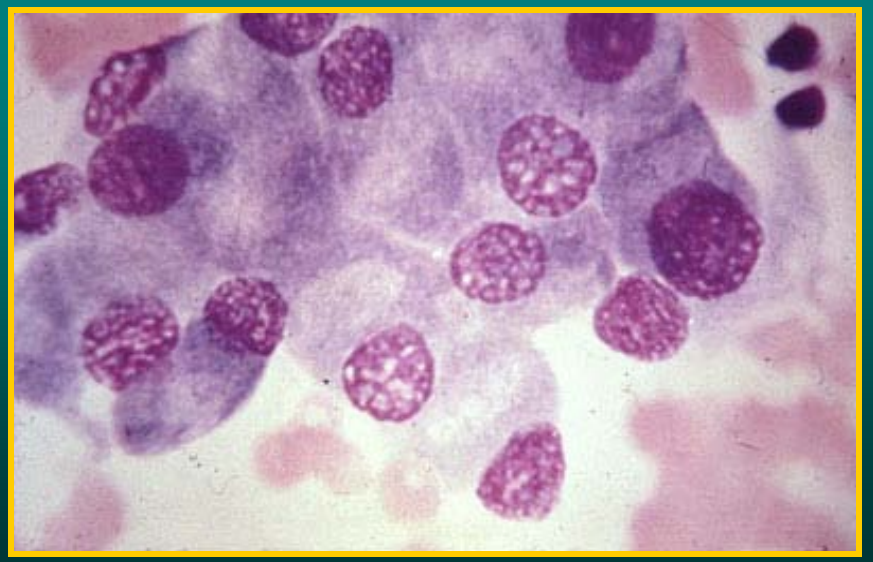
  * complete demineralization leaves a flexible collagen framework,
  * complete removal of organic part leaves a bone with its original shape, but extremely brittle.

Bone homeostasis



Osteoblasts

- Cells of mesenchymal origin, similar to fibroblasts
- Are located on the bone surface.
- Are responsible for osteoid synthesis (therefore have an abundant rough endoplasmic reticulum and Golgi complex).
- They produce extracellular matrix and are necessary to form bone and to its growth in length.
- Their differentiation is regulated by Cbfa-1 (inhibited by vitamin D) and indian hedgehog (Ihh).

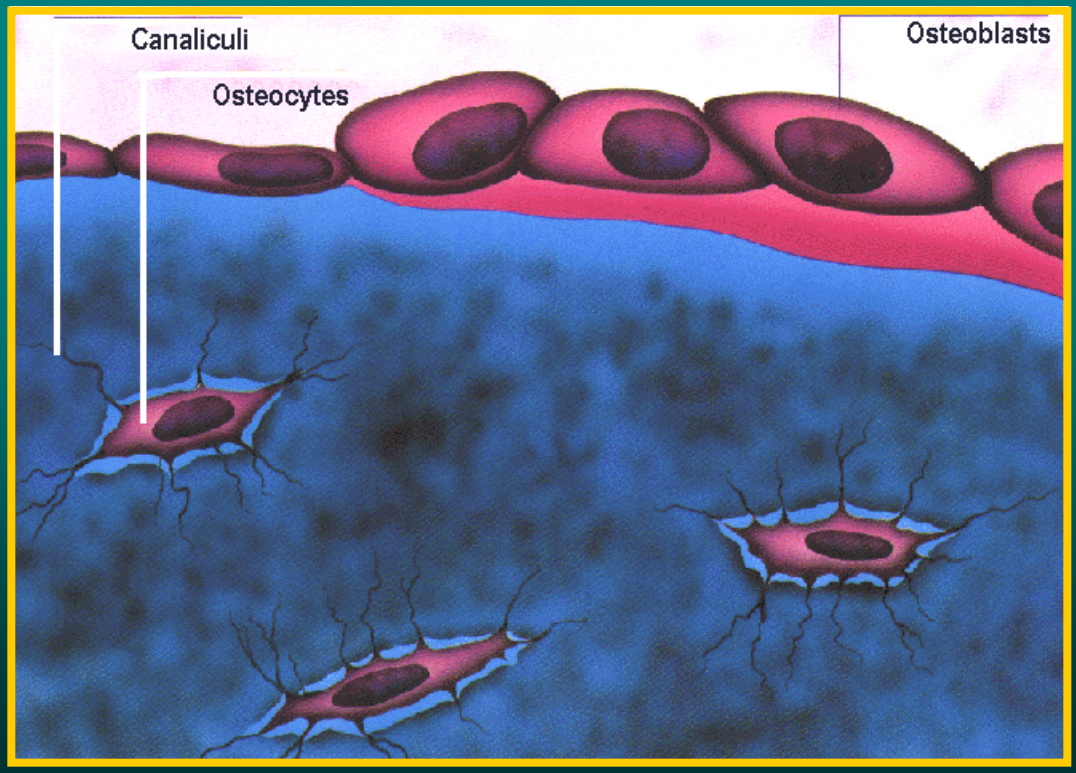


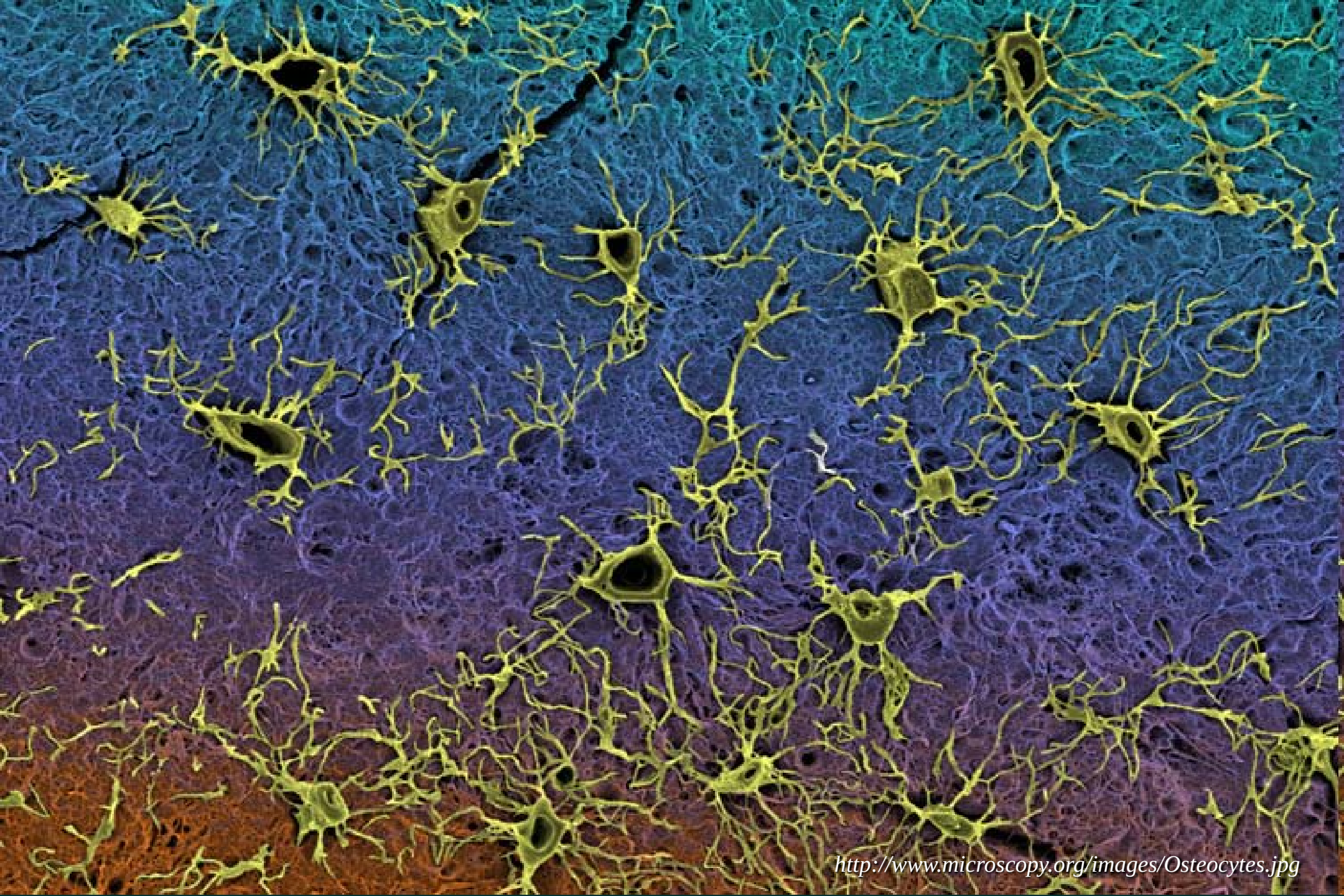
- Proteins characteristic for osteoblasts are:
  - * Bone sialoprotein (expressed also in other cells, downregulated by vitamin D)
  - * Osteocalcin (upregulated by vitamin D)

Osteocytes


Klein-Nulend, Bacabac, Veldhuijzen, van Loon

- Numerous cytoplasmatic processes connect adjacent osteoblasts and connect osteoblasts with osteocytes deeper in bone.
- Osteoid produced by osteoblasts is secreted into the space adjacent to the bone.
- Eventually, new osteoid becomes mineralized, and in the process osteoblasts are surrounded by mineralized bone.
- As osteoblasts are progressively engulfed by mineralized bone, they lose much of the bone-forming ability and become more quiescent osteocytes.
- Many of the cytoplasmatic connections are maintened and became visible channels (canaliculi), that provide direct contact for osteocytes for transfer of nutrients, hormones and waste products.



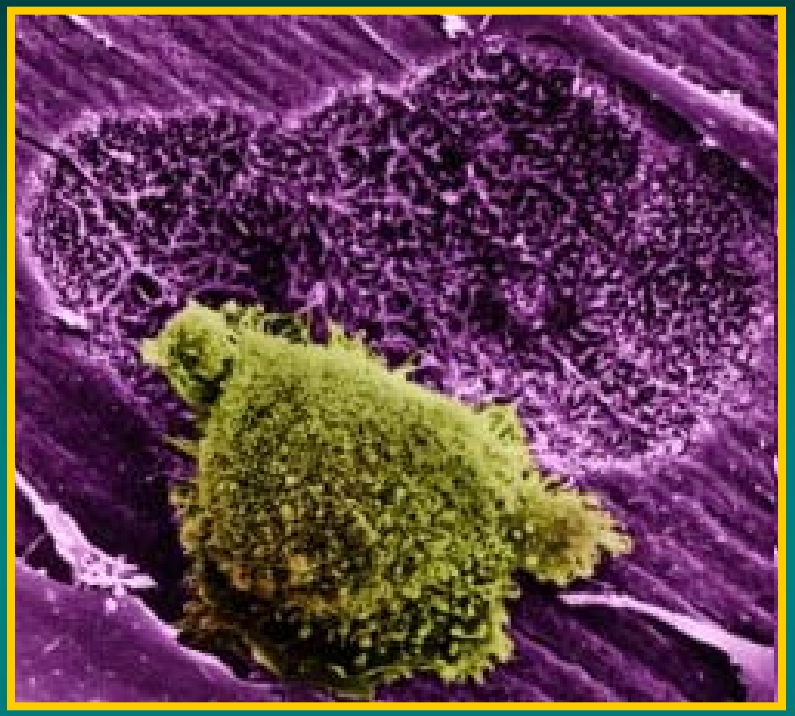

http://www.microscopy.org/images/Osteocytes.jpg

Osteoclasts

- A cell type whose function is to constantly destroy the bone hosting it.

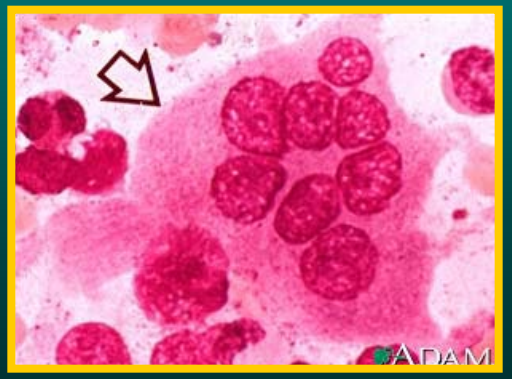
- Osteoclasts belong to the monocyte/macrophage cell lineage.

- They are giant multinucleated cells found in contact with calcified bone surfaces and are responsible for bone resorption.



- Bone resorption is regulated by:

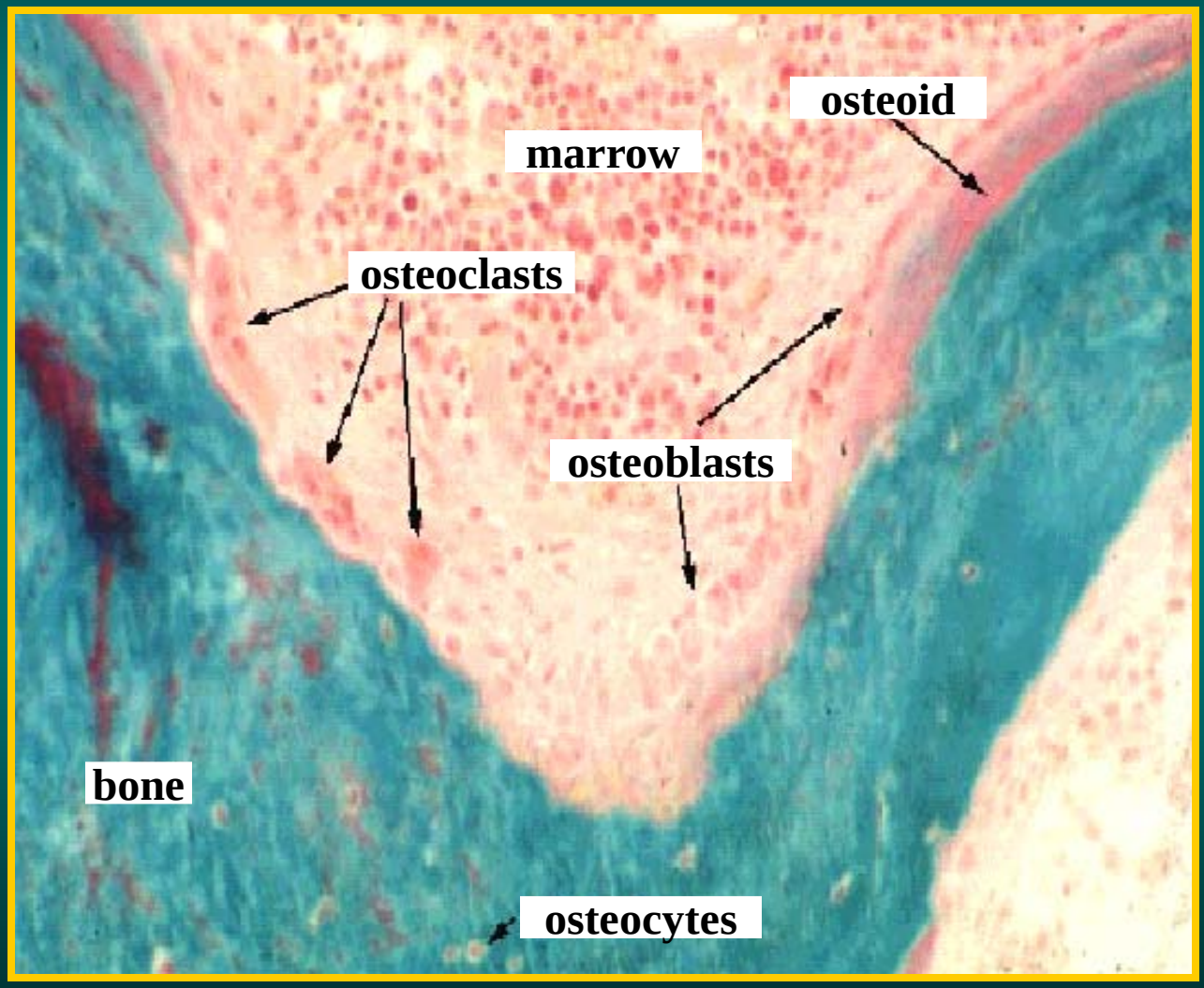
  * PTH (parathyroid hormone, increased resorption, systemic influence)
  * IL-1β (increased resorption)
  * TNFα (increased reserption)
  * IL-6 (maturition of osteoclasts precursors)
  * M-CSF (maturition of osteoclasts precursors)
  * estradiol (inhibits generation of IL-1β, TNFα, IL-6, M-CSF)



