Keynote Address Oct 15, 2010
Nebraska American College of Physicians

VITAMIN D

THE ICEBERG UNDER THE SURFACE

Key

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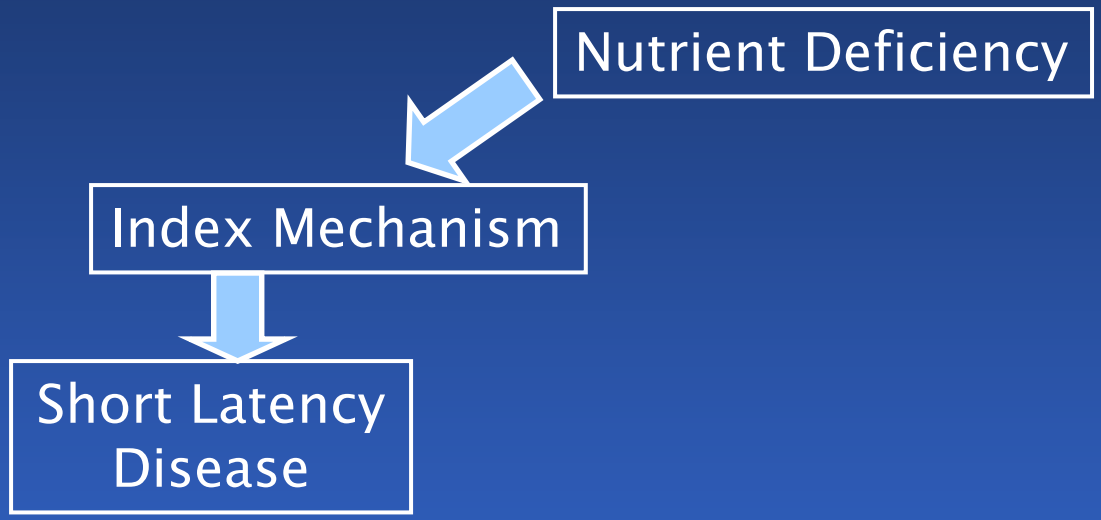
DISCLOSURES

- Robert P. Heaney, M.D.
  - no personal financial relationships to disclose

Working definition:

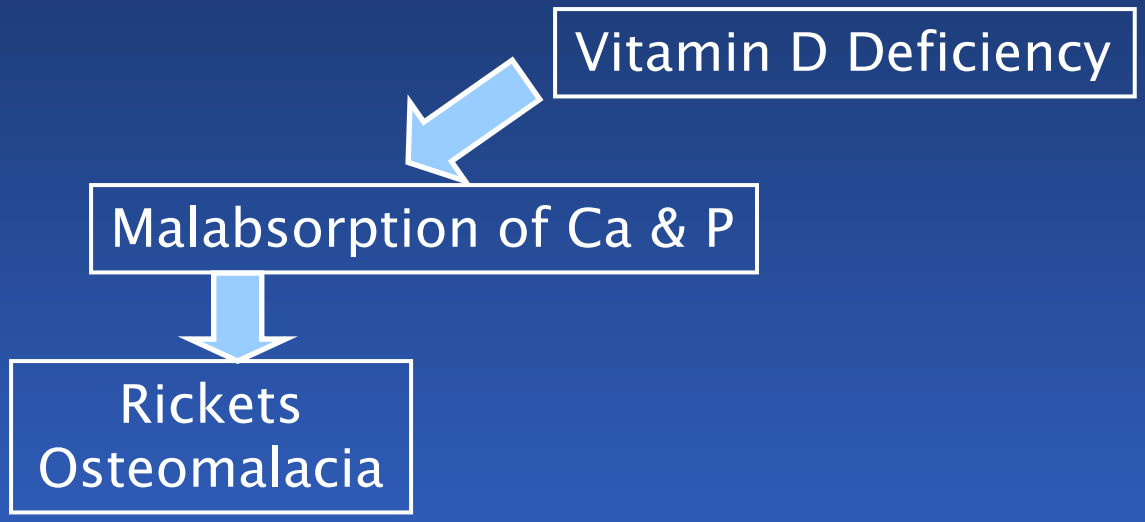
- a deficiency is any condition in which inadequate intake of a nutrient results in significant dysfunction or disease
- conversely, nutrient adequacy is the situation in which further increases in intake produce no further reduction in dysfunction or disease

RETHINKING DEFICIENCY DISEASE



In the early days of nutrition as a science, short latency of the disease/dysfunction was necessary in order to recognize the connection between cause and effect.

