Vitamin D Deficiency: The Crucial Hormonal Imbalance

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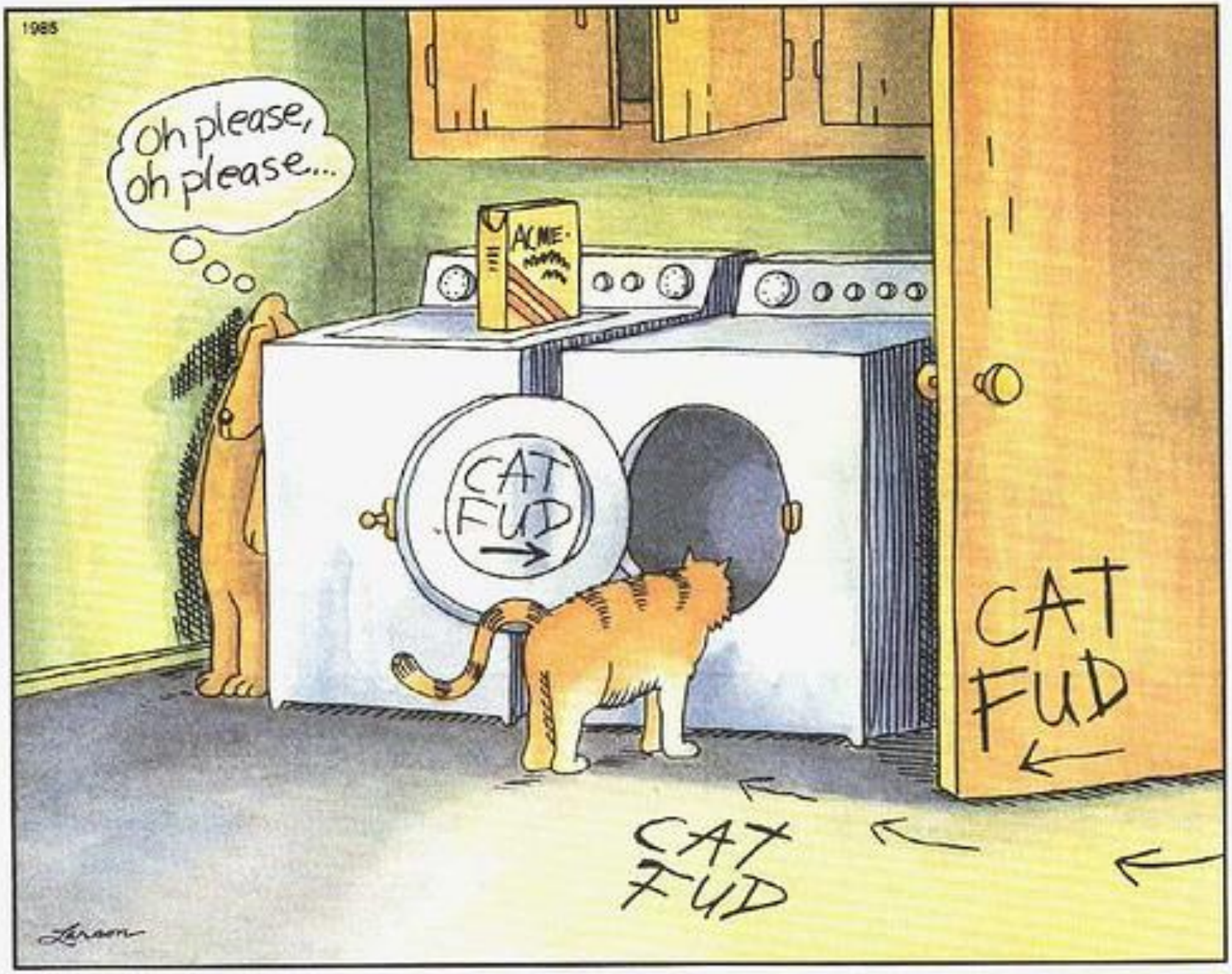
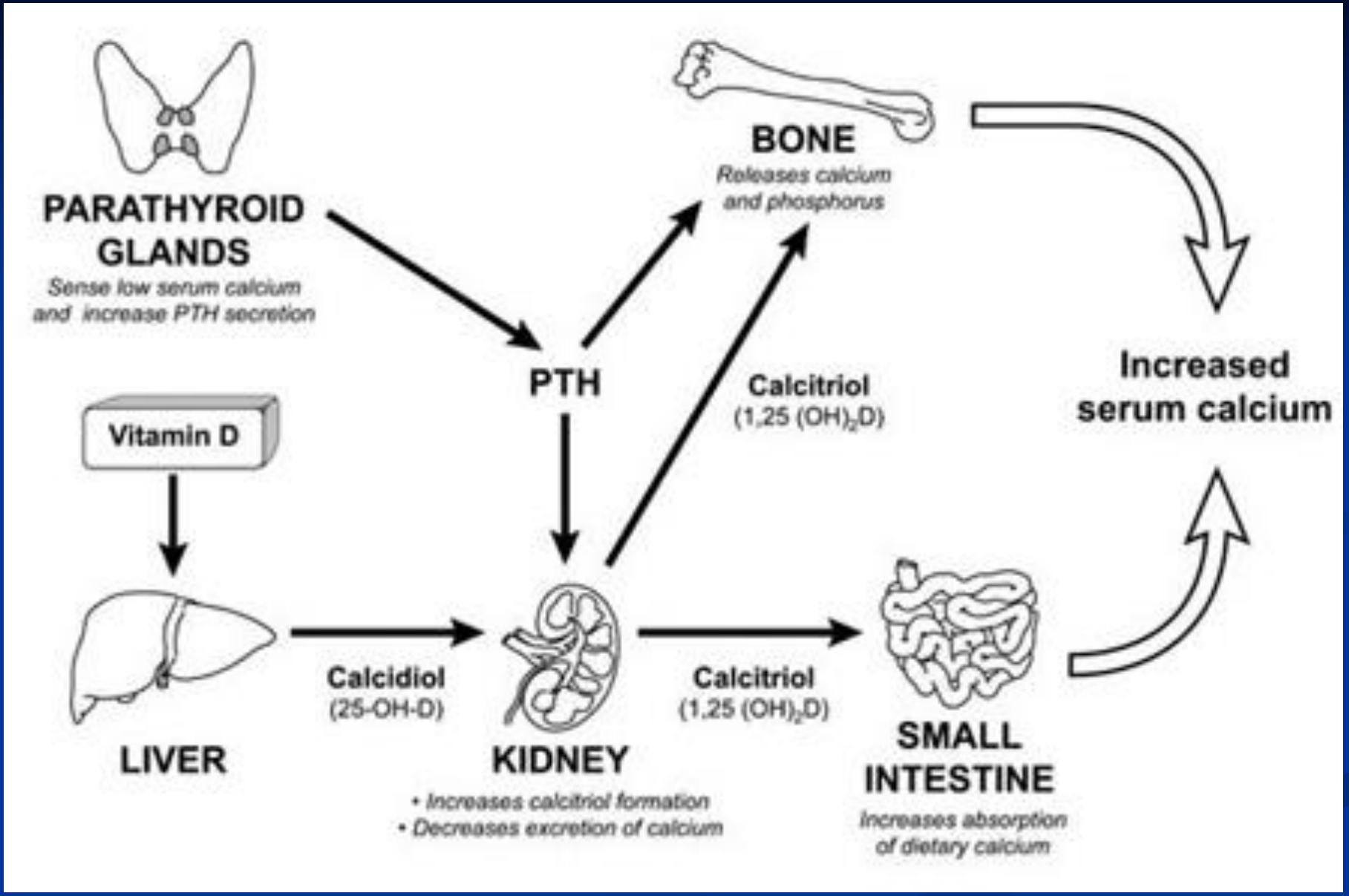
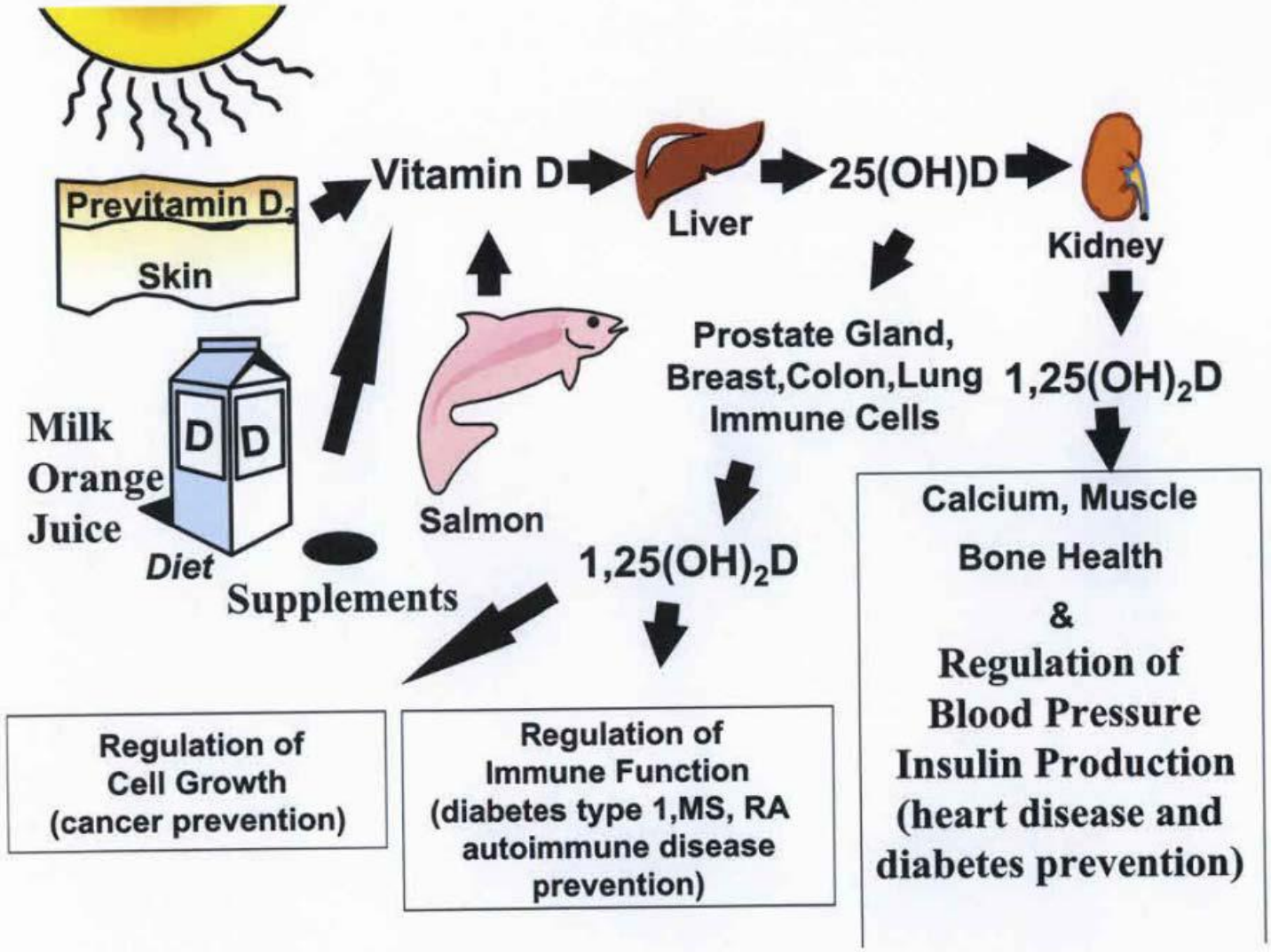