Osteoclast

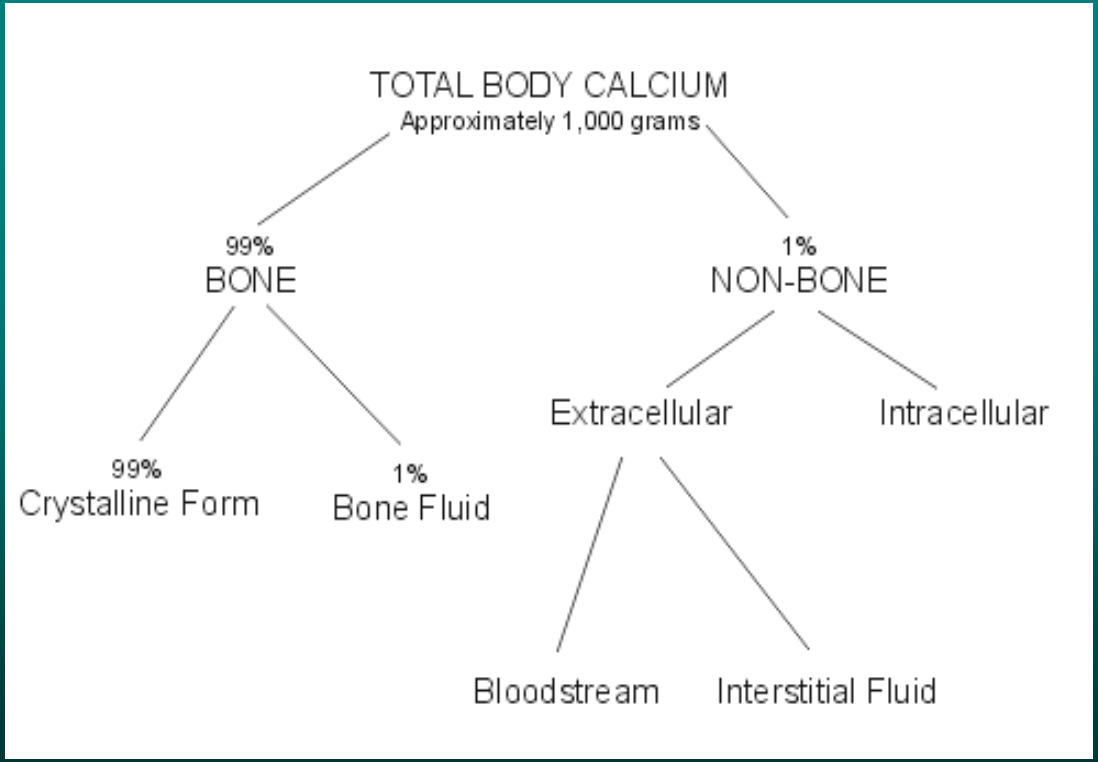
http://annasbones.files.wordpress.com/2009/10/arnett_osteoclast1.jpg

Bone morphology



Calcium

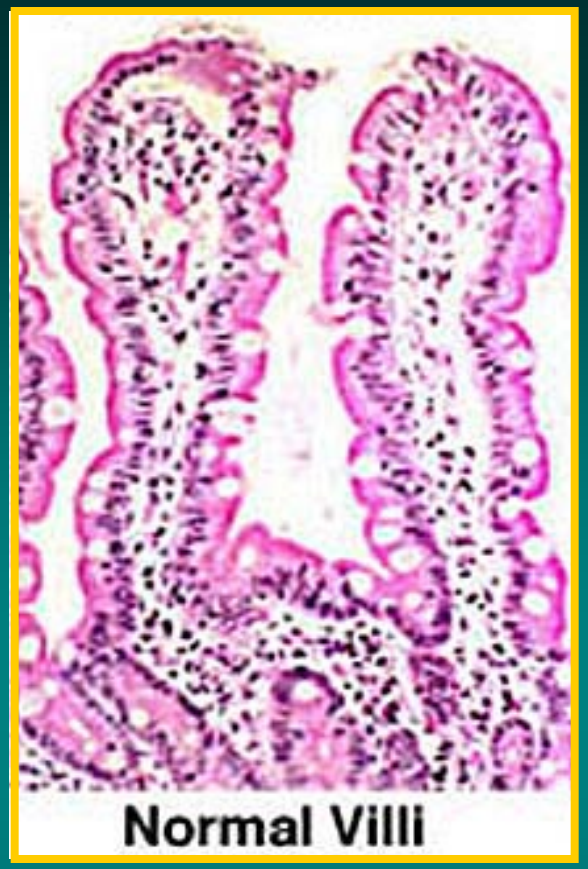
- Calcium and phosphorus are the most abundant minerals in the body.
- Calcium intake is about 900 mg/day (comes mainly from milk products in the diet).
- ~750 mg/day is excrected in feces, the remaining (~150 mg/day) is excreted in urine.
- Calcium exists in two forms that have quite different functions.



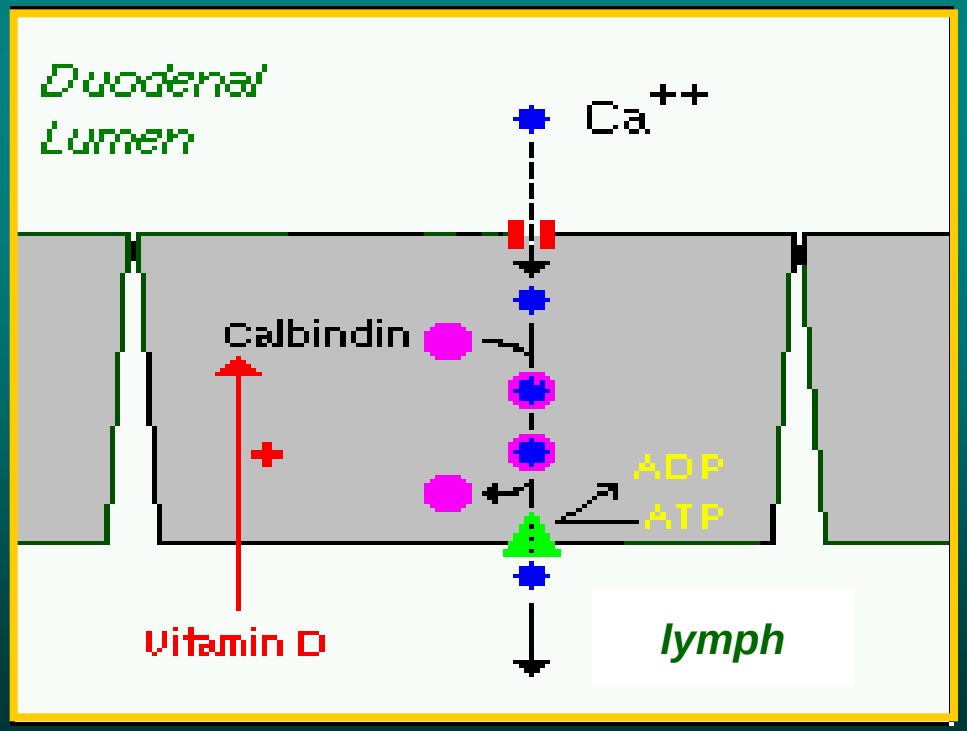
1) Most of the calcium in the body is found as calcium phosphate crystals in the bones and teeth (a cement-like structure that gives strength).

2) Calcium is also found in an ionic form that performs critical functions in muscle contraction, nerve impulses, ion transport, and transmission of signals across membranes e.t.c.

Calcium – absorption



- Calcium absorption on the small intestine occurs both by active transport and diffusion.
- At very high levels of calcium intake most of the uptake occurs by diffusion. With moderate or low calcium intake, however, active transport predominates (because gradient for diffusion is low).



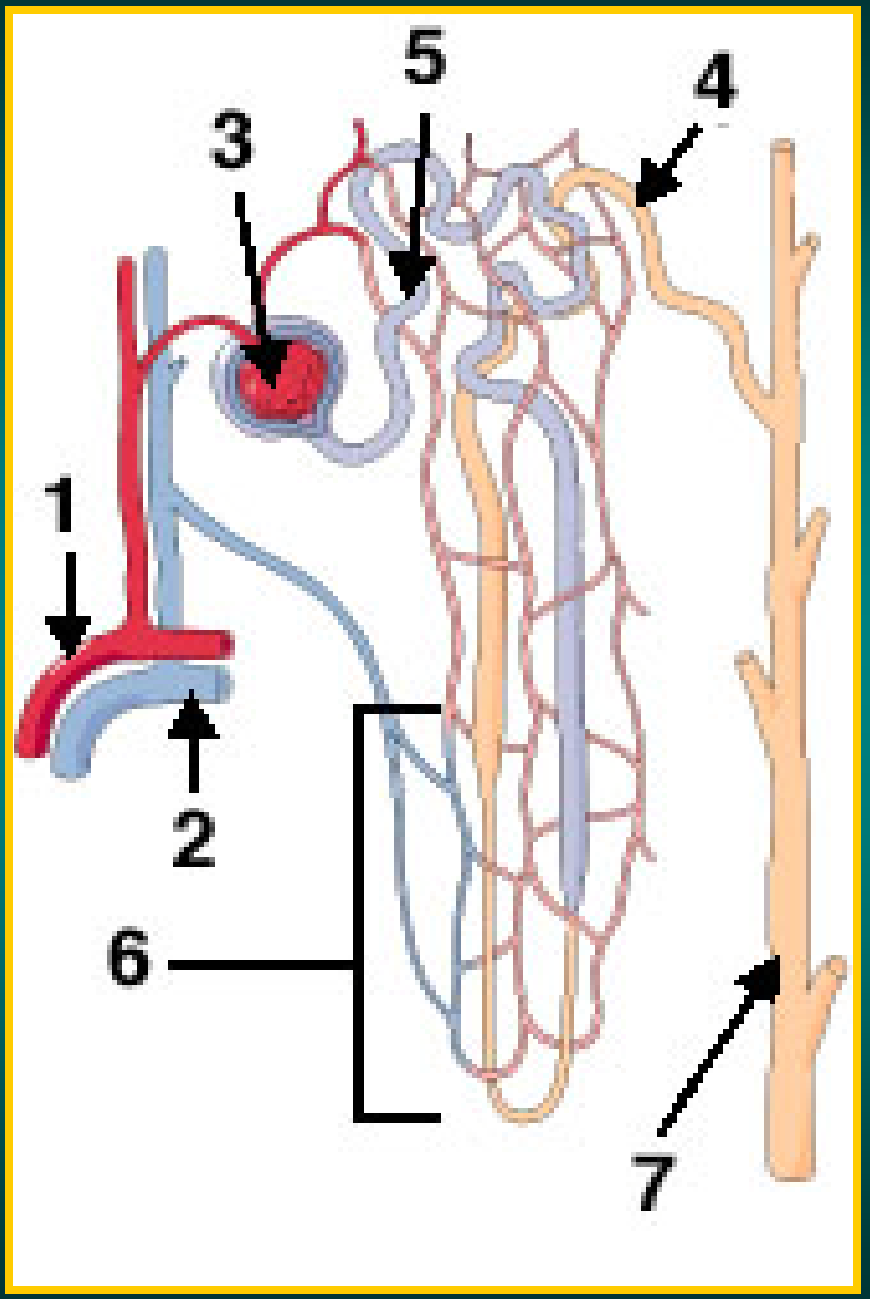
- Active transport is regulated by vitamin D.
- Vitamin D3 augments expression of calcium binding proteins (calbindin) in intestinal mucosal cells, and thereby increases capacity of these cells to transport calcium.

Calcium – renal filtration

- Of 100% of the filtered load of calcium in Bowman's space, only 0.5-2.0% remains in the urine.

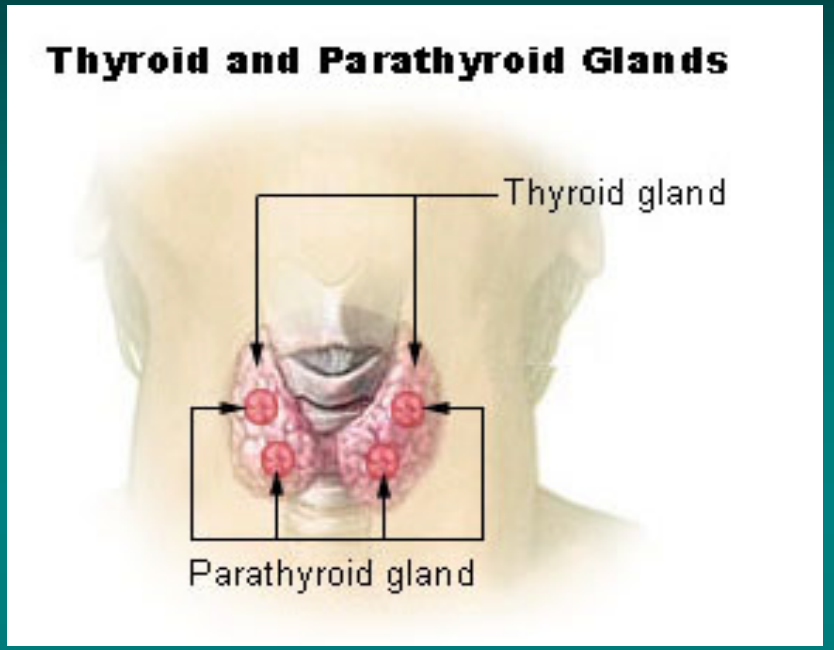
- The majority of the filtered load of calcium (~60%) is reabsorbed in the proximal tubule, 20% in the loop of Henle and 5-10% in the distal tubule.

- Renal reabsorption is stimulated by parathyroid hormone (produced by a parathyroid glands) and vitamin D and regulated by calcitonin (hormone produced by a thyroid gland).



1-Artery to Kidney; 2-Vein from Kidney; 3-Bowman's Capsule (Glomerulus); 4-Distal Convoluted Tubule; 5-Proximal Convoluted Tubule; 6-Loop of Henle; 7-Collecting Tubule

Calcium – hormonal regulation



I. PTH (parathyroid hormone)

Small protein produced by parathyroid gland:

* Increases level of plasma calcium

* Stimulates calcium reabsorption in kidneys

* Stimulates actvity of 1α-hydroxylase in kidney,

thus increases production of active vitamin D;

on the other hand vitamin D inhibits expression of PTH

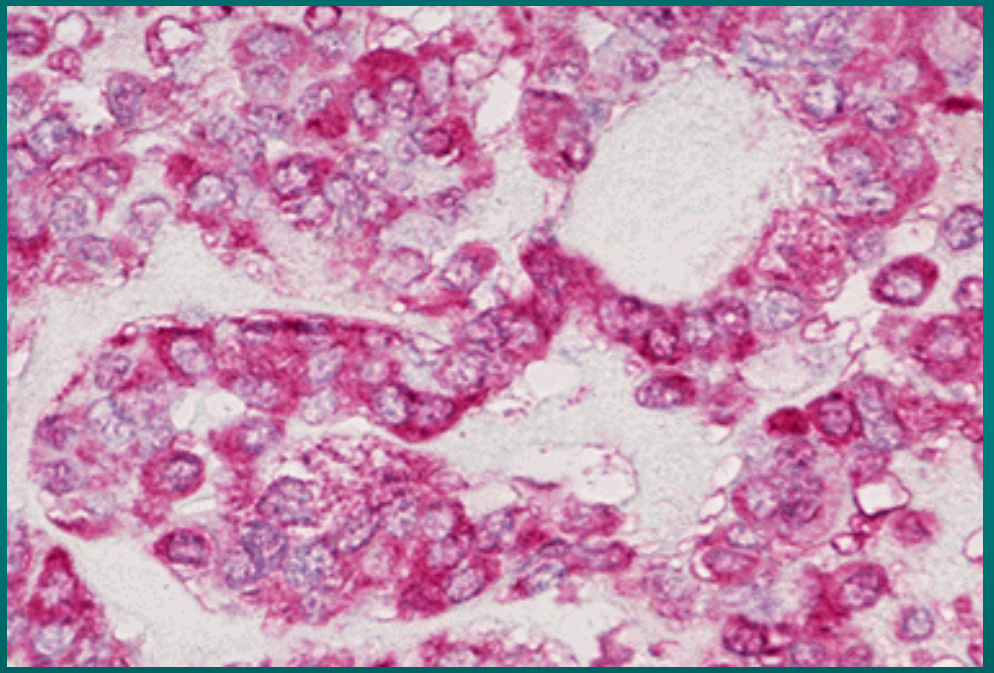
* Activates maturition of osteoclasts and increases bone resorption (increased delivery of calcium from bones to plasma)

* Inhibits collagen synthesis by osteoblasts, thereby decreasing bone formation and decrease a flow of calcium from plasma into bone mineral.