RETHINKING DEFICIENCY DISEASE



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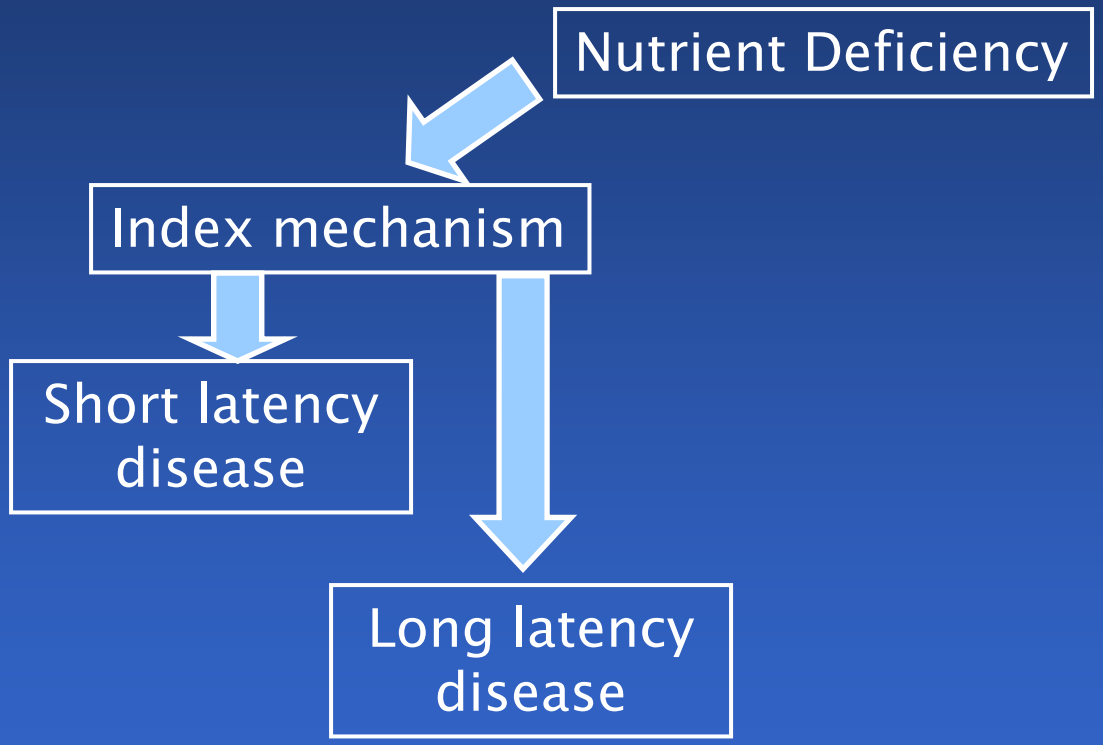

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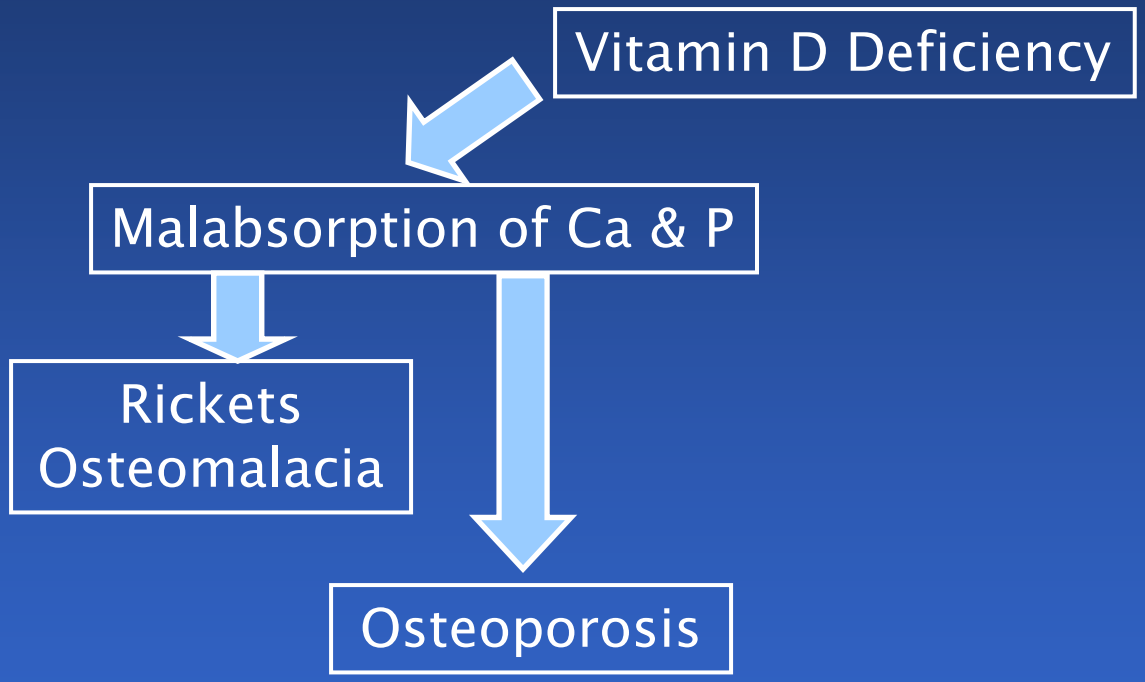