1985
Oh please, oh please...
ACME
CAT FUD
CAT FUD
CAT FUD


PARATHYROID GLANDS
Sense low serum calcium and increase PTH secretion
BONE
Releases calcium and phosphorus
PTH
Calcitriol
(1,25 (OH)$_2$D)
Increased serum calcium
Vitamin D
LIVER
Calcidiol
(25-OH-D)
KIDNEY
• Increases calcitriol formation
• Decreases excretion of calcium
Calcitriol
(1,25 (OH)$_2$D)
SMALL INTESTINE
Increases absorption of dietary calcium

Physiology of Vitamin D

- Vitamin D (cholecalciferol) is formed in the skin from exposure to sunlight.
- Then it is converted in the liver to 25-hydroxyvitamin D (***calcidiol***, 25(OH)D) by the enzyme vitamin D-25-hydroxylase.
- 25(OH)D then is transformed in the kidney to 1,25-dihydroxyvitamin D (***calcitriol***) by 25-hydroxyvitamin D3-1alpha-hydroxylase (1-OHase).


Previtamin D_3
Skin
Vitamin D
Liver
25(OH)D
Kidney
Prostate Gland,
Breast,Colon,Lung
Immune Cells
$1,25(OH)_2D$
Milk
Orange
Juice
D
D
Diet
Supplements
Salmon
$1,25(OH)_2D$
Calcium, Muscle
Bone Health
&
Regulation of
Blood Pressure
Insulin Production
(heart disease and
diabetes prevention)
Regulation of
Cell Growth
(cancer prevention)
Regulation of
Immune Function
(diabetes type 1,MS, RA
autoimmune disease
prevention)

Vitamin D Vocabulary

- Vitamin D_3 = Cholecalciferol
- Vitamin D_2 = Ergocalciferol
- 25 Hydroxy Vitamin D_3 = 25(OH) D_3 = 25(OH)D = 25 Hydroxy Cholecalciferol = Calcidiol = Vitamin D blood test = Vitamin D serum level
- 1, 25 Dihydroxy Vitamin D_3 = 1,25$(OH)_2$D 1, 25 Dihydroxy Cholecalciferol = Calcitriol