* No direct effect on gastrointestinal tract.

Calcium – hormonal regulation

II. Calcitonin – polypeptide produced by thyroid gland:



* Promotes calcium deposition in bones
* Decreases both calcium and phosphate levels in plasma
* Primary target is bone (inhibition of osteoclasts activity), some lesser effects also occur in kidney
* No effect on gastrointestinal tract
* It is more important in lower vertebrates, in mammals its role is less important.
* Calcitonin induces 25-α hydroxylase.

Calcium – hormonal regulation

III. Vitamin D – its derivative 1,25-dihydroxy (calciferol)

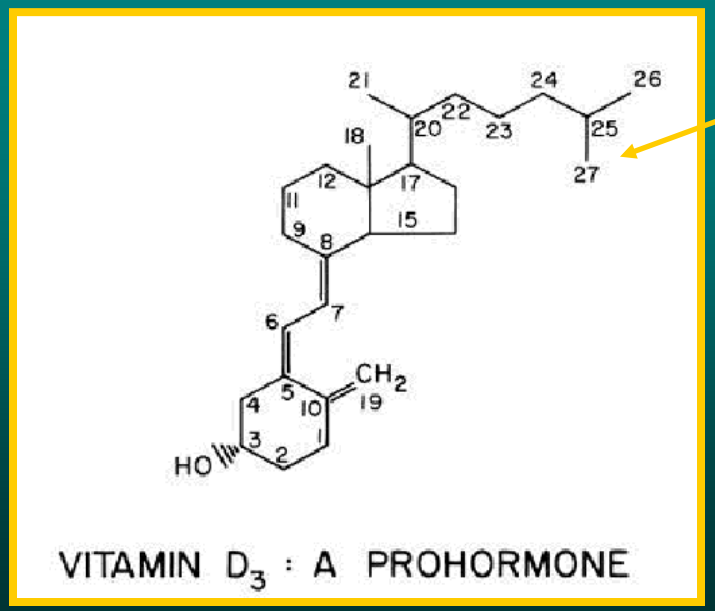
* increase both calcium and phosphate concentration in plasma

* acts mostly on gastrointestinal tract, but some effects are exerted also in kidneys and bones

- About 90% of vitamin D is produced endogenously
- Relatively few natural foods contain significant amounts of vitamin D.
- Fatty fish, e.g. herring and mackerel, contain the highest concentrations of vitamin D, with eggs and milk also being a rich source.
- The vitamin is stable in foods and on storage; processing and cooking do not appear to affect its activity.

Cutaneous production of VitD

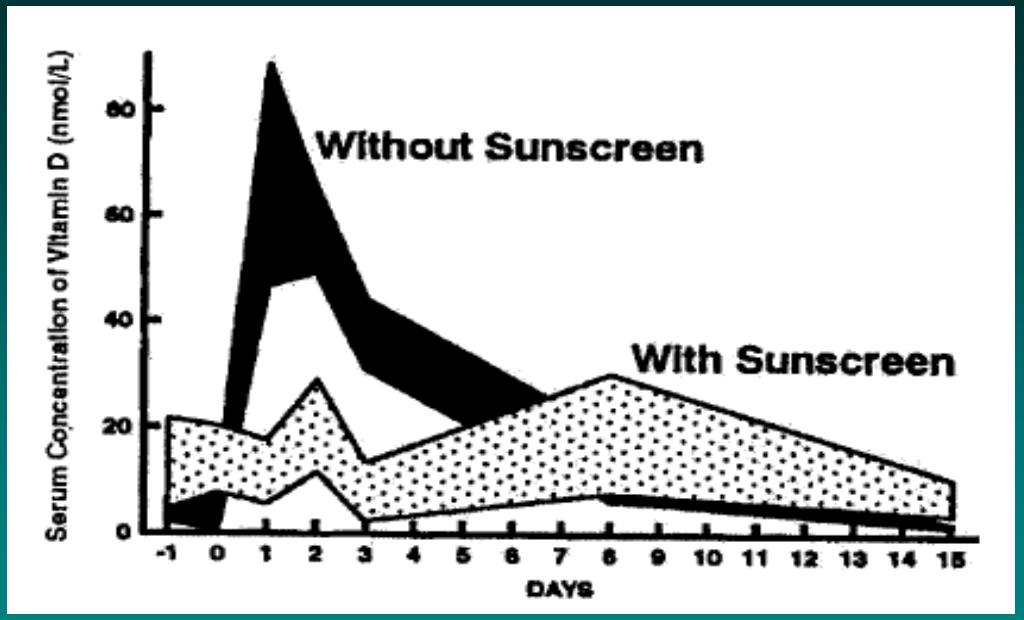
- Requires light of 290 - 315 nm (UVB)
- Produced primarily in epidermis (exposure of 30-120 minutes daily is sufficient to provide enough vitamin D to supply body needs without dietary supplementation)
- **7-dehydrocholesterol**, primarily synthesised in the sebaceous glands, is secreted onto the surface of the skin then reabsorbed into the various layers of the epidermis. **Absorption of UVB by 7-dehydrocholesterol results in formation of vitamin D.**



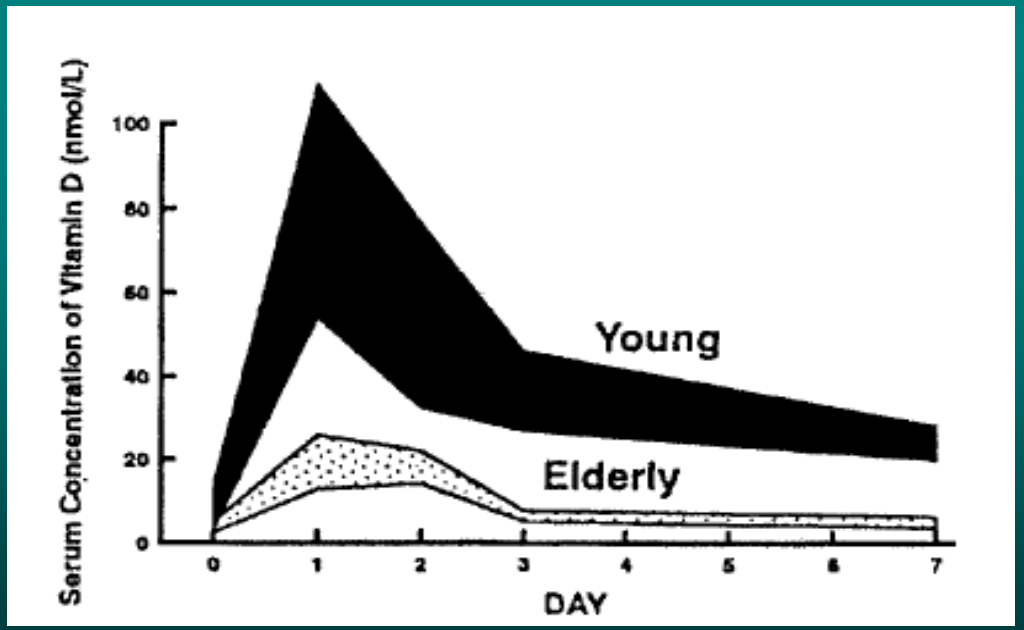
VITAMIN D_3 : A PROHORMONE

Production efficacy dependents on:

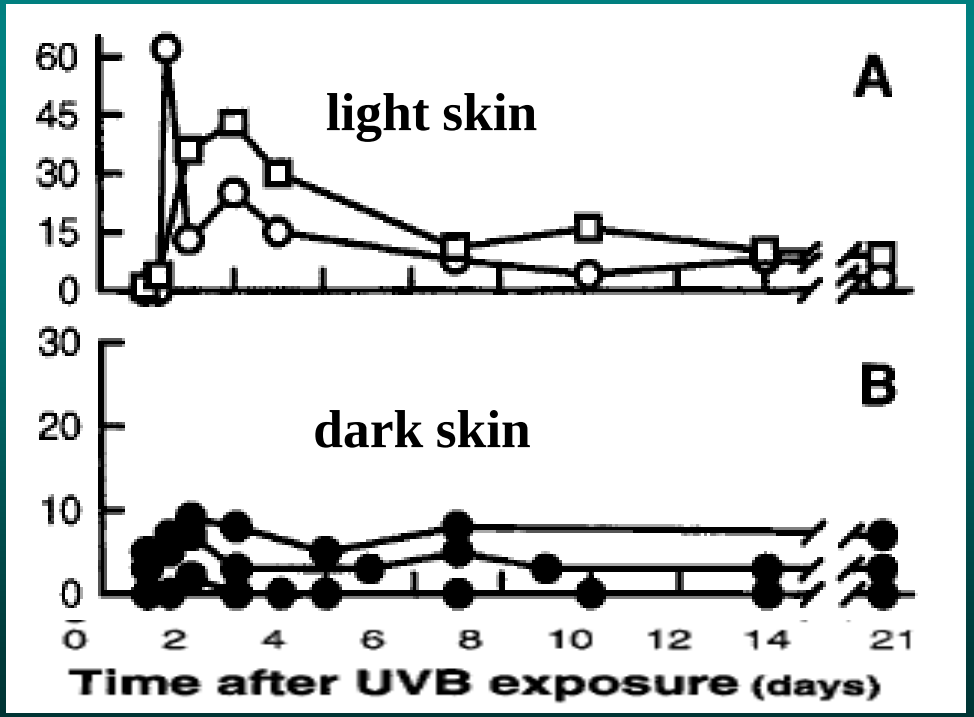
- latitude, time of day, season of year
- pigmentation of skin and presence of sunblocks
- age



Circulating concentrations of vitamin D after single exposure to UVB

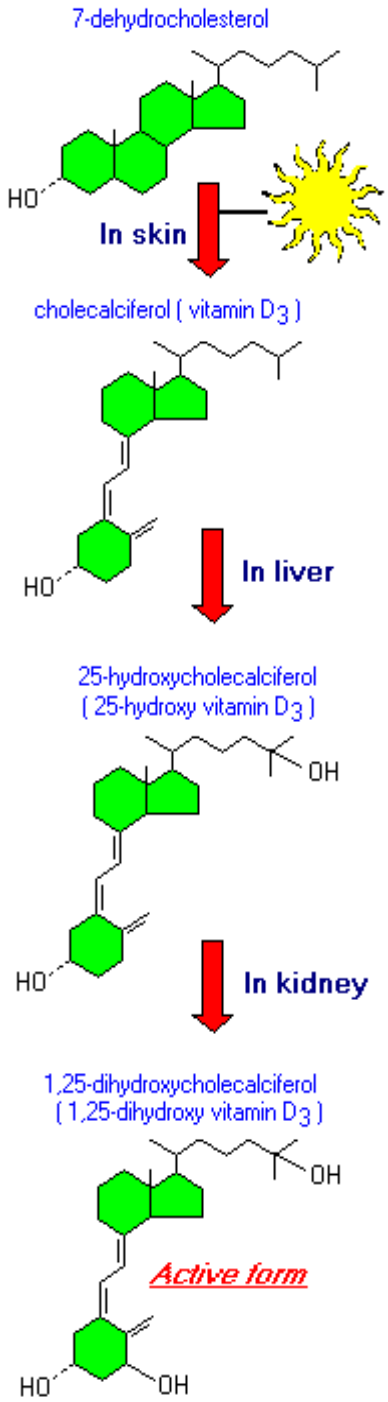


Holick, Am. J. Clin. Nutr. 2004.



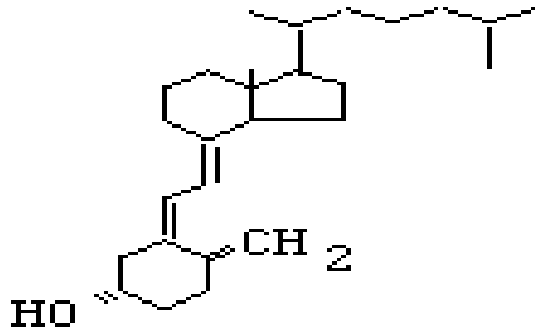
Metabolism and excretion of vitamin D

- The liver and kidney are the main sites for the metabolic activation of vitamin D3.
- Vitamin D3 is first hydroxylated in the liver at the 25-carbon atom by a vitamin D3-25-hydroxylase enzyme (calcitonin-dependent). The product of this hydroxylation, 25-OHD, also known as calcidiol, is the principle circulating metabolite.
- 25-OHD is carried from the liver, in plasma bound to an α2-globulin and is transported to the kidney, where it undergoes a second hydroxylation before it becomes functional.
- The second hydroxylation is catalysed by 25-hydroxy-vitamin D3–1-hydroxylase and produces 1,25-$(OH)_2$D (calcitriol).
- Calcitriol stimulates intestinal calcium transport, intestinal phosphate transport, bone calcium mobilisation and other functions attributed to vitamin D.
- The rate of conversion to 1,25-(OH)2D by the kidney is parathyroid hormone (PTH) dependent.



SKIN PRODUCTION

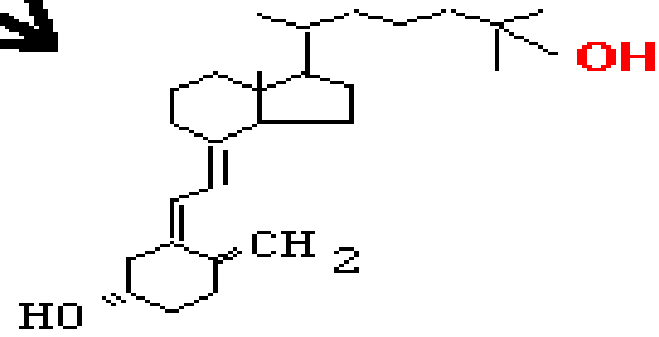
DIET



Vitamin D

Biologically inert

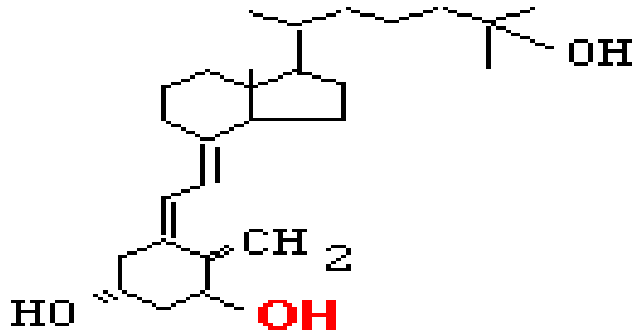
LIVER



25 (OH)-Vitamin D

calcidiol; 2-5 x as potent as VitD
15-40 ng/mL

KIDNEY

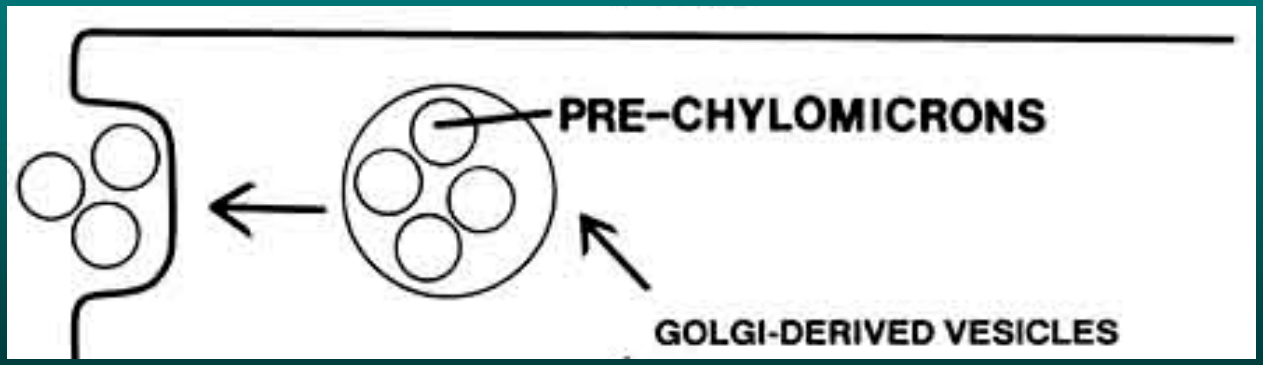


1,25 $(OH)_2$ Vitamin D

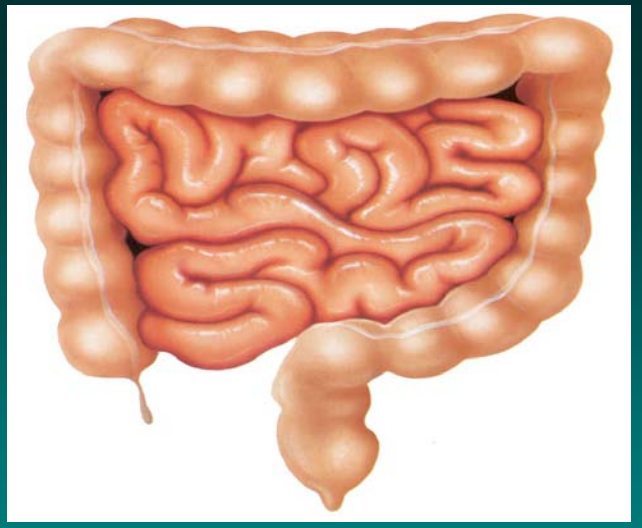
calcitriol; 10-2000 x as potent as VitD
17-80 pg/mL

Absorption of Vitamin D

- Vitamin D is absorbed in small intestine passively and dependently on its micellar solubilization by bile salt.
- It is transported from small intestine in the free form, predominantly in the association with chylomicrons.
- During metabolism of chylomicrons, vitamin D is transferred to a binding protein in plasma (vitamin D binding protein).
- Unlike vitamin A, vitamin D is not stored primarly in the liver but is distributed between the various organs, depending on their lipid content.