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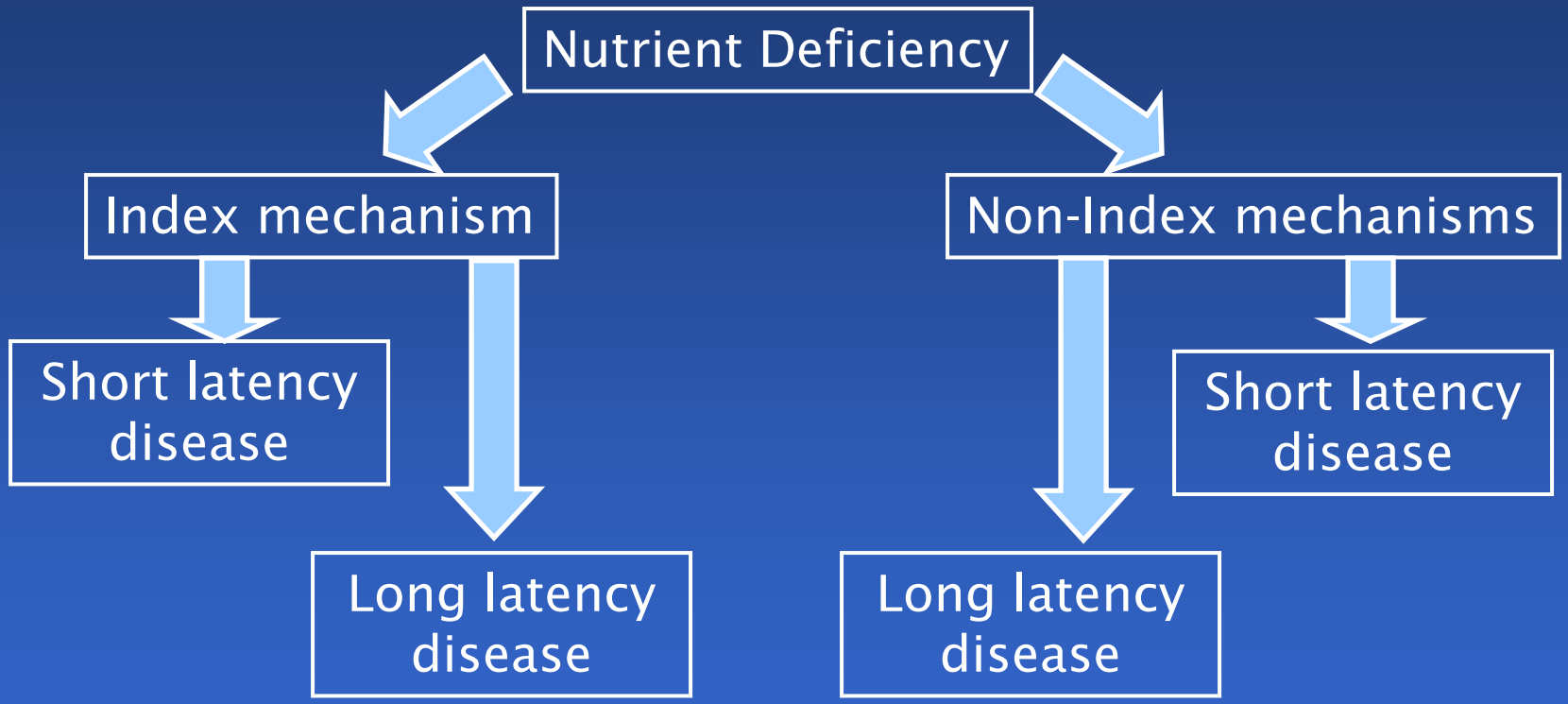

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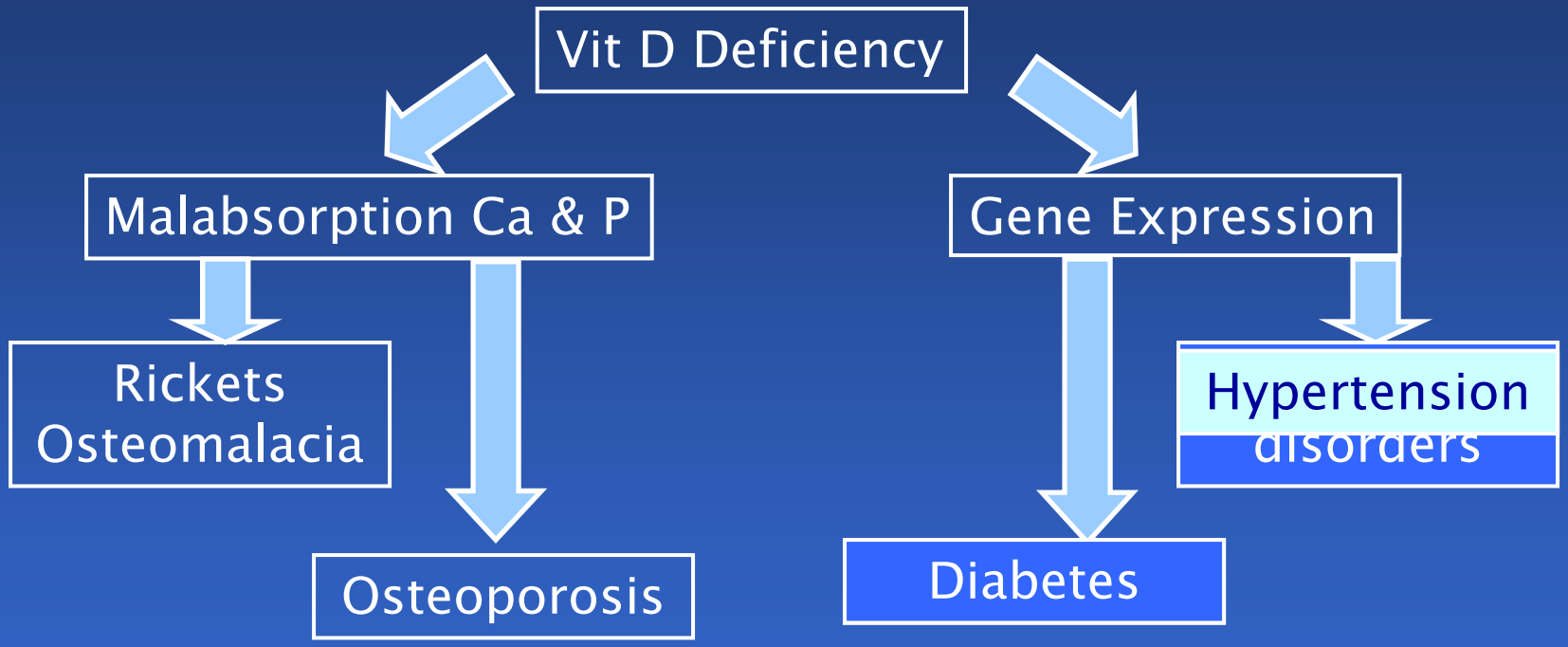