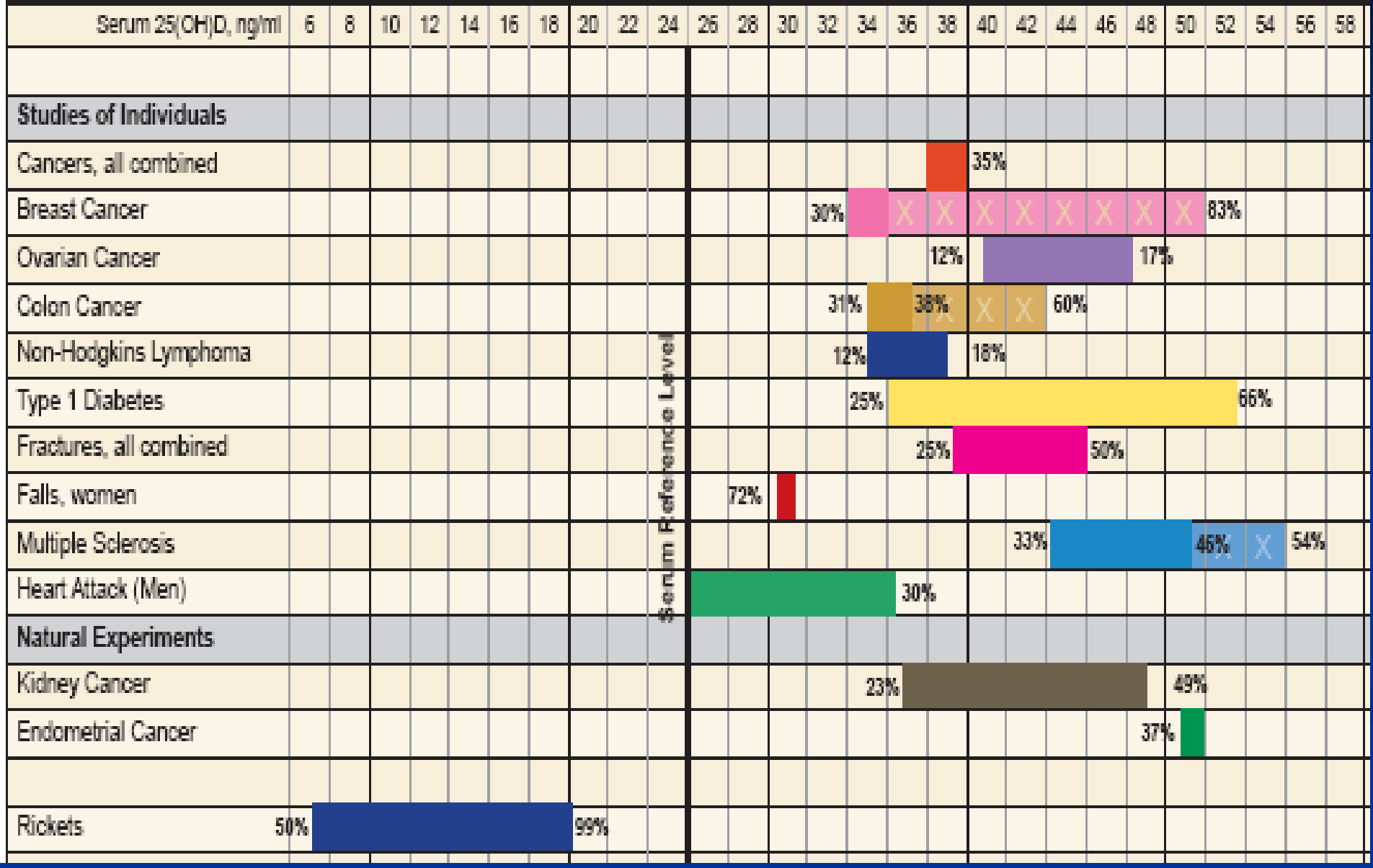
Vitamin D Math

- 1 microgram = 40 IU
- 1 milligram = 40,000 IU
- nmol/L divided by 2.49 = ng/mL
- 100 IU D_3 per day raises Calcidiol 1 ng/mL
- Vitamin D Deficiency: < 20 ng/mL 25(OH)D
- Vitamin D Insufficiency < 32 ng/mL
- 25(OH)D reference range 32-100
- 25(OH)D optimal range 60-100 ??

"Mr. Osborne, may I be excused? My brain is full."

- What is one of the cheapest and easiest interventions in medicine that would save the most lives and the most money?

Disease Incidence Prevention by Serum 25(OH)D Level



Inhibits Cutaneous Vitamin D Production

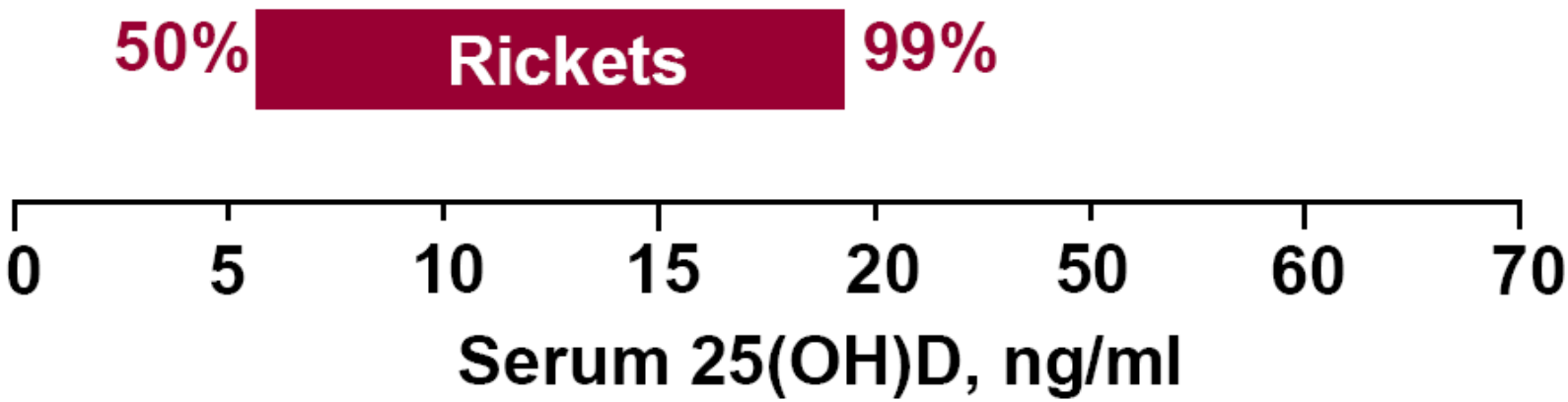
- Clothing, Cultural Practices
- Sunscreen
- Latitude > 37 in winter, Early and late hours
- Skin pigmentation
- Body fat
- Age: 70 y/o produces 4 x less than 20 y/o
- Drugs
- Anticonvulsants, corticosteroids, rifampin

Few foods contain vitamin D

- Fish liver oils, such as
  - cod liver oil, 1 Tbs. (15 mL) provides 1,360 IU
- Fatty fish species, such as:
  - Herring, 85g (3 oz) provides 1383 IU
  - Catfish, 85g (3 oz) provides 425 IU
  - Salmon, cooked, 3.5 oz provides 360 IU
  - Mackerel, cooked, 3.5 oz, 345 IU
  - Sardines, canned in oil, drained, 1.75 oz, 250 IU
  - Tuna, canned in oil, 3 oz, 200 IU
  - Eel, cooked, 3.5 oz, 200 IU
- One whole egg, 20 IU
- Fortified Milk 100 IU/cup
- For every 100 IU ingested, 25(OH) D_3 increases 1 ng/ml

"We should write that spot down."