Small intestine



- The active form of vitamin D increases the intestinal absorption of calcium from the diet.

- Proximal calcium absorption through the enterocyte involves increased luminal permeability, intracellular calcium transport and extrusion through the basolateral membrane into the extracellular fluid. Transport is facilitated by 1,25-$(OH)_2$D dependent calcium binding proteins, calbindins.

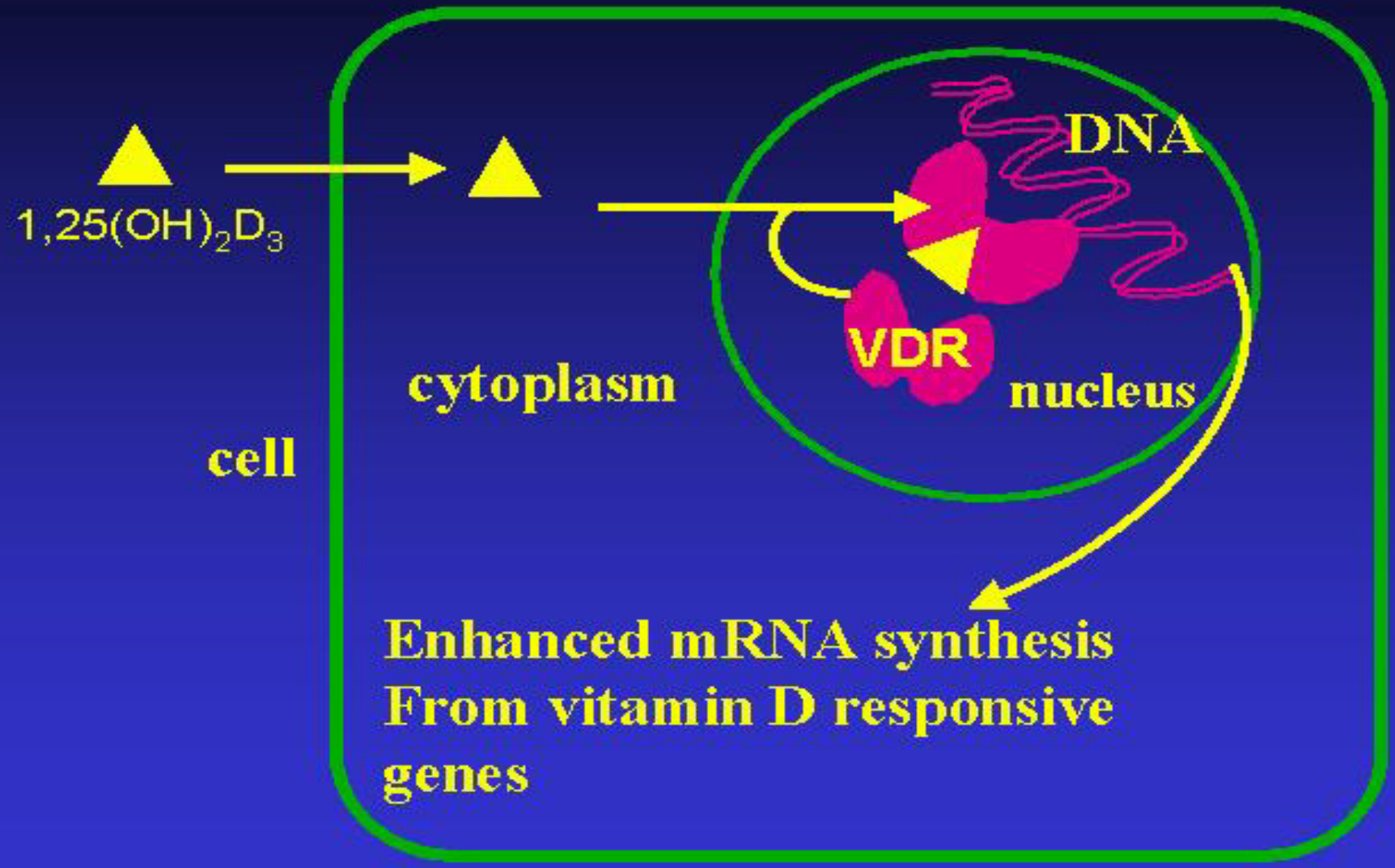
- In the distal bowel calcium is absorbed both by a 1,25-$(OH)_2$D mediated carrier process and by passive pericellular diffusion down a concentration gradient.

- Although mRNA for a range of genes responds to 1,25-$(OH)_2$ vitamin D in a number of tissues, it is only the transcription of the calbindin genes in the intestine that is dependent on the hormone. Thus, it is recognised that the major response of the intestine to vitamin D is an increase in calbindin synthesis.

Bones

- Early studies assumed that the predominant effects of $1,25(OH)_2D3$ on bone were mediated via the osteoblast.
- $1,25(OH)_2D3$ modulates the expression of a number of osteoblastic marker genes, including osteocalcin, osteopontin and alkaline phosphatase. Additionally, it stimulates collagen synthesis.
- $1,25\text{-}(OH)_2D$ is also involved in the regulation of the migration of the vesicles containing calcium phosphate from the osteoblast to the zone of mineralisation.
- $1,25(OH)_2D3$ has a profound effect on the differentiation and proliferation of both osteoblasts and osteoclasts.
- However, VDR is <u>not</u> expressed in osteoclasts; in response to $1,25(OH)_2D3$, osteoblasts secrete factors (e.g. interleukin-6) which stimulate osteoclastic bone resorption and osteoclast differentiation.

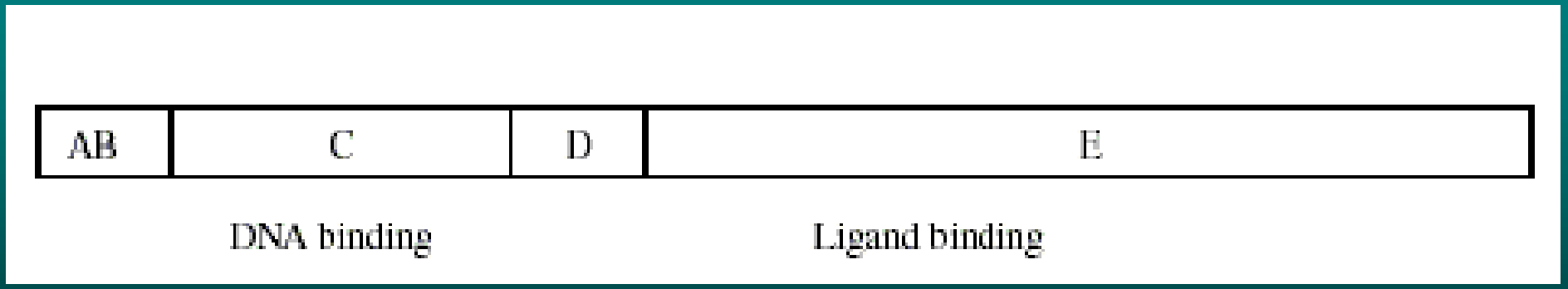
Mechanism of action of vitamin D



VDR

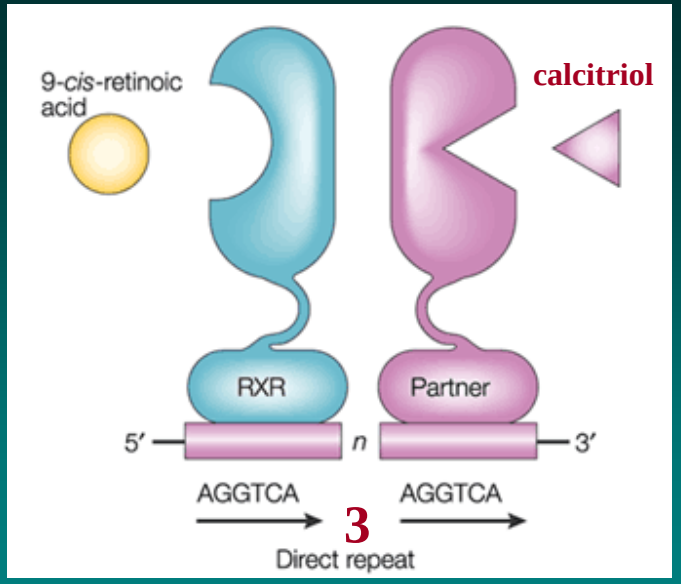
*** Human VDR comprises ~75 kb on chromosome 12 and consists of 11 exons. Three of them (1a, 1b, 1c) are located within 5' untranslated region, while 8 exons (2-9) encode for product.**

*** There are 3 variants of VDR mRNA (depending on the first exon). The protein product is always the same, of structure typical for nuclear receptors.**



427 aminoacids, 48 kDa, no domain F

VDR



- Vitamin D receptor (VDR) is a receptor for vitamin D3 (namely calcitriol), and some metabolites of bile acids

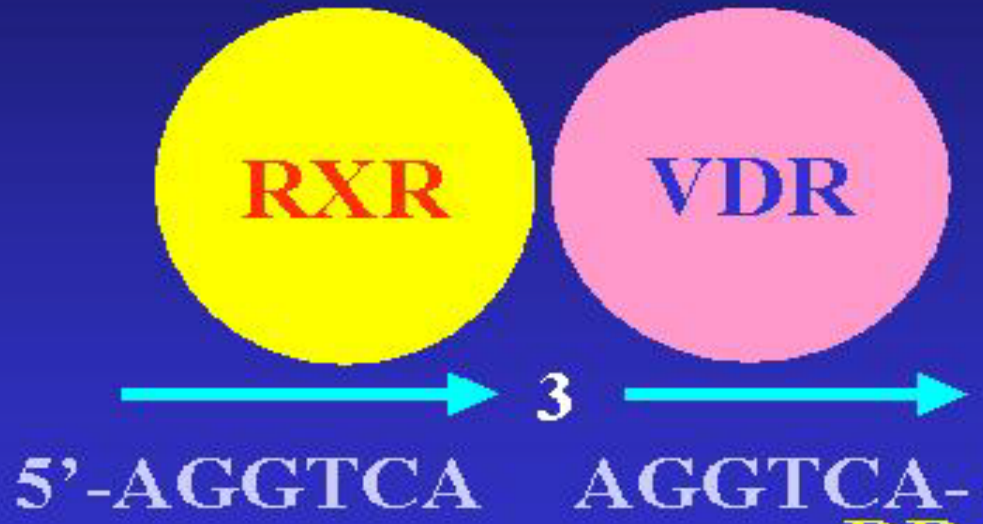
- Forms heterodimers with RXR and recognizes DR3 sequence

- High expression was found in many cell types, including enterocytes and osteoblasts (18 000 – 37 000/cells), but possibly not in osteoclasts. Osteoclasts of VDR-/- mice differentiate normally

- Newborn mice VDR-/- look normally, but with time they suffer from several abnormalities, leading to preterm death:
  * growth inhibition (at the age of 6 week they are 50% smaller than healthy mice).
  * alopecia
  * decreased density of bones (by 40% when compared to healthy mice)
  * low level of calcium and phosphates in blood
  * rickets

Interaction of VDR with VDREs

Heterodimerization with RXR



DR 3 VDRE in promotor region of target gene

Distribution of VDR in normal human tissues

Tissue	Immunocytochemical staining
Liver	+/++
Kidney	++/+++
Thyroid	++/+++
Adrenal	+/++
Stomach	+/++
Duodenum	++
Jejunum	++
Colon	+++
Skin	++
Breast epithelium	++
Skeletal muscle	-

(+) weak, (++) moderate, (+++) strong, (-) negative

Role of VDR

- Increase in uptake of calcium and phosphates from intestine and in reabsorption of calcium in kidneys

- Increase in mineralization of bones but also in mobilization of calcium from the bone.

- Increase in growth of hair.

- Inhibition of cell proliferation and induction of cell diffrentiation (especially lymphocytes T and other cells of immune system).

- Inhibition of renin expression – role in regulation of blood pressure (too low level of vitamin-D may contribute to hypertension).

- Possibly: role in regulation of insulin release and insulin resistance (too low level of vitamin-D may be associated with increased symptoms of diabetes).

alopecia - VDR dependent, but Vit D independent

Evolution of VDR

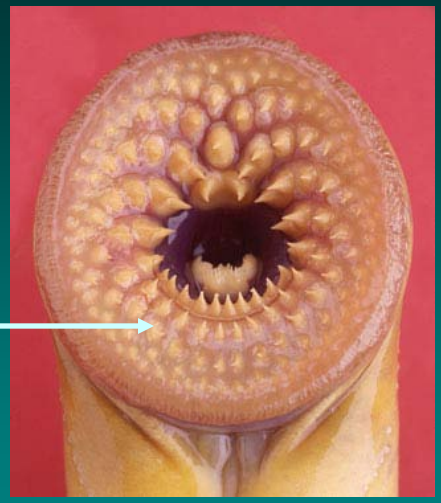
- VDR is known exclusively in vertebrates

- The nearest homolog in invertebrates is ecdysone receptor (30% identity at aminoacid level with human VDR)

- Functional VDR (3 isoforms) has been described in the sea lamprey:

  * homology with human VDR was ~60%, but within DBD – 88%.
  * it can be activated by Vitamin-D3 after transfection to mammalian cells.

Evolution of VDR



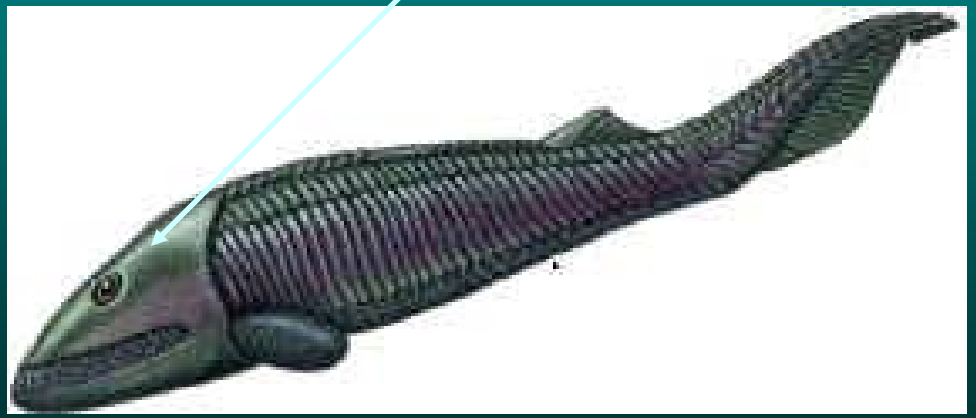
- In lamprey there is no calcified skeleton;

- The highest expression of VDR in lamprey has been found in mouth,

  while relatively low in intestive (opposite than in mammals)

- possibly VDR was formed independently of tissue calcification; it is hypothesised that it was involved in activation of cytochrome p450 and tissue detoxication.