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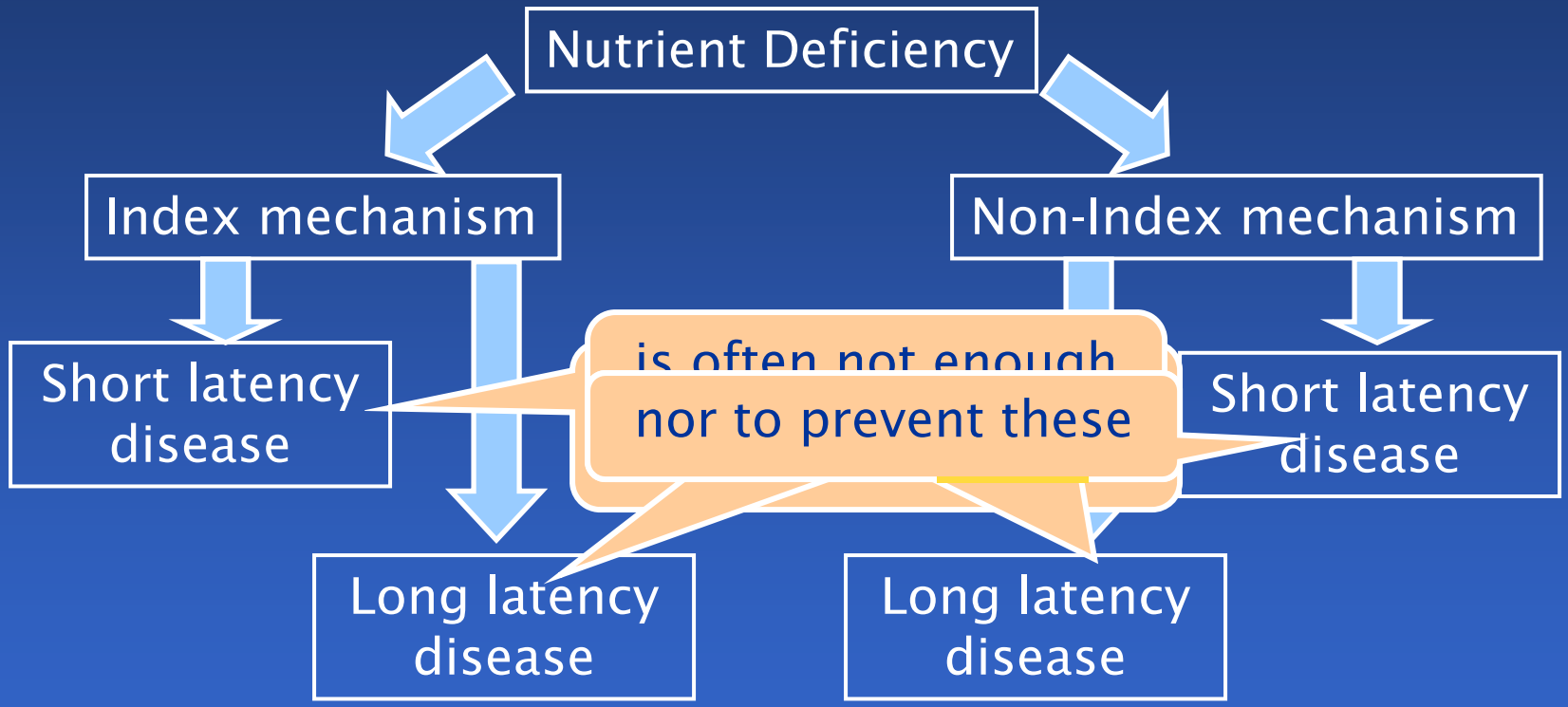

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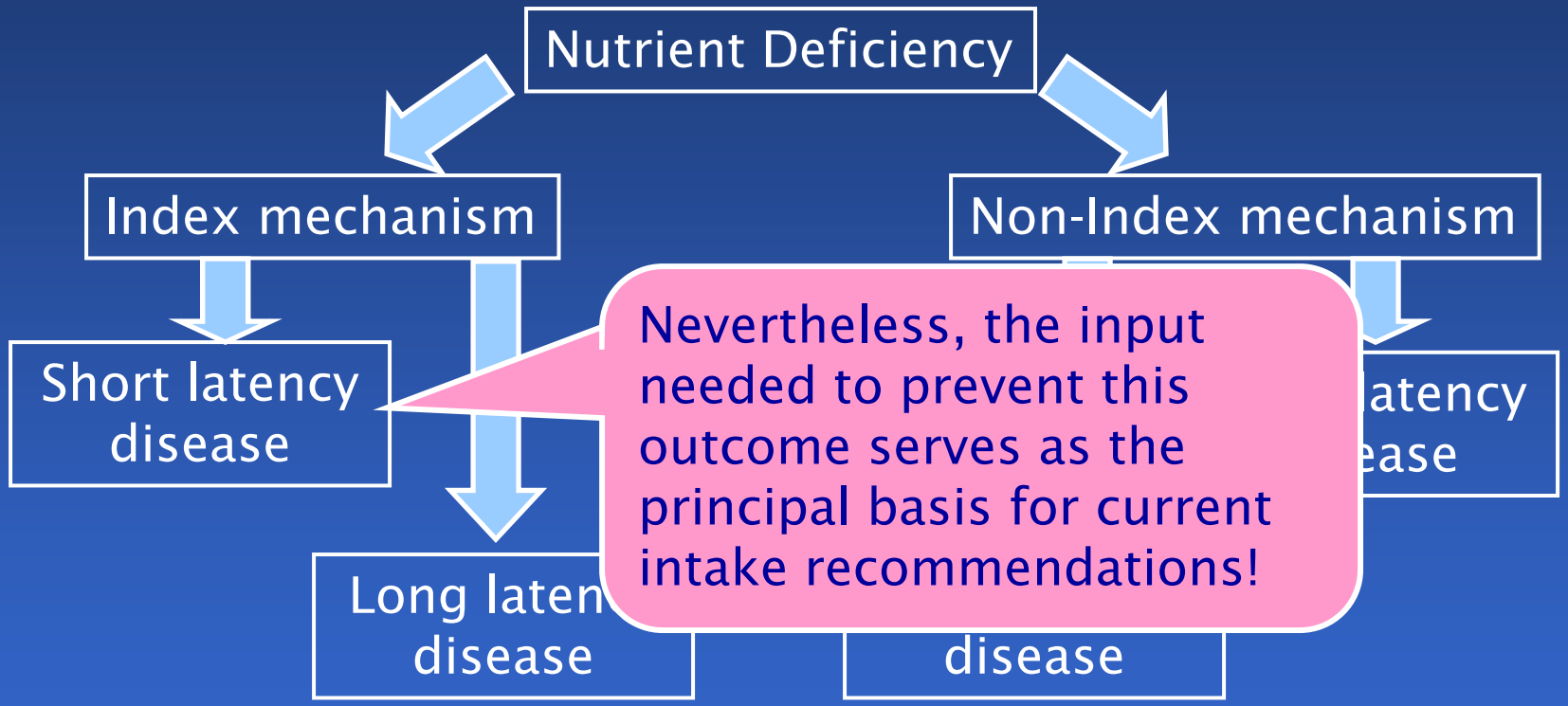
RETHINKING DEFICIENCY DISEASE