Proportion of Rickets Prevented, by Serum 25(OH) D Level

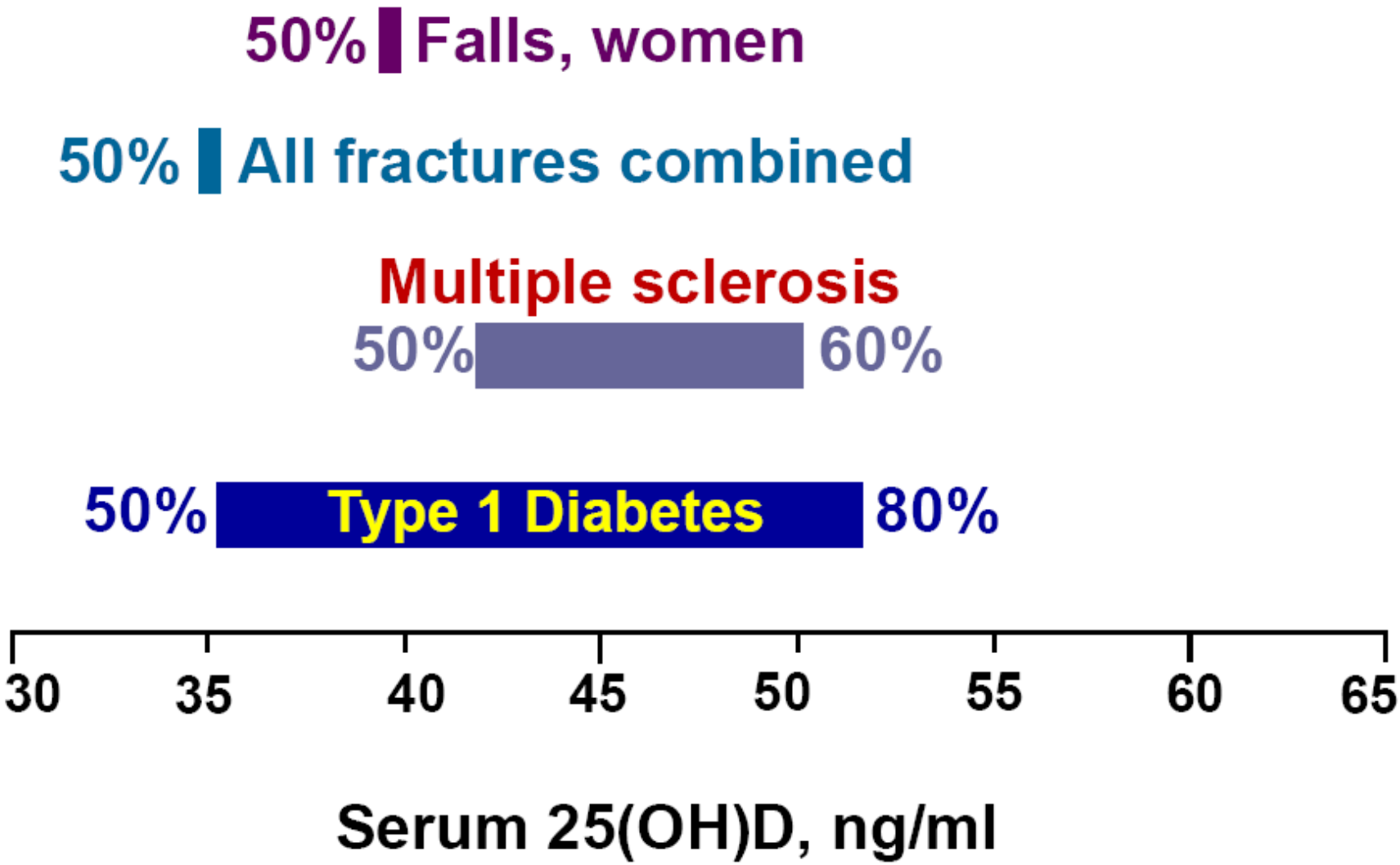


Source: Arnaud SB et al. Serum 25-hydroxyvitamin D in infantile rickets. *Pediatrics*. 1976 Feb;57(2):221-5