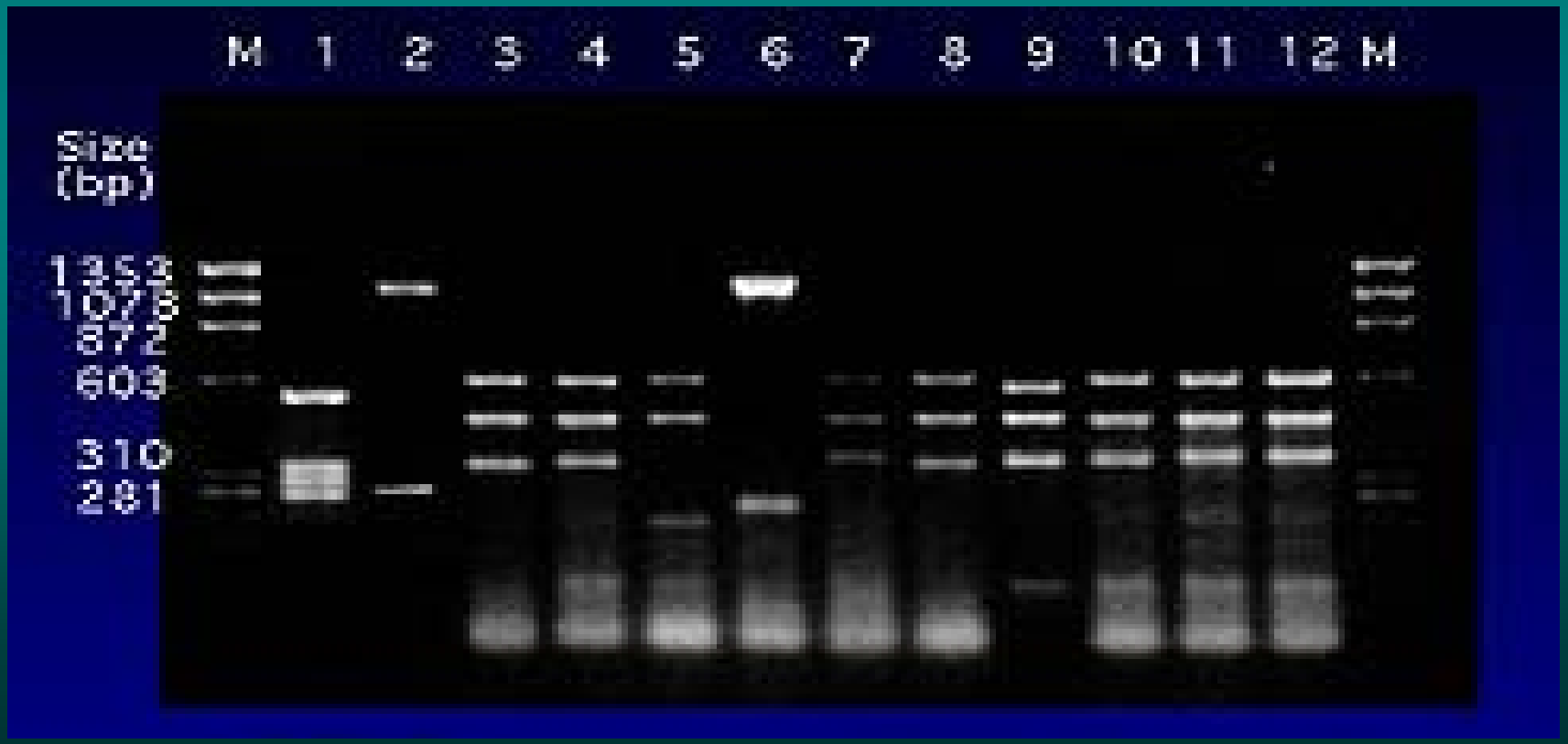
- Paleozoic forms of lampreys had calcified bone plates on the body surface. Maybe VDR was involved in their mineralization.



VDR polymorphism

- The vitamin D receptor is reported to be polymorphic.

- Depending on whether the gene can be cut by the restriction enzymes Bsm I, Apa I or Taq I, the polymorphisms are classified as either B or b, A or a, T or t respectively the lower case letters indicating lack of cutting sites.



VDR polymorphism

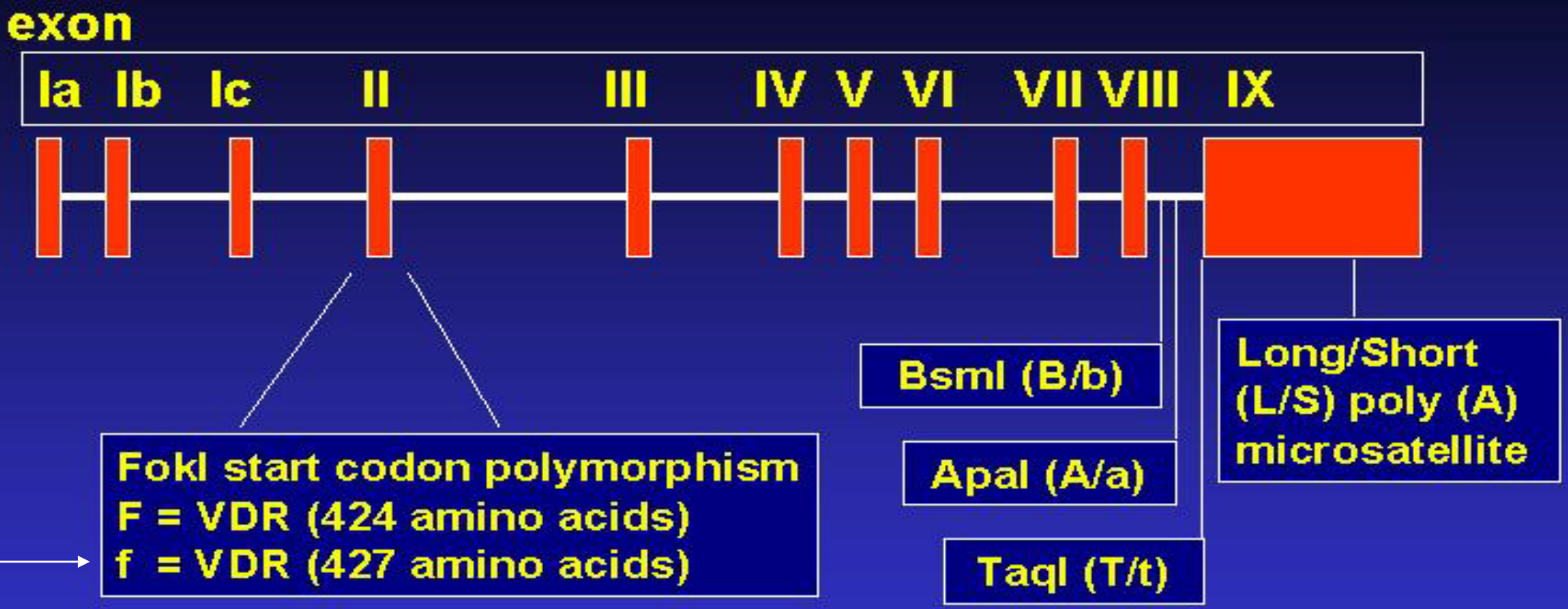
- Among many analyses there was also the paper by Tokita et al. (1996). Here VDR polymorphism (analysis using three enzymes: Taq I, Apa I i Bsm I) in Japanese and Australians of european origin).

*There were significant differences in frequency of alleles. Researchers postulated that those differences are responsible for lower rate of osteoporosis in Japan.

- VDR gene polymorphism can be related with risk of bone diseases. It has been postulated that it can determine the risk of osteoporosis, but data are not univocal, and most analysis show only a weak association.

* However, all those polymorphisms are located in non-coding region and do not have any influence on protein product.

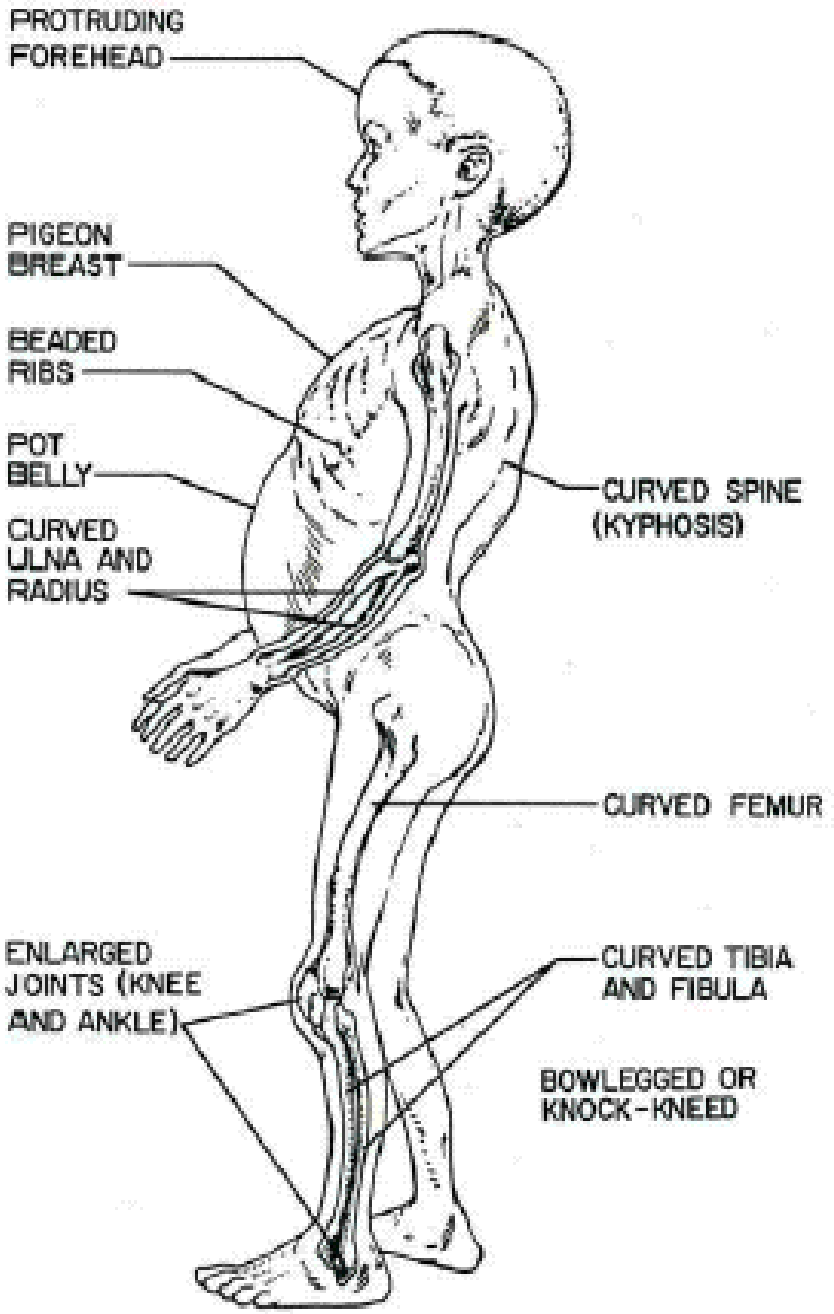
Polymorphisms in the VDR Gene



more active receptor

Digestion with Fok I endonuclease:

Allows for detection of polymorphism which influences the protein sequence (F: exchange T to C results in start of transcription from codon 4 instead of 1). Analyses performed in different populations have demonstrated that ff genotype leads to synthesis of more active protein and decreases frequency of osteoporosis (e.g. 7% versus 13% comparing to genotype FF).



Rickets

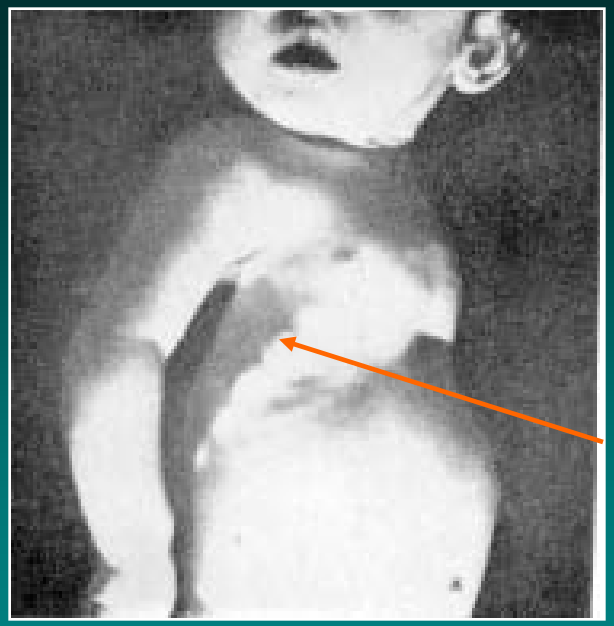
Insufficient vitamin D delivery – e.g. too low exposure to sunlight, low-fat diet

Renal osteodystrophy – kidney damage leading to **loss of 1-hydroxylase activity**, low $1,25(OH)_2D_3$, impaired intestinal calcium absorption (rickets/osteomalacia)

Hereditary rickets type I – inherited **defect of kidney 1-hydroxylase** prevents formation of active hormone; treatable with exogenous calcitriol

Hereditary rickets type II – end organ resistance due to **mutation in the VDR receptor** DNA or hormone binding domains; DNA binding domain mutations unresponsive to administered calcitriol; ligand binding domain mutations can sometimes respond to very high dose $1,25D_3$ treatment

Rickets



Late closure of the fontanelle (craniotabes) is the earliest sign of rickets. It is detected in infants less than 12 months of age as round unossified areas in the skull.

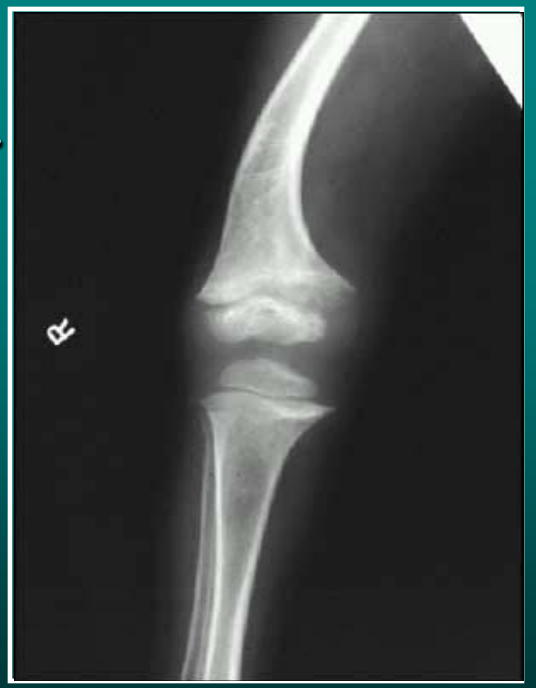
Beading of the ribs, termed ‘rachitic rosary’, is an almost consistent sign after 6 months of age. This is caused by the swollen cartilaginous ends of the ribs.

The chest may be narrow and rather funnel shaped, described as ‘pigeon chest’, in severe cases this may interfere with breathing.

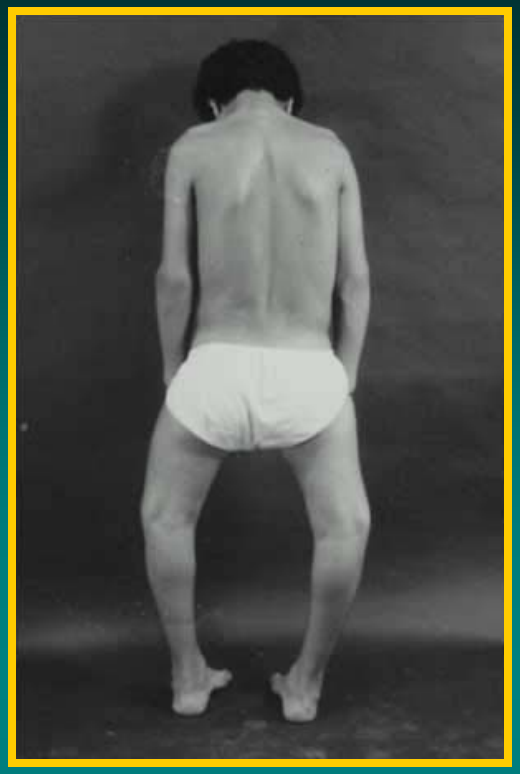
When the child begins to toddle, putting weight on the legs results in the femur becoming bowed and separation of the knees. Greenstick fractures are common.

Severe vitamin D deficiency reduces the growth rate and causes microcephaly, with reduction in brain growth and the eruption of teeth is delayed.

Clinically the child is miserable, apathetic and in pain.