more useful

What is the ~~right~~ endpoint?

What is the operative model for nutrition?

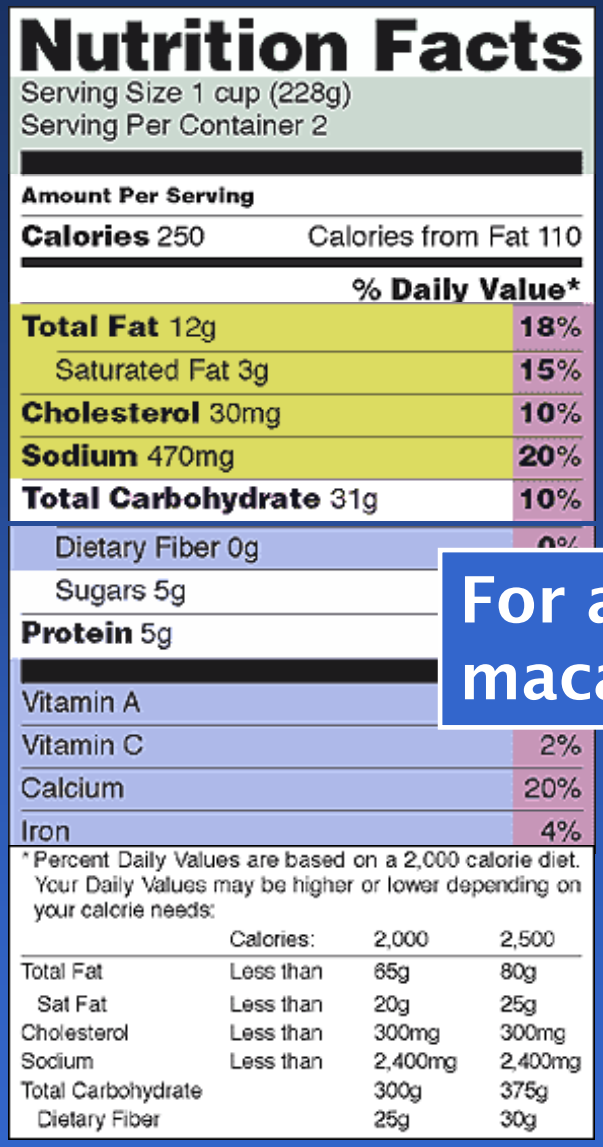
WHAT IS THE OPERATIVE MODEL?

- for the media?
- for regulators?
- for nutritional policy makers?
- for nutritional physiologists?

WHAT IS THE OPERATIVE MODEL?

- *for the media and for regulators*

  - nutrition is about killing yourself with a fork
  - it's about avoiding risks
  - it's about warnings & cautions



Nutrition Facts

Serving Size 1 cup (228g)
Serving Per Container 2

Amount Per Serving

Calories 250	Calories from Fat 110
	% Daily Value*
Total Fat 12g	**18%**
Saturated Fat 3g	**15%**
Cholesterol 30mg	**10%**
Sodium 470mg	**20%**
Total Carbohydrate 31g	**10%**
Dietary Fiber 0g	**0%**
Sugars 5g	
Protein 5g	
Vitamin A	
Vitamin C	2%
Calcium	20%
Iron	4%