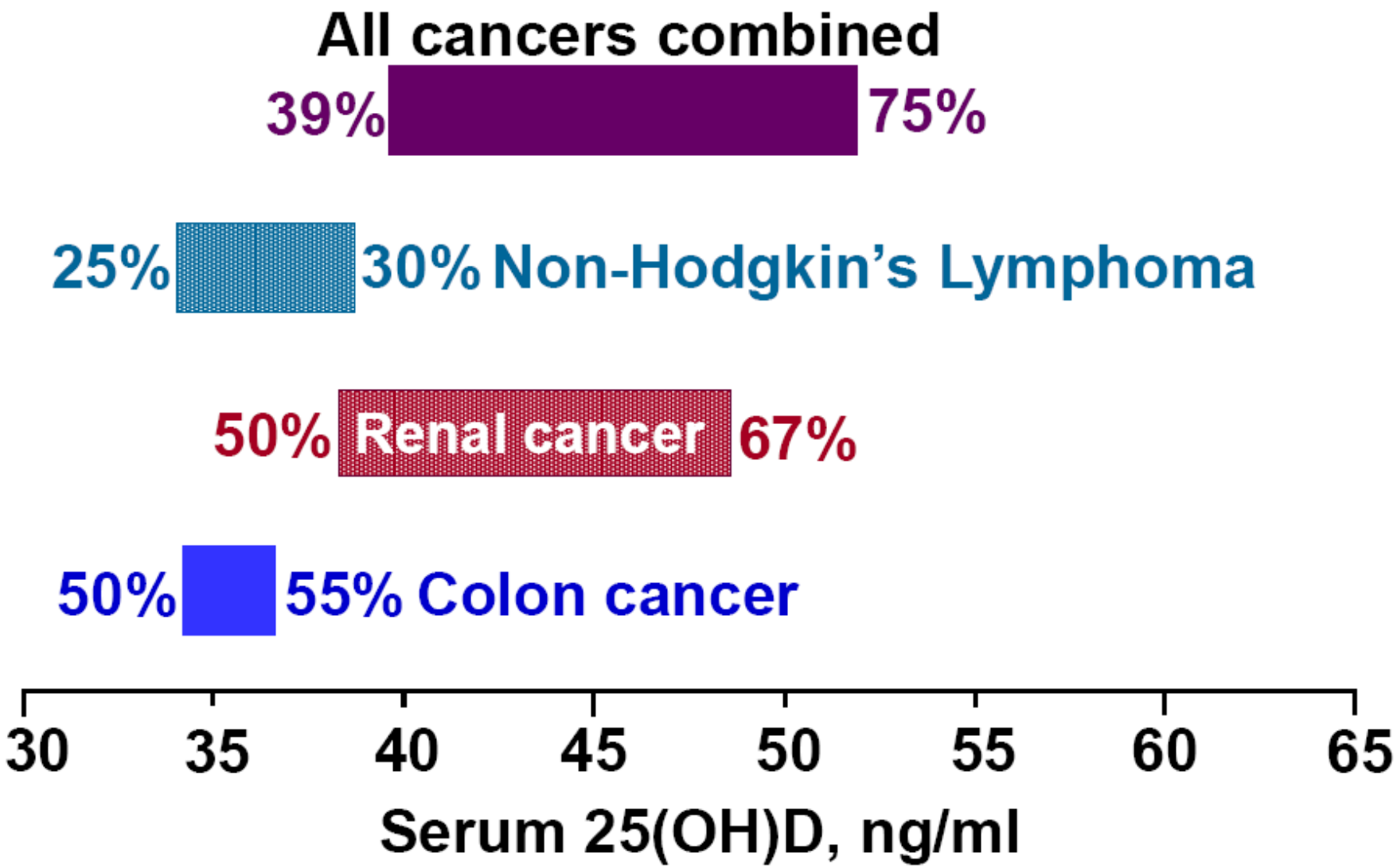
London 1889

Idaho 1989

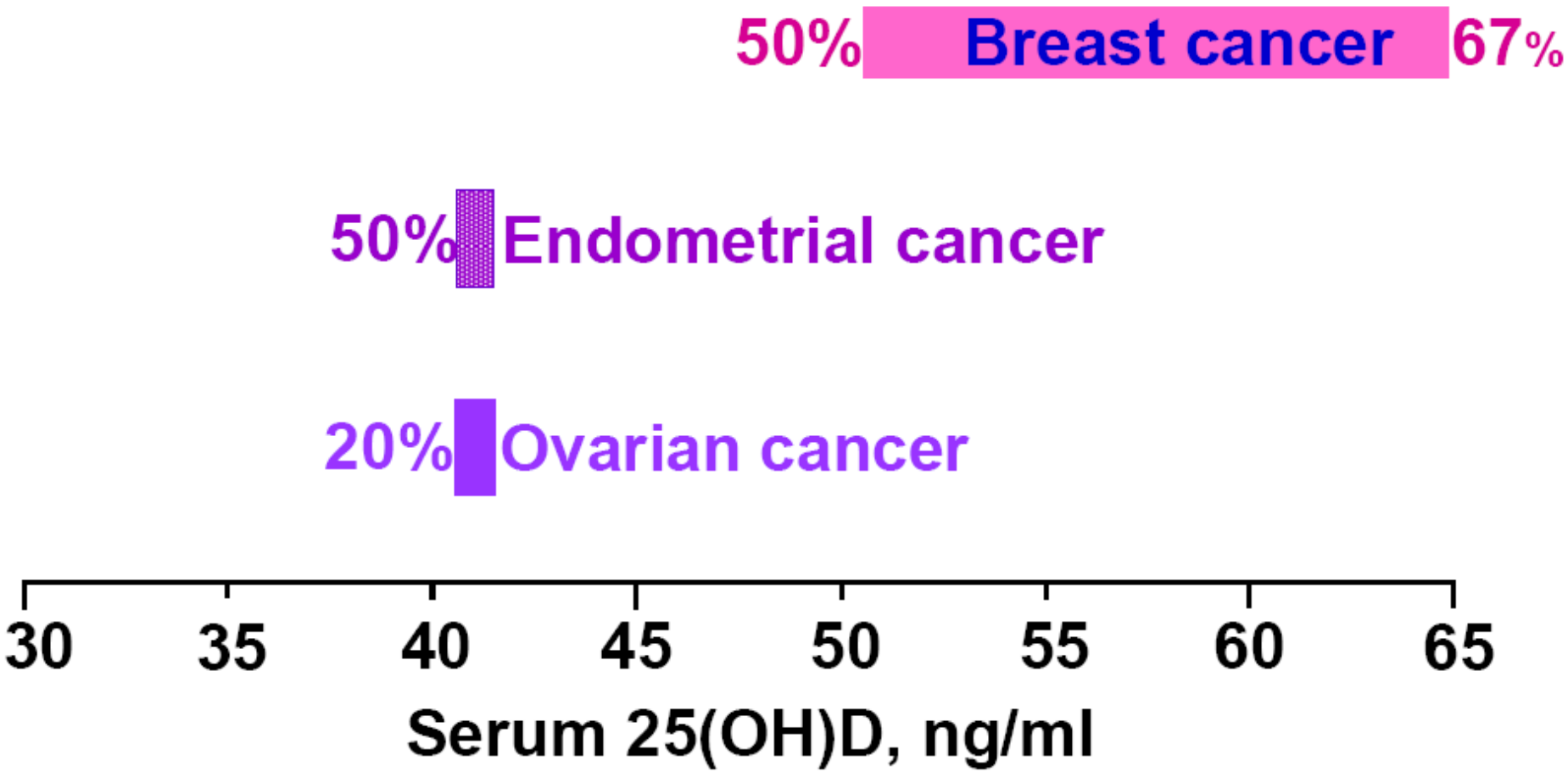
Estimated Proportion of Conditions Preventable by Specified Range of Serum 25(OH) D Level



Estimated Proportion of Cancers Preventable by Specified Range of Serum 25(OH) D Level



Estimated Proportion of Cancers Preventable by Specified Range of Serum 25(OH) D Level



Trying to calm the herd, Jake himself was suddenly awestruck by the image of beauty and unbridled fury on the cliff above. Pink Shadow had returned.

Vitamin D Insufficiency

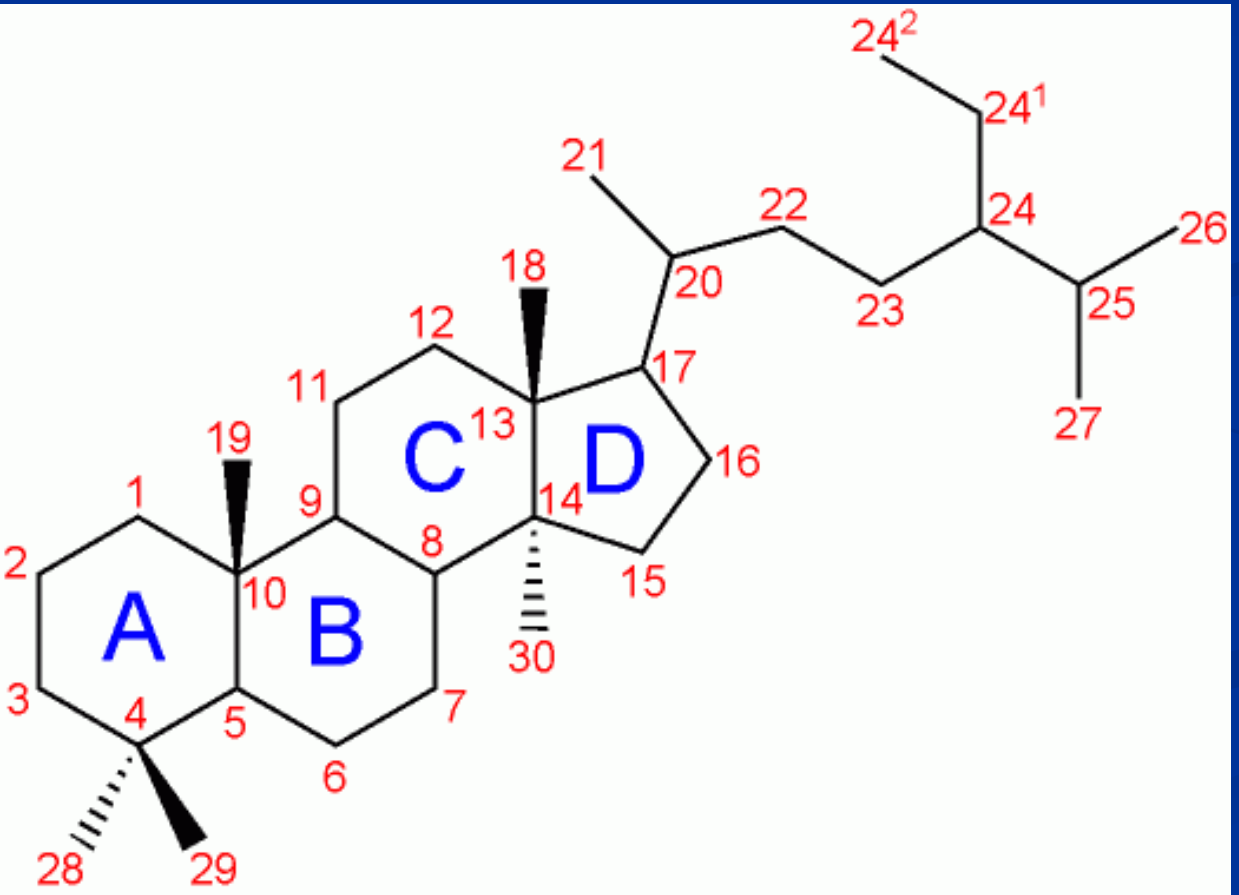
- At least 17 varieties of cancer
- Heart disease, stroke, hypertension
- Autoimmune diseases, MS
- Diabetes, type 1 and 2
- Depression
- Chronic pain
- Osteoarthritis
- Osteoporosis
- Muscle weakness
- Periodontal disease
- Childhood bone health
- Infectious disease