Rickets



• During and after the Second World War, it had become commonplace in Great Britain for dried milk and infant cereals to be fortified with ergocalciferol (vitamin D2), and to give supplementary concentrated vitamin D to infants. Additionally the cod-liver oil was regularly supplied.

• Increases in vitamin D intake since the recognition of the aetiology of rickets, improvement in nutrition, and the 'milk in schools' scheme of 1934 had seen a dramatic reduction in the incidence of rickets since its prevalence in the 1920s, and the purpose of the fortification was to ensure that all children received sufficient vitamin D.

Jedrzej Sniadecki
1768-1838

1822: desribes the method for treatment of rickets by exposure to sun

Inherited vitamin-D3 insensitivity type II – mutation in LBD or DBD of VDR

* Inherited, recessive autosomal disease.

* Insufficient mineralization of new-formed bones and ossified cartilages.

* Symptoms of rickets start to be visible during the first few months of live. There are:
  - pain of bones
  - general weakness and weakness of muscles
  - sometimes convulsions resulting from too low level of calcium

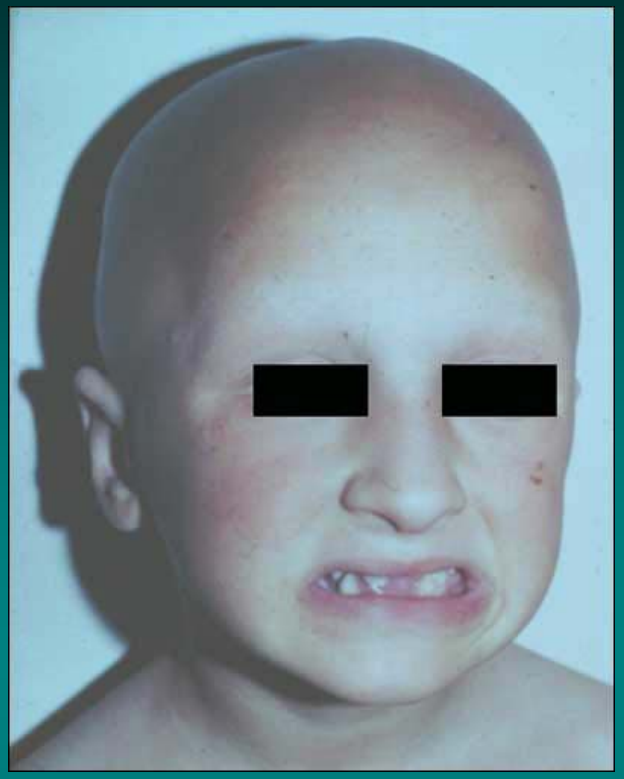
* Inhibited growth, underdevelopment of teeth.

* Many children do not have hair or have alopecia both on the head and on the eyebrows or eyelash.

* High doses of vitamin-D are not effective, especially in children with alopecia. Better results can be obtained using high doses of calcium.

* There were cases of spontaneous recovery in children. Perhaps it results from activation of retinoid receptors or thyroid hormone receptors.

Inherited vitamin-D3 insensitivity type II – mutation in DBD of VDR



* Biochemical features:

- low level of calcium and phosphates in blood

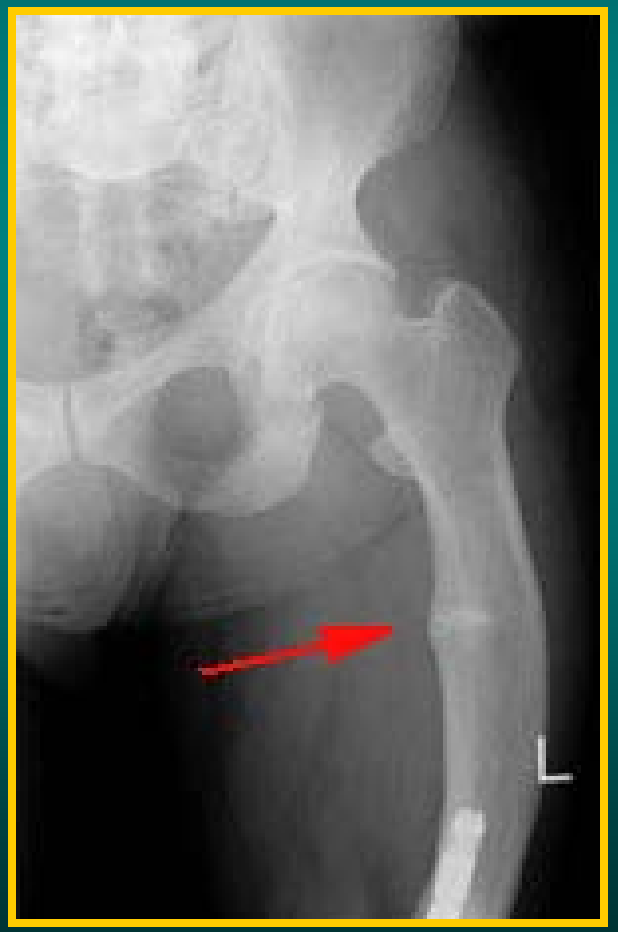
- increased level of alkaline phosphatase in blood

- increased level of PTH

- high level of calcitriol (there is a difference comparing to rickets type-I, where level of calcitriol is diminished because of deficiency in 1α-hydroxylase).

Osteomalacia

- The main clinical features of osteomalacia are skeletal pain and muscle weakness.
- As the disease progresses, severe pain occurs in the thorax, shoulder, hips, thighs, forearms and feet.
- Bone density is reduced, as in osteoporosis. However, in contrast to osteoporosis, poor mineralisation is seen more commonly in the peripheral bones than in the vertebrate and pain is less common in the axial skeleton.
- The most characteristic radiological signs of osteomalacia are pseudofractures. Fractures are also common.
- Often occurs in women after bearing several children.
- Treatment with vitamin D reverses the clinical signs of osteomalacia and results in healing of fractures.



Successful Treatment

Year of Treatment	Fracture Incidence Fractures/100 Patient Years	
	Placebo (calcium)	Treated (0.5 µg/day 1,25-$(OH)_2D_3$)
1st	10 .3	8.8
2nd	25	9.3
3rd	31.5	9.9

Tilyard et al. New Eng. J. Med 326, 357-362 (1992)

Clinical trials with vitamin D supplementation

- In a randomised, double-blind, placebo-controlled trial, volunteers aged >70 were given a daily tablet of 10 μg (400 IU) vitamin D3 for up to 3.5 years to investigate whether this reduced the risk of hip or other fractures. Serum 25-(OH)-D levels were increased in the treated group compared to the controls. However, there was no difference in fracture incidence. No adverse effects were reported.

- In a 3 year randomised placebo-controlled study of 17.5 μg/day vitamin D3 and calcium supplementation, bone mass density was significantly increased in the supplemented group. No adverse effects were reported. In a follow-up study, in which no supplements were given to the previously supplemented group for two years, these benefits were reversed and bone turnover returned to the levels they were before supplementation.

- Short term supplementation of elderly women, with 800 IU/day vitamin D3 and calcium for 8 weeks, has been shown to decrease body sway and the incidence of fractures during a 1 year follow-up period, compared to supplementation with calcium only.

- In a randomised controlled trial of 800 IU per day vitamin D3 supplementation in 64 monozygotic twin pairs over two years no adverse effects were observed, nor was any significant difference in bone mass density.

Overloading with vitamin D

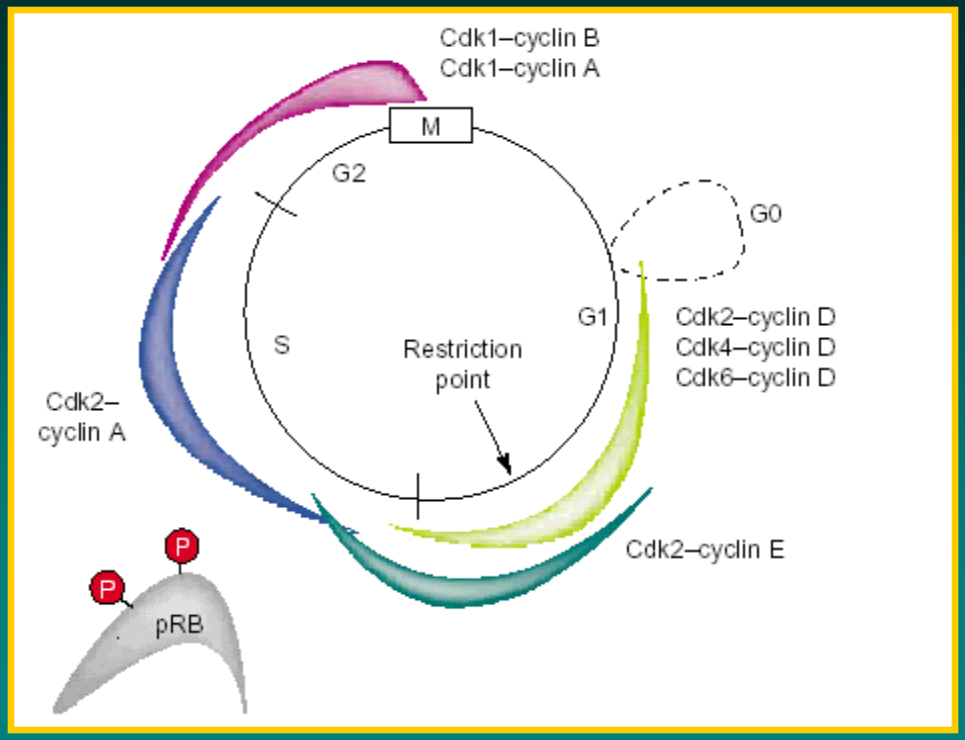
- The condition of infantile hypercalcaemia was first described in 1952 from cases in both Switzerland and Great Britain.
- The condition presented as a range of mild and severe clinical symptoms, including failure to thrive and, in the most severe cases, osteosclerosis, mental retardation and death, associated with raised plasma calcium levels.
- The effects of excessive vitamin D intake include hypercalcaemia and hypercalciuria, leading to deposition of calcium in soft tissues, diffuse demineralisation of bones and irreversible renal and cardiovascular damage. This occurs as a result of vitamin D-mediated increases in calcium absorption and bone resorption.
- In most adults, a daily intake in excess of 1.25 mg (50,000 IU) is needed to produce toxicity. This is manifested as muscle weakness, nausea, vomiting, polyuria, dehydration, hyperlipidaemia, hypercalcaemia and metastatic calcification of soft tissue. The central nervous system may also be involved, a severe depressive illness has been reported with hypervitaminosis D; anorexia has also been reported.

Vitamin D and other diseases

- Vitamin D has been shown to reduce colorectal epithelial cell proliferation and to induce differentiation, which may be mediated through the VDR. It has been suggested that vitamin D is inversely associated with the risk of colorectal, prostate or breast cancers, but epidemiological data are contradictory.

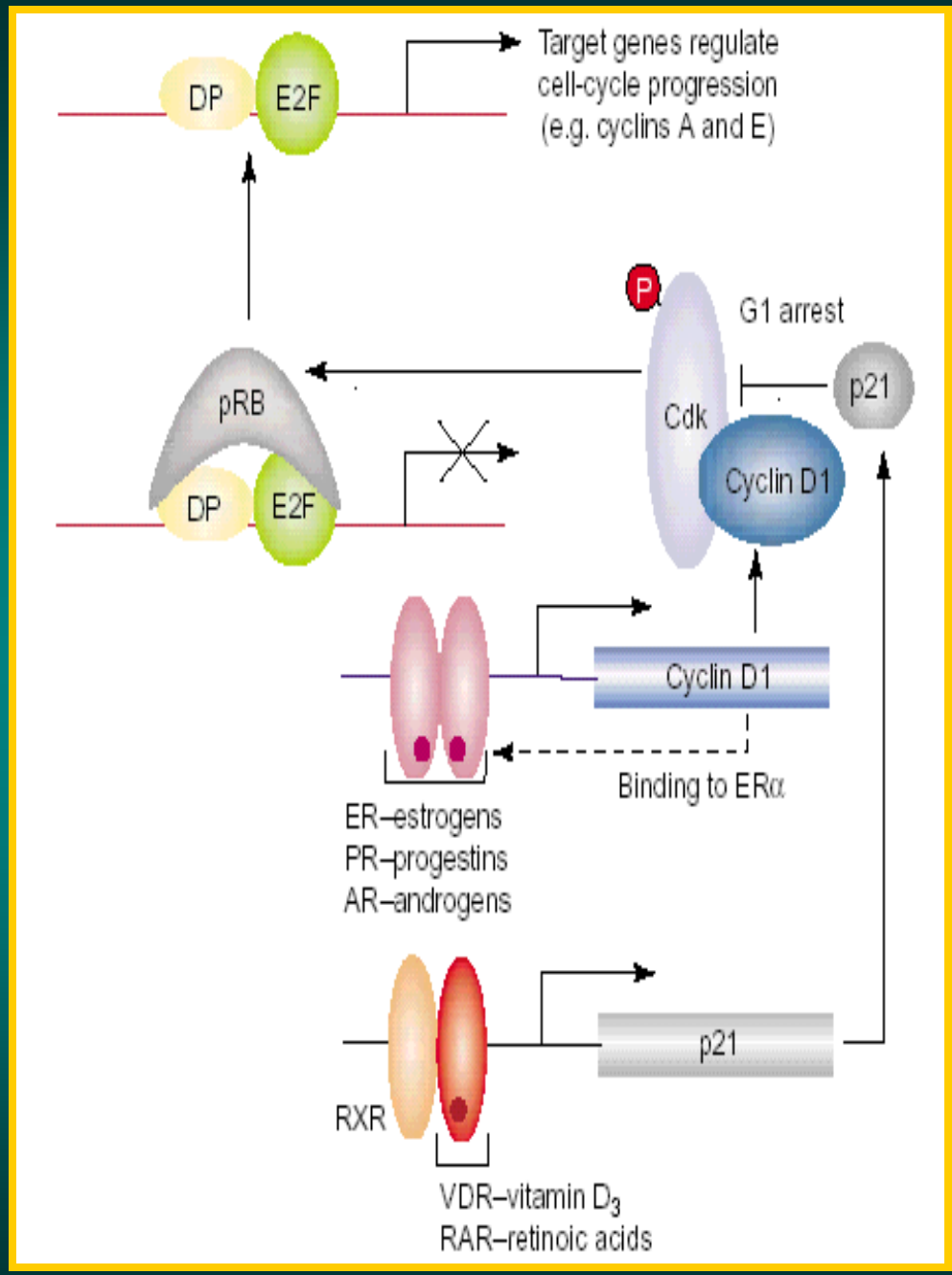
- There is some evidence that vitamin D supplementation may inhibit or stop the progression of multiple sclerosis (MS). Most MS patients suffer from vitamin D deficiency. Furthermore, MS prevalence increases with decreased exposure to the sun, and diets rich in fish, which is rich in vitamin D, may lower MS severity. Studies in Japanese population suggested an association between the less active form of VDR and frequency of MS.

- Experiments in animals suggest that vitamin D may be of use in treating the insulin-dependent diabetes, rheumatoid arthritis and in suppressing transplant rejection.



Some nuclear receptors (ER, AR, PR) stimulate expression of cyclin D, which activates Cdk4. It leads to phosphorylation of pRB, and increases transcription of genes increasing proliferation.

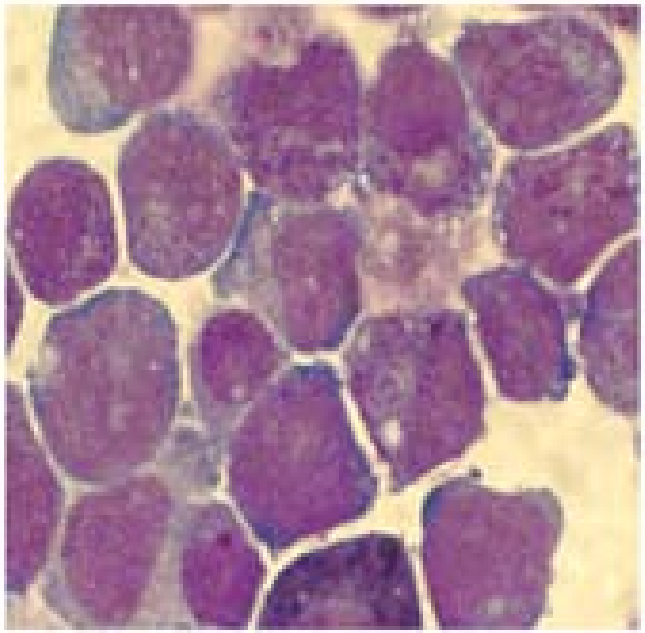
Others receptors (VDR, RAR) increase p21 expression, thus block Cdk activity, which keeps cells at G1 phase.



Immunomodulatory actions of 1,25-dihydroxyvitamin D_3

- Activates monocytes and promotes differentiation of myeloid stem cells
- Suppresses lymphocyte proliferation, immunoglobulin production and cytokine synthesis

Differentiation of leukaemia cells by $1,25(OH)_2D_3$



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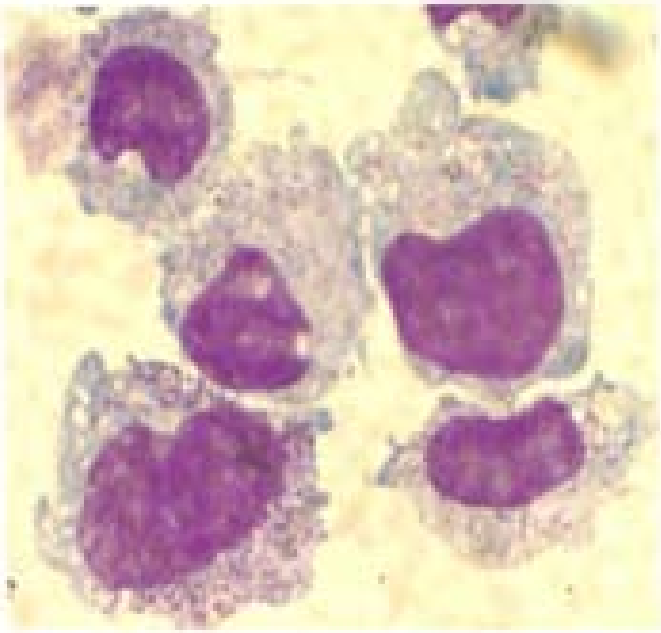

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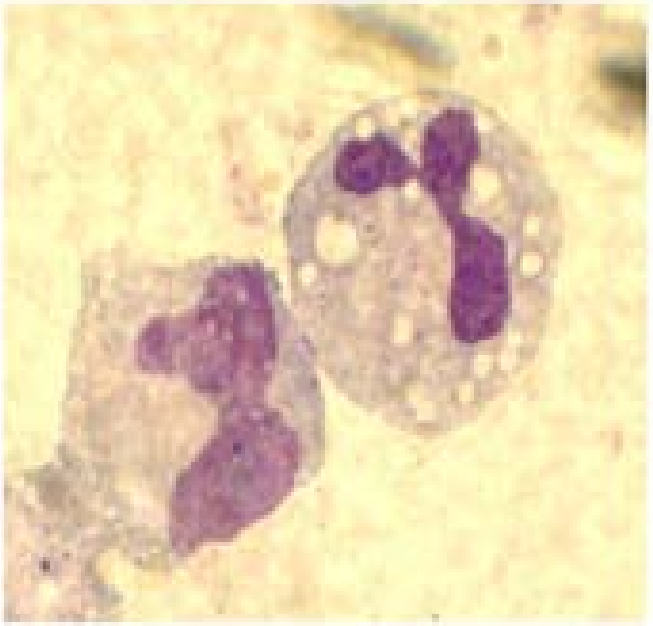
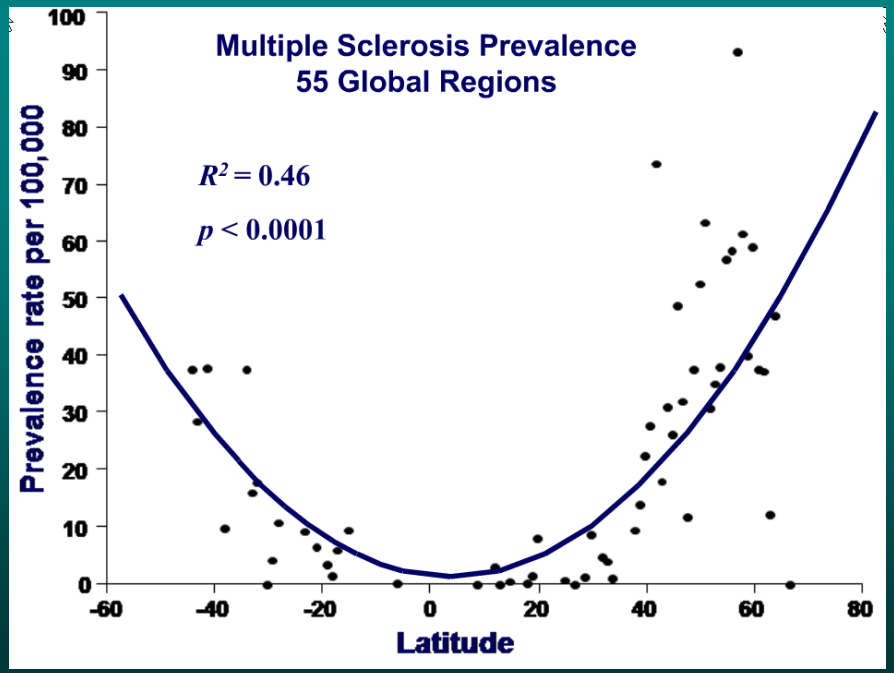


ATRA

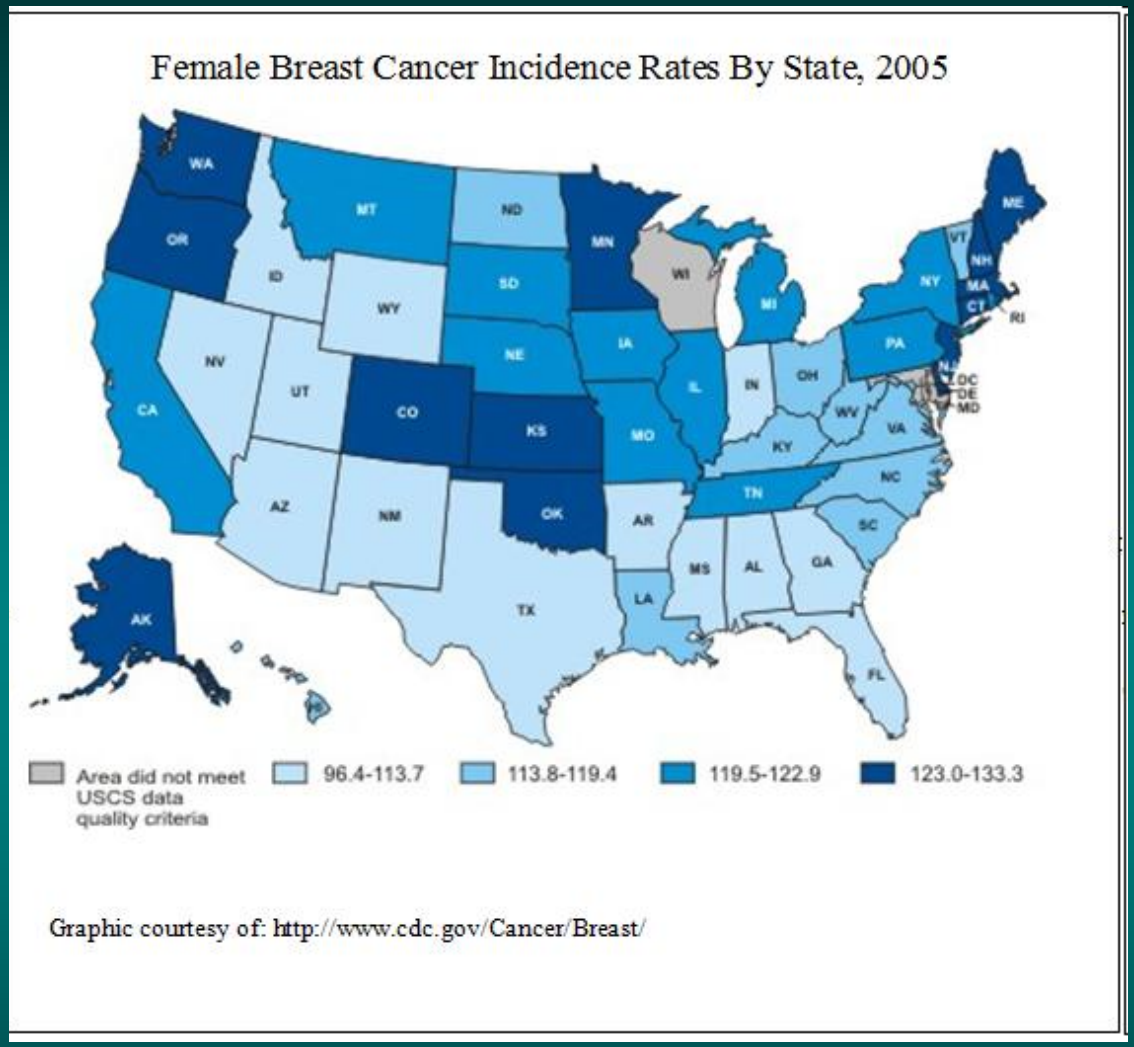
Vitamin D and breast cancer

- **Risk of breast cancer inversely related to intensity of local sunlight and 1,25-D levels**
- **Low serum 1,25-D levels correlated with disease progression and development of bone metastases**
- **>80% breast tumour specimens VDR positive and presence of receptor is associated with increased disease free survival**
- **1,25-D and its analogues inhibit growth and promote apoptosis *in vitro* and *in vivo***

Prostate Cancer mortality amongst white men. Highest in the north (21.0 to 20.7 per 100,000) and lowest in the south (20.1 to 19.8)



Development of breast cancer per 100,000 women in 2005

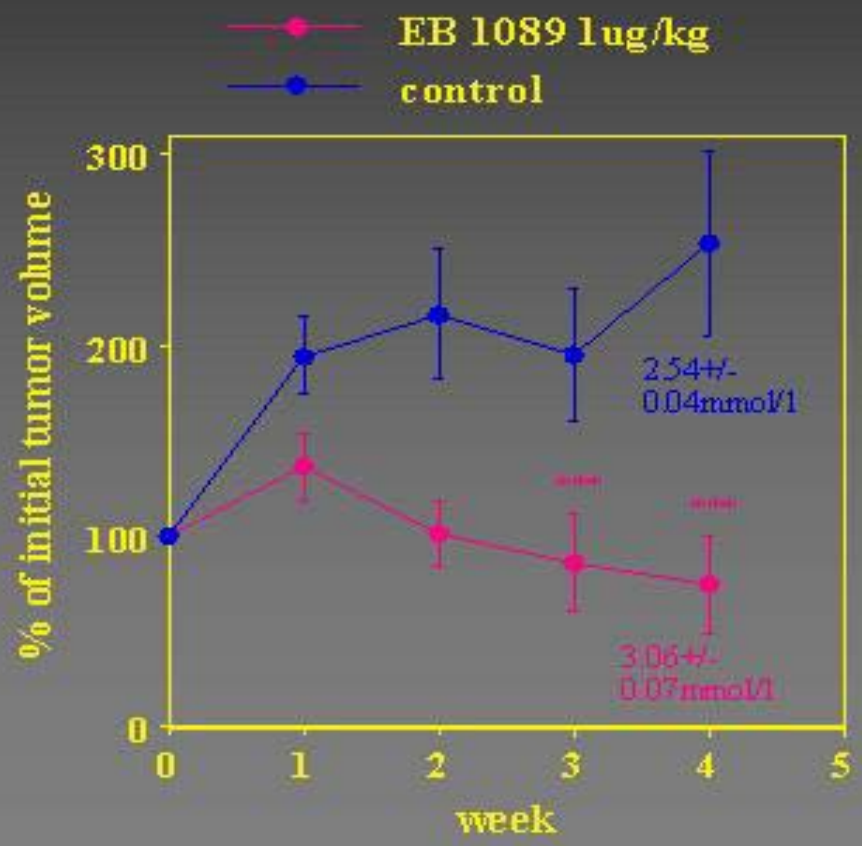


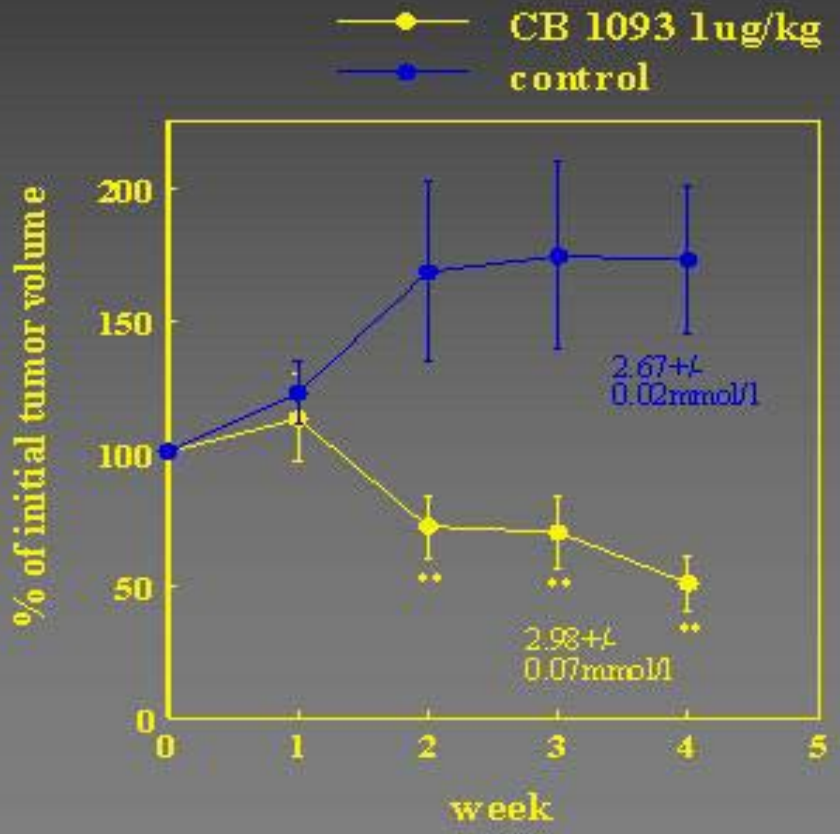
Graphic courtesy of: http://www.cdc.gov/Cancer/Breast/

Processes involved in the tumour suppressive activity of vitamin D analogues

- Inhibition of cell proliferation
- Induction of apoptosis
- Promotion of cell differentiation
- Inhibition of angiogenesis
- Altered elaboration or response to growth factors
- Inhibition of metastasis