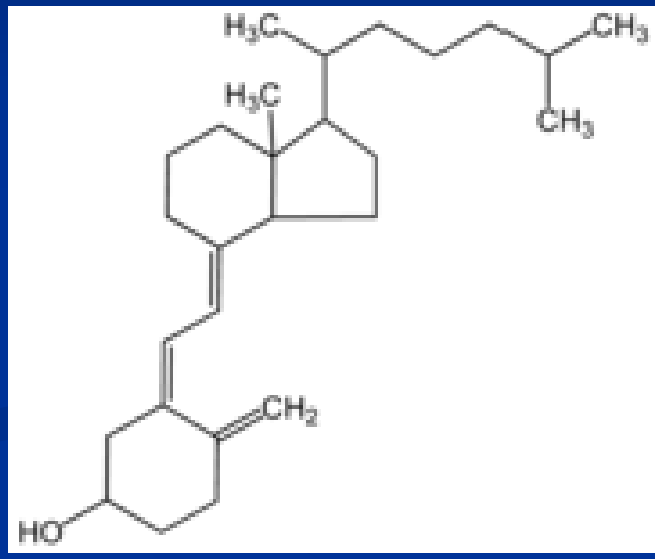
and more

Vitamin D Physiology

- Technically not a "vitamin"
- Vitamin D is in a class by itself.
- Its metabolic product, 1,25 dihydroxyvitamin D = *calcitriol*, is a *secosteroid hormone* that targets over 1000 genes
- Every cell has a vitamin D receptor that responds to 1,25 dihydroxyvitamin D

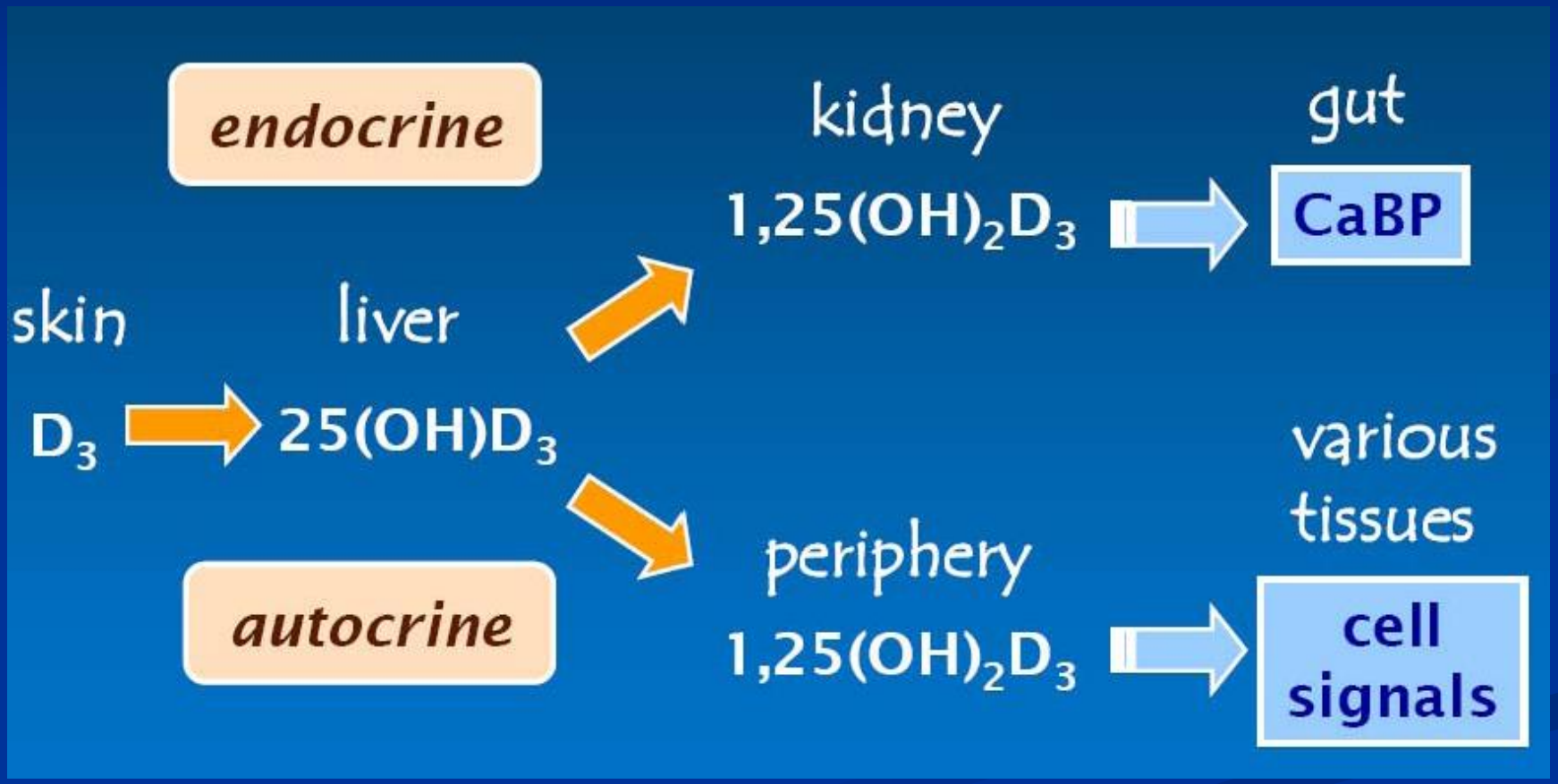
Secosteroid hormone
Vitamin D_3 = Cholecalciferol
"B" Ring is "Broken"





- Calcitriol Made in Kidneys via 25(OH) D_3 -1-hydroxylase
- Most potent steroid hormone in the human body
- First pathway:
  - Calcitriol made by the kidney circulates in the blood to maintain blood calcium levels
- Second Pathway:
  - The second vitamin D pathway leads to cells and genomic and non genomic effects and that is where all the action is.
- The amazing health benefits of vitamin D discovered in the last 10 years are from vitamin D going down the second pathway

The "Secret" Life of Vitamin D



"And now Edgar's gone. ... Something's going on around here."

Calcidiol

- Storage form of vitamin D
- Calcidiol is what fills your vitamin D gas tank.
- After your liver turns cholecalciferol into calcidiol
- Calcidiol follows one of two pathways.
- Calcidiol (25-hydroxyvitamin D) is a prehormone that is directly made from cholecalciferol.
- When being tested for vitamin D deficiency, calcidiol is the only blood test that should be drawn.
- When someone refers to vitamin D blood levels, they are referring to calcidiol levels.

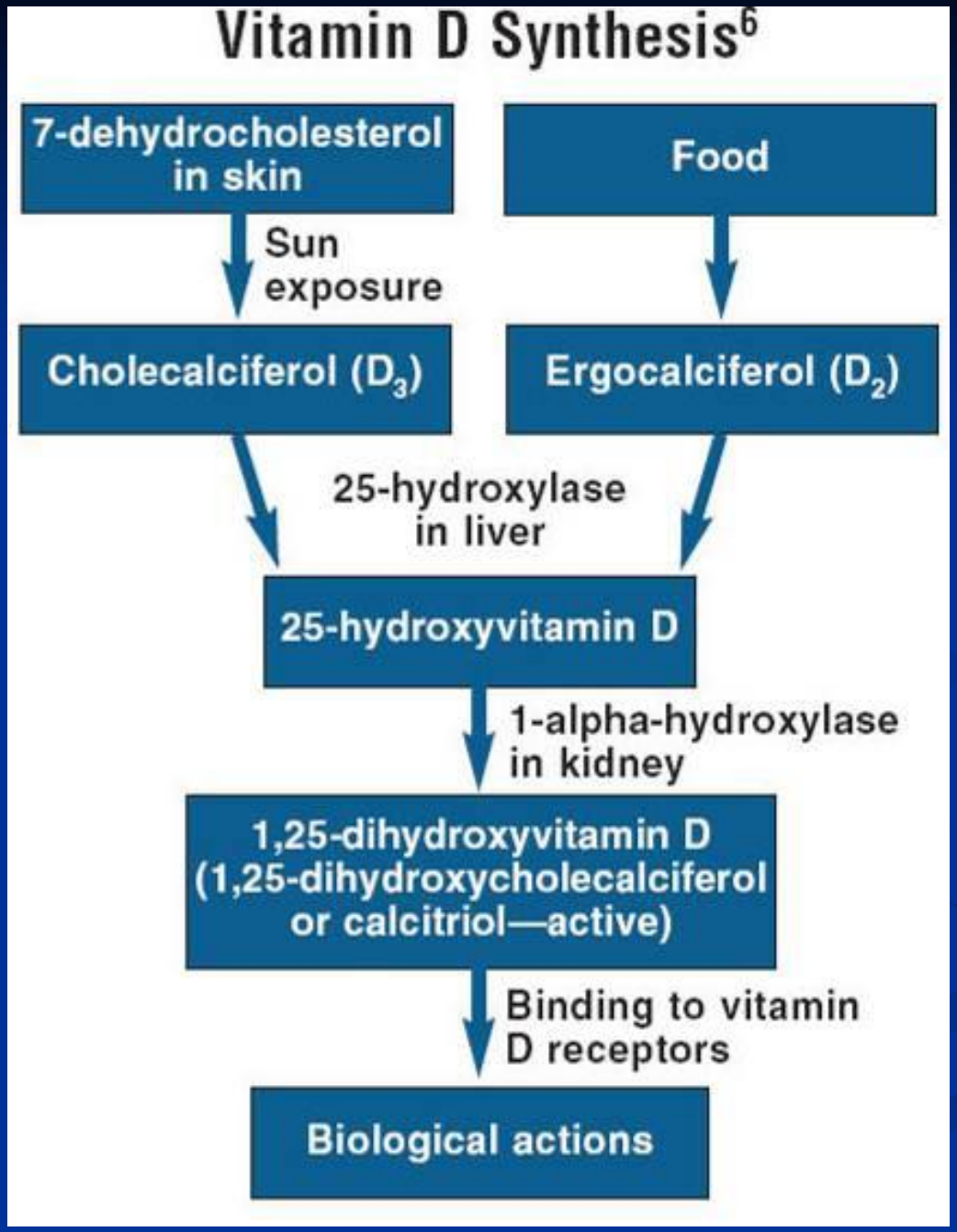
- Calcidiol is converted to calcitriol in many tissues, including prostate, colon, breast, lung, immune cells, monocytes, macrophages
- Regulates cell growth controls immune function, controls genome
- If Calcidiol is left over—if your tank is full and your kidneys are getting all the calcidiol they need to maintain serum calcium—then calcidiol is able to take the second pathway, one that leads directly to the cells.
- Avalanche of current research on calcitriol in cancer and autoimmune disease, infectious disease, diabetes, cardiovascular disease
- Autocrine and paracrine effects

Cholecalciferol = Vitamin D_3

- Cholecalciferol is the naturally occurring form of vitamin D.
- Cholecalciferol is made in large quantities in your skin when sunlight strikes bare skin.
- Can synthesize 20,000 IU per day by direct sun exposure at lower latitudes, especially with sweating in the sun
- It can also be taken as a supplement
- Ergocalciferol = Vitamin D_2, which comes from ergosterol, the biological equivalent of cholesterol in fungal cell membranes when exposed to ultraviolet light.
- Not bioequivalent to D_3, only reason to use D_2 is to make Eli Lilly money.

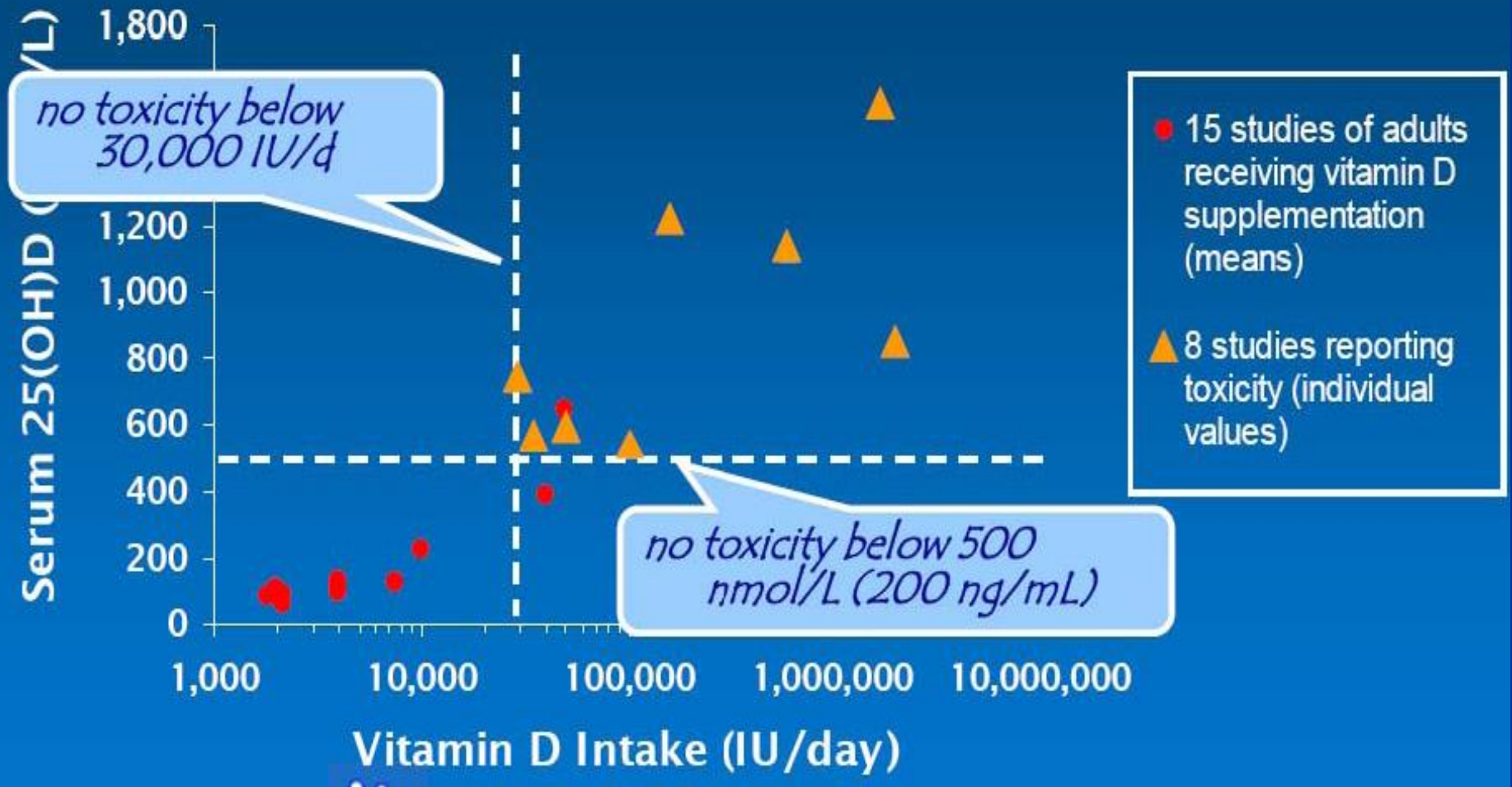
Use Vitamin D_3

- Supplementation should be with D_3 not D_2
  - Trang, H., et al., "Evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D_2. Amer Jour Clin Nutr 1998; 68:854-58.
  - Armas, L., et al., "Vitamin D_2 is much less effective than vitamin D_3 in humans," Jour Clin Endocrinol Metab 2004; 89:5387-391.