Effects of vitamin D analogues on progression NMU-induced rat mammary tumours



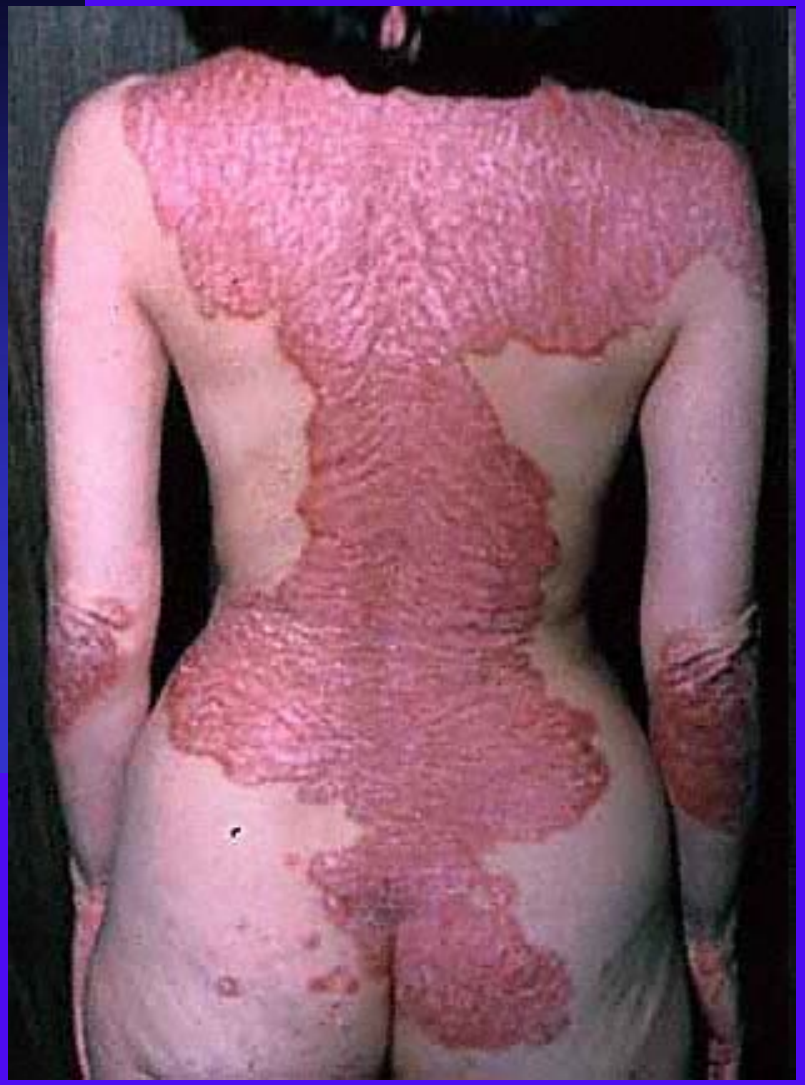


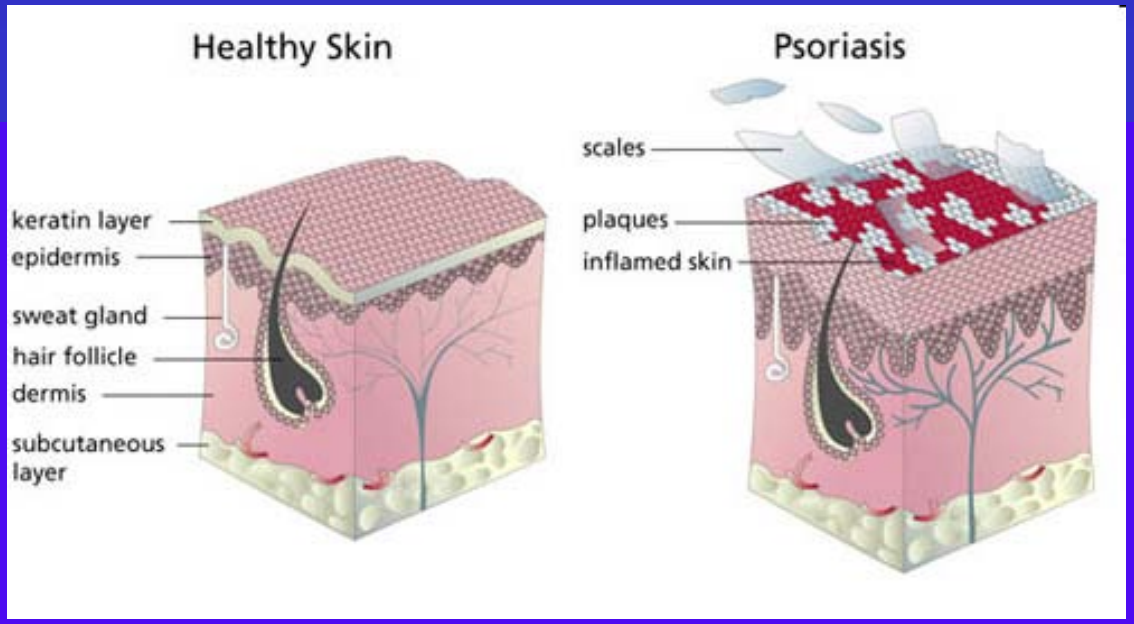
Trial of topical calcipotriol (MC903) therapy in advanced breast cancer

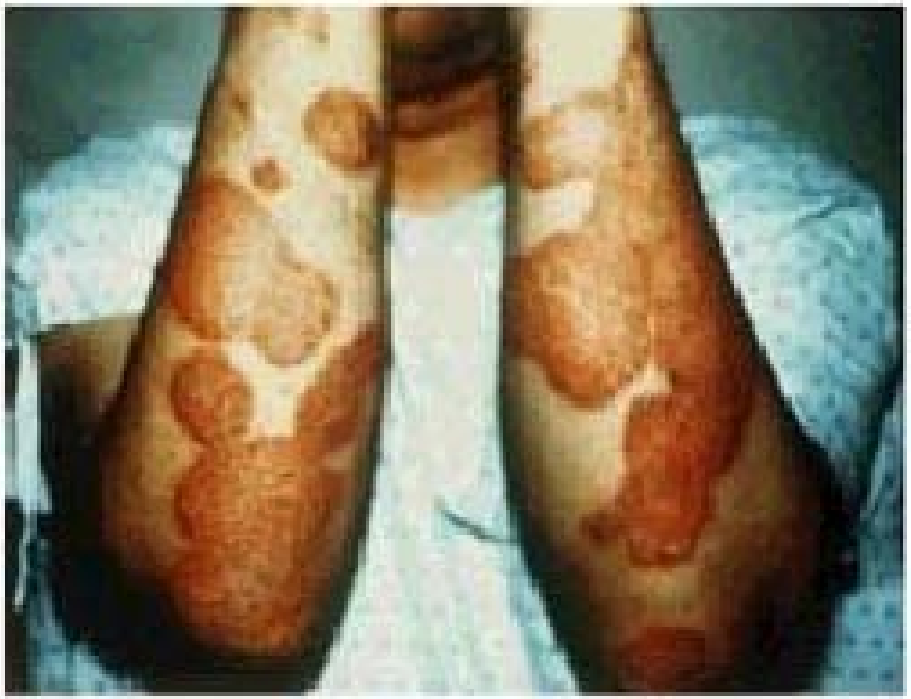
- 19 patients with locally advance or metastatic breast cancer and evaluable cutaneous deposits were treated daily with one gram calcipotriol (MC903) ointment
- All patients were normocalcaemic at entry
- 14 patients completed 6 weeks of treatment. 3 showed a partial and one a minimal response

Pathogenesis of psoriasis

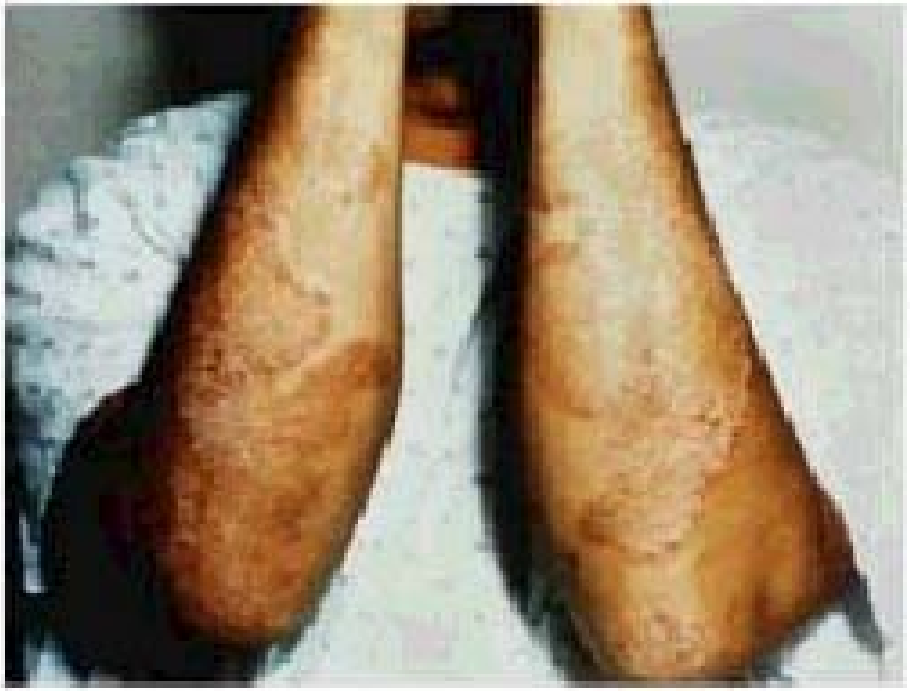
- Chronic or chronically relapsing skin disease
- ? Susceptibility heritable
- Results form epidermal stem cell growth, initiated by lymphokines released from activated T cells







Before treatment



After 2.5 months

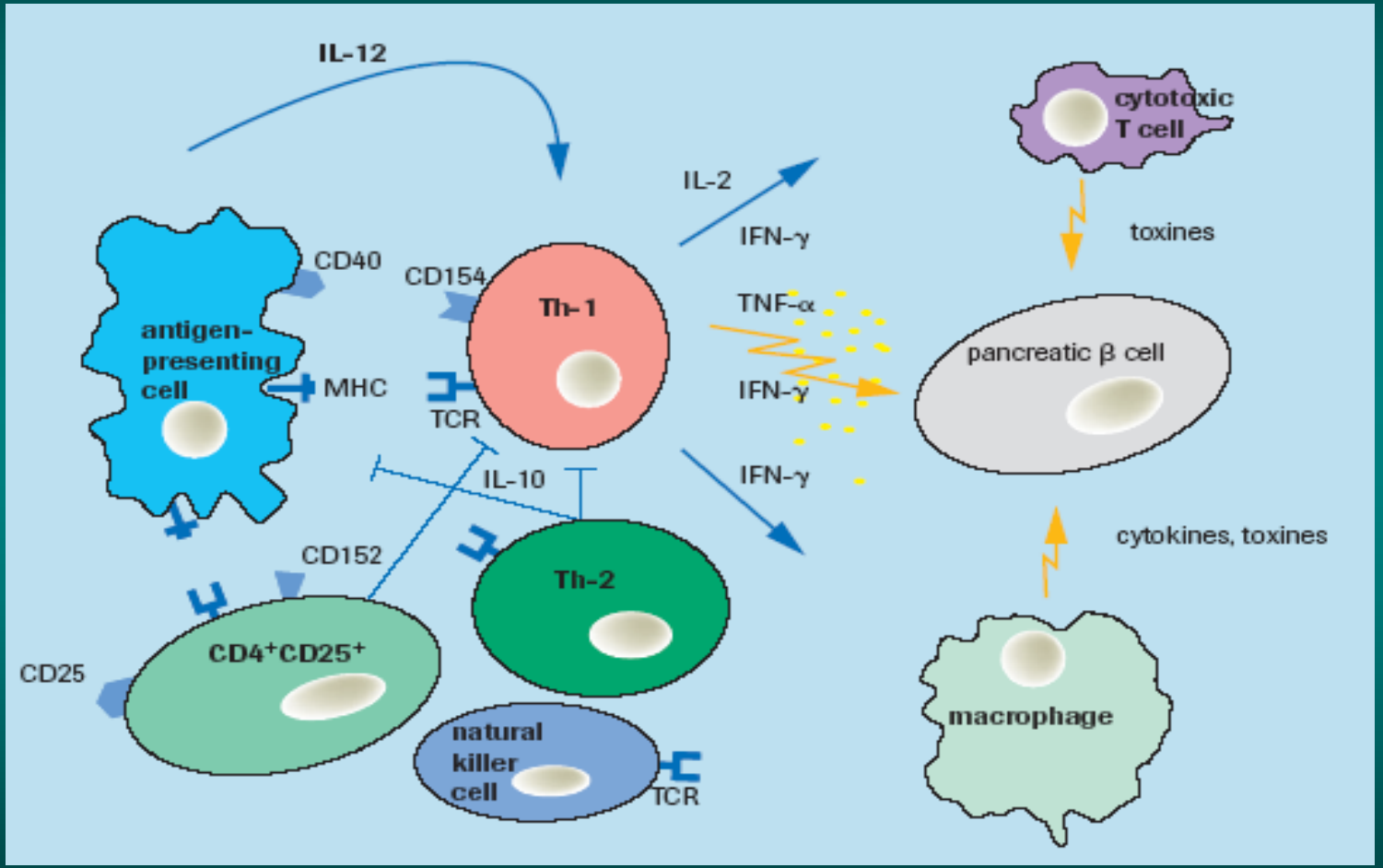
Treatment of psoriasis with vitamin D3

- 1983 - 1,25-dihydroxyvitamin D_3 shown to promote keratinocyte differentiation
- 1985 - a patient with osteoporosis receiving 1α hydroxyvitamin D3 showed a dramatic improvement in her severe psoriasis
- Development of vitamin D analogues for topical treatment of psoriasis

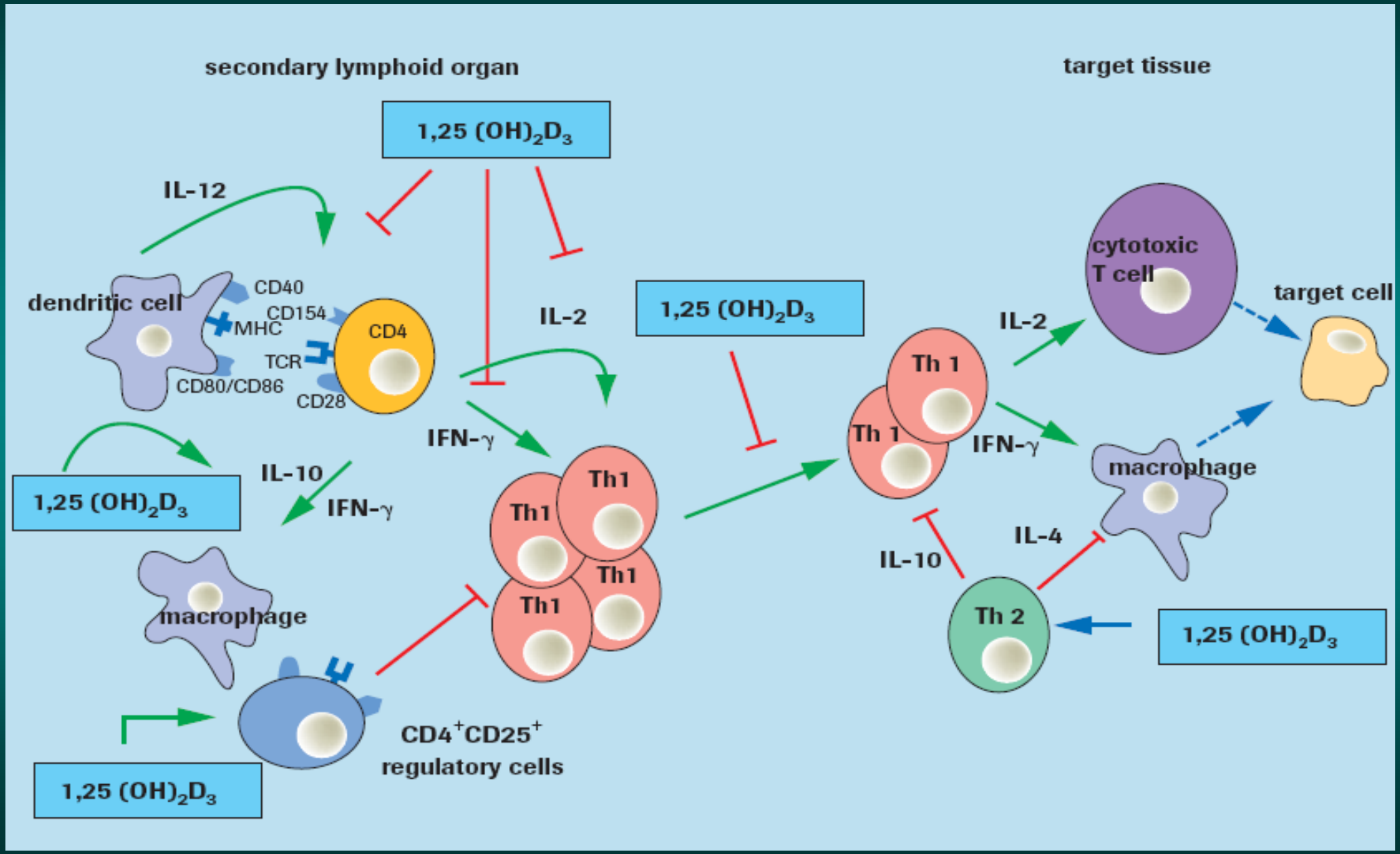
Development of type I diabates

Vit D3 deficiency increases the risk of type I diabetes?:

- The greater prevalence of T1D at northerly latitudes than in sunnier climates.
- study based on large population groups showing that vitamin D supplementation in early childhood not only helps preventing rickets, but also leads to a significant reduction in the risk of developing type 1 diabetes



Influence of vitamin D on immune response



Thank you and see you next week...

What would be profitable to remember in June:

- vitamin D and calcium metabolism: target tissues

- effects of vitamin D deficiency and overloading

- activity and structure of VDR: effects of mutations in LBD

Slides can be found in the library and at the Heme Oxygenase Fan Club page:

https://biotka.mol.uj.edu.pl/~hemeoxygenase