Vitamin D Synthesis[6]
7-dehydrocholesterol in skin
Food
Sun exposure
Cholecalciferol (D_3)
Ergocalciferol (D_2)
25-hydroxylase in liver
25-hydroxyvitamin D
1-alpha-hydroxylase in kidney
1,25-dihydroxyvitamin D (1,25-dihydroxycholecalciferol or calcitriol—active)
Binding to vitamin D receptors
Biological actions

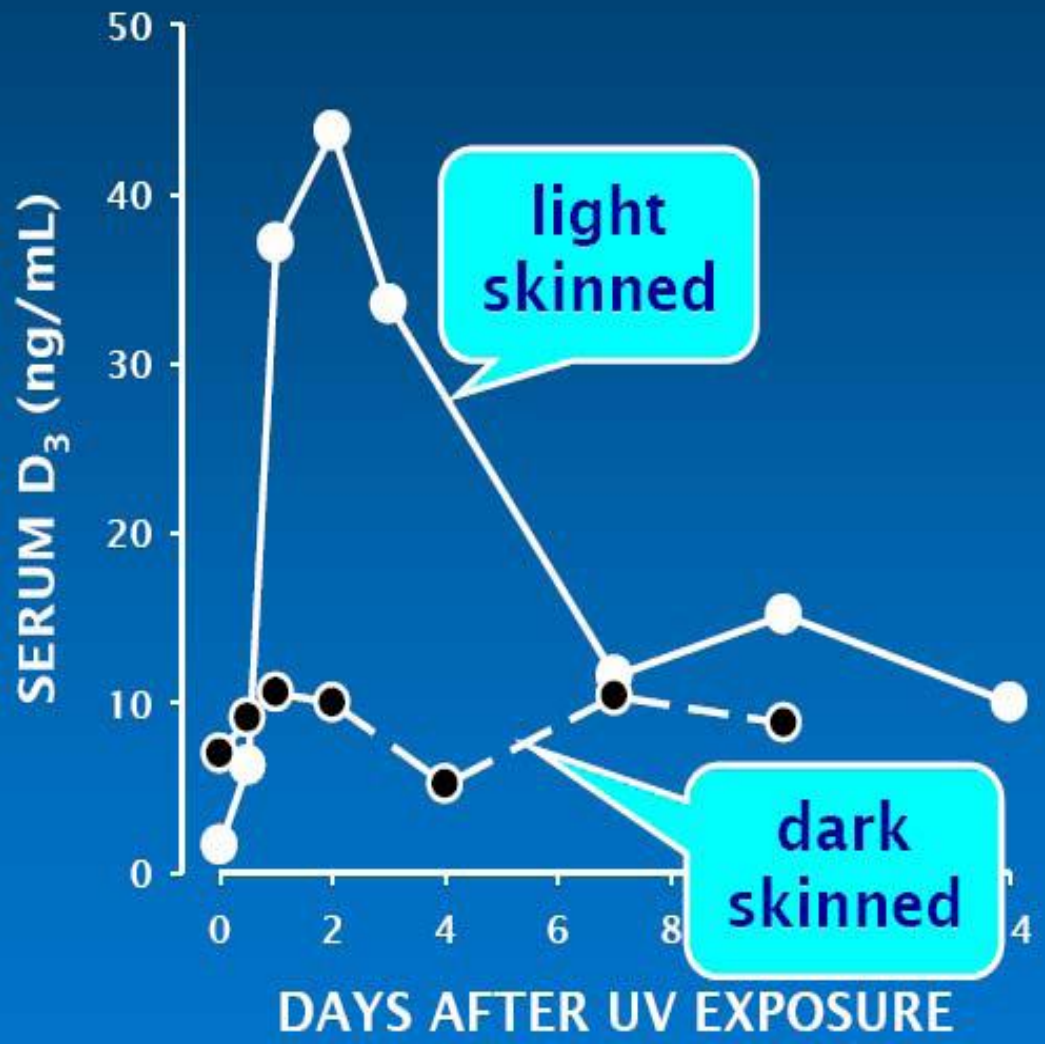
"Say … what's a mountain goat doing way up here in a cloud bank?"

VITAMIN D INTAKE & TOXICITY*



SKIN COLOR & VIT D SYNTHESIS

- total body exposure to 0.054J/cm^2 UV (1.5 MED for light skinned individuals)
- Holick *Ann NY Acad Sci* 1985



Safety of Vitamin D_3 in adults with multiple sclerosis.

- 28 weeks. Doses increased from 28,000 to:
- 280,000 IU/week = 40,000 IU/day
- Calcidiol rose from 31 to 155 ng/mL
- No hypercalcemia or other metabolic disturbance or toxicity
- Disease progression and activity were not affected, but the number of gadolinium-enhancing lesions per patient decreased from the initial mean of 1.75 to the end-of-study mean of 0.83 (P = 0.03).

Kimball, S. **Safety of vitamin D_3 in adults with multiple sclerosis** Am J Clin Nutr. 2007 Sep;86(3):645-51

Molecular Actions of Vitamin D

- Contributing to Cancer Prevention
- Vitamin D or metabolites have direct inhibitory action on initiation and progression of various cancers
- Renal production of Calcitriol regulates Calcium metabolism with PTH
- Extra renal production of Calcitriol relates to cancer risk
- Calcitriol is anti-inflammatory and turns off NFKB
- Growth Arrest of malignant cells

Fleet, James PhD. Molecular Actions of Vitamin D Contributing to Cancer Prevention. *Molecular Aspects of Medicine.* 2008

- Cell Junction effects
- Apoptosis
- Anti-Metastasis
- Primary molecular action of Calcitriol is binding to Vitamin D Receptor (VDR) , a member of steroid hormone receptor superfamily
- Initiates gene transcription
- VDR needed for growth arrest of cancer
- Calcitriol also has non-genomic rapid actions
- Binds to cell membrane
- VDR turns on genes for increase in production of IGFBP-3
- Cancer can turn off CYP27b1 inhibiting Calcitriol production

"Here, Fifi! C'mon! ... Faster, Fifi!"

Cancer

- Grant proposes in this article that 23,000 American lives per year could be saved from a reduction in cancer mortality by supplementing with vitamin D or providing adequate exposure to UV light.

– Grant, W., "The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates," Anticancer Res 2006; 26:2687-699.

Cancer

- Garland, et., al in their article discuss that if everyone had a 25 OH vitamin D level that is > or equal to 55 ng/mL there would be at least 60,000 cases per year of colorectal cancer and 85,000 cases per year of breast cancer that would be prevented in North America.
- This same article goes on to say that the projected number of cases that could be prevented annually in the world with this serum level of vitamin D would be approximately 250,000 cases of colorectal cancer and 350,000 cases of breast cancer.

—Garland, C., et al., "What is the dose-response relationship between vitamin D and cancer risk? Nutrition Reviews 2007; 65(8):S91-S95.

Inevitably, their affair ended: Howard worried excessively about what the pack would think, and Agnes simply ate the flowers.