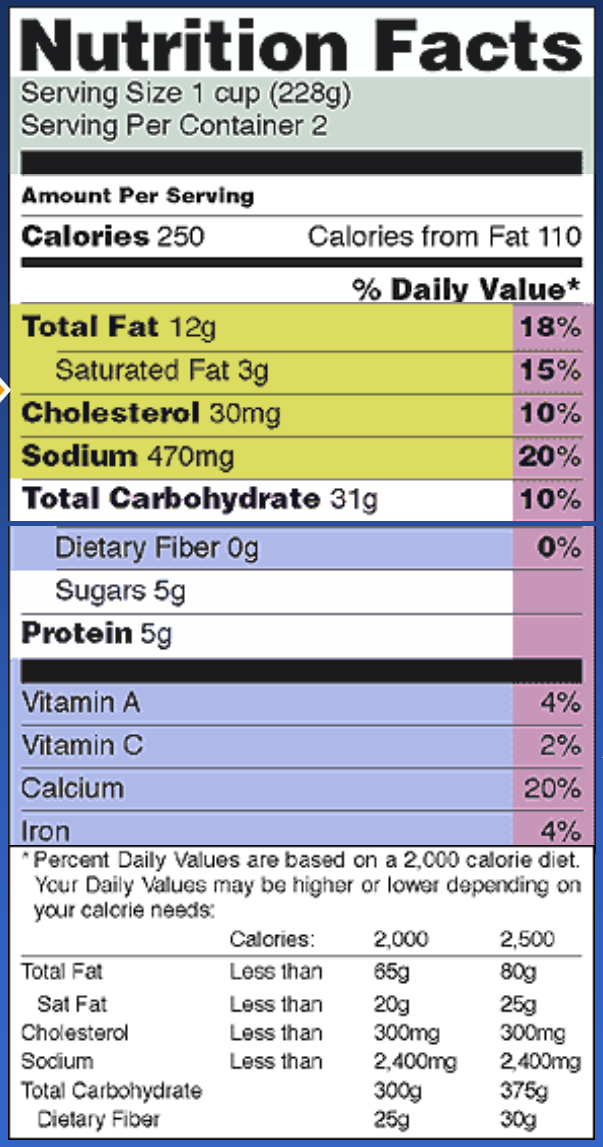
* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

For a package of macaroni & cheese

http://vm.cfsan.fda.gov/~dms/foodlab.html

Limit these nutrients



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Get enough of these nutrients

MEDIA REPORTING

- the overwhelming majority of media reports about nutrition emphasizes harm and risk
- while the explanation is partly that harm is more newsworthy than benefit (and the media battens on controversy)
- still the impression unwittingly conveyed to the general public is one of concern and danger

WHAT IS THE OPERATIVE MODEL?

- *for nutritional policy makers*

  - nutrition is about determining the least one can get by on without suffering overt disease of a specific type
  - (once called MDRs)

WHAT IS THE OPERATIVE MODEL?

- *for nutritional physiologists*

  - adult nutrition is about preventive maintenance of tissues and organs
  - it's about keeping them from wearing out or breaking down prematurely
  - its referent is the intake that prevailed when human physiology evolved

THE PREVENTIVE MAINTENANCE MODEL

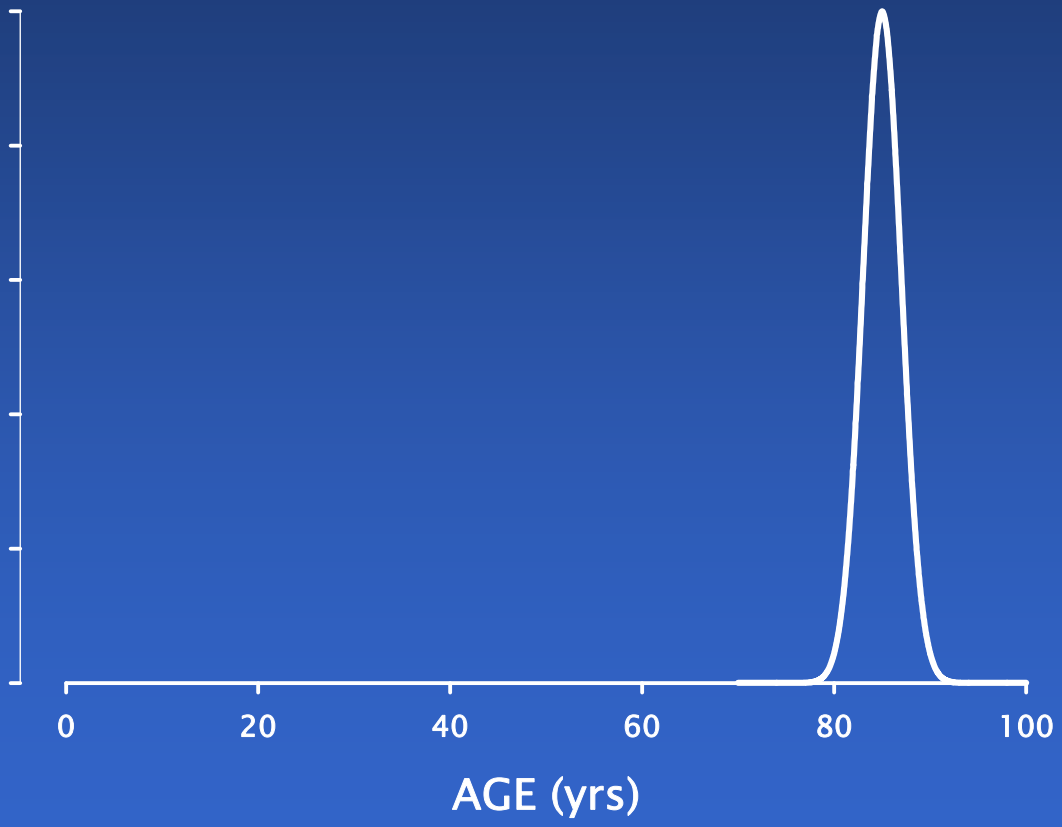
foundational premises:

- all tissues need all nutrients
- shortages impair the functioning of *all* body systems
- premature organ/system "wearing out", as a consequence of nutrient deficiency, will vary from person to person, depending on variable genetic composition
- therefore, expression of nutrient deficiency will usually be pluriform – both between and within individuals

THE PREVENTIVE MAINTENANCE MODEL

- *also recognizes that:*
  - the organism will work perfectly well without maintenance – *for a while . . .*
- it thus reconciles the seeming paradox that an organism can be "deficient" without being clinically "sick"
  - *for a while . . .*
- it's also about squaring the morbidity/ mortality curve

THEORETICAL MORTALITY CURVE



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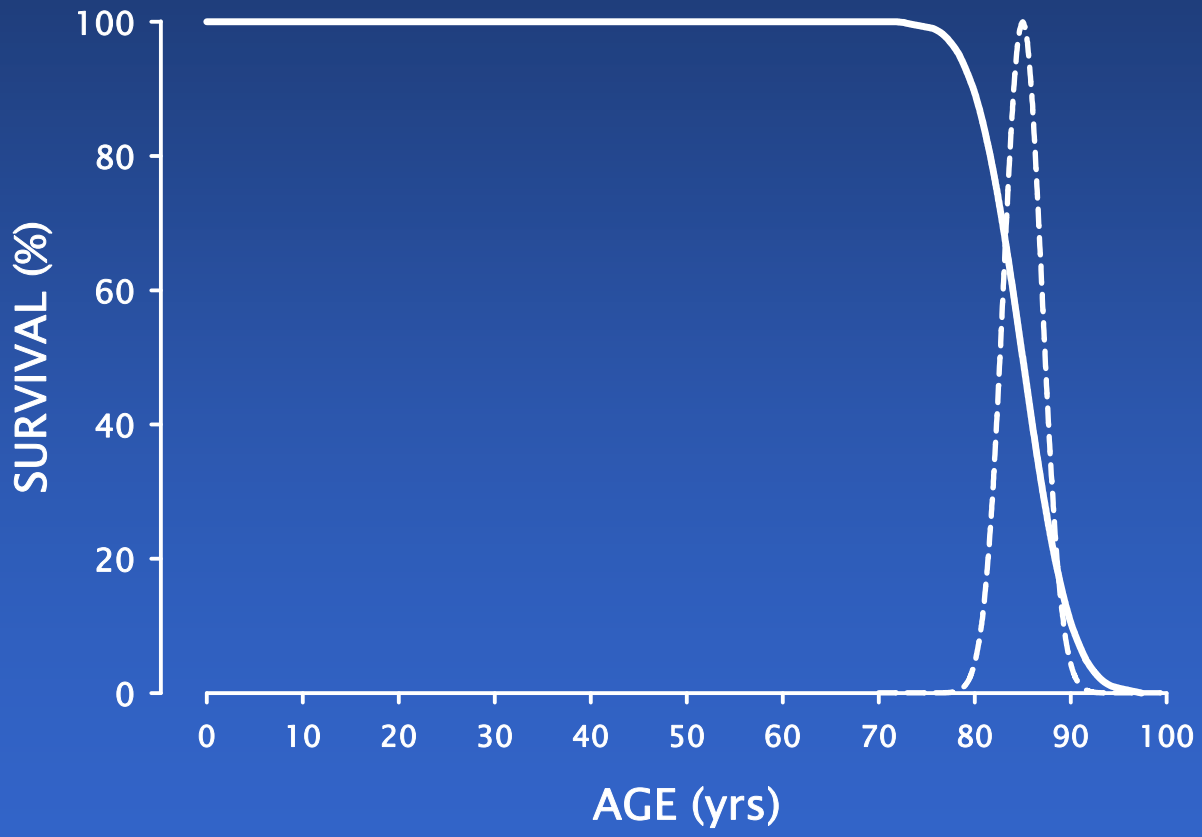
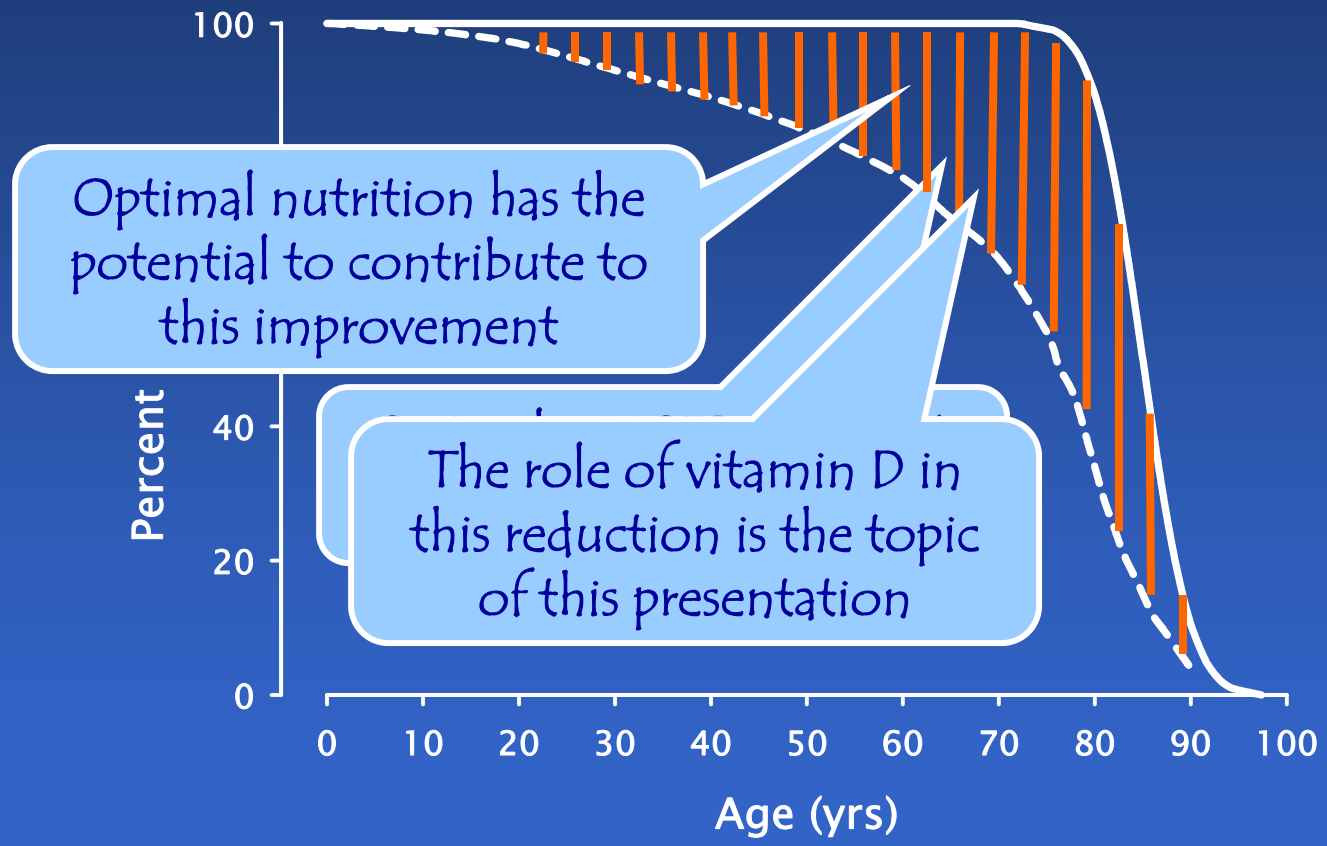
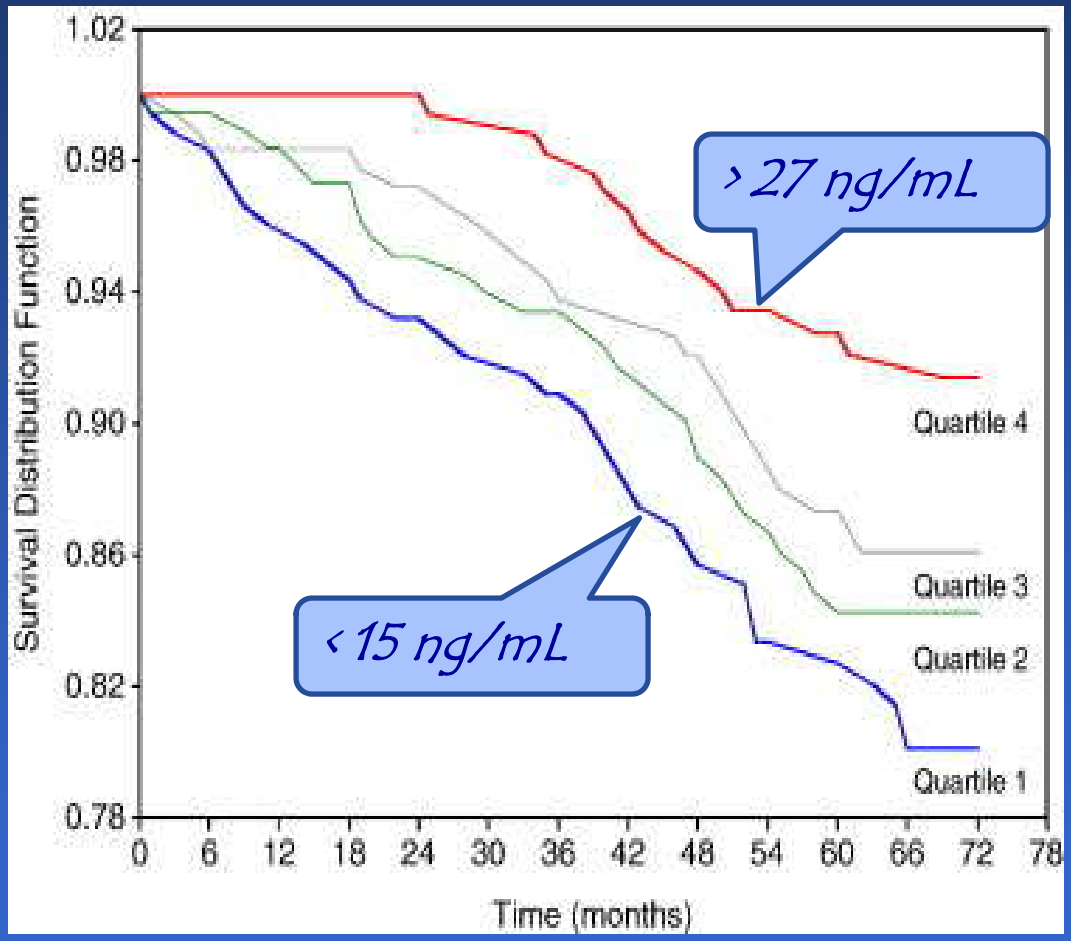


SQUARING THE MORTALITY CURVE



ALL-CAUSE MORTALITY*

- 714 community dwelling women
- aged 70–79
- Baltimore Women's Health & Aging Studies I & II
- median follow-up: 72 months
- risk adjusted for age, race, BMI, & other factors associated with mortality



* Semba et al. (2009) Nutr Res 29:525–530

CHRONIC DISEASE PERSPECTIVE

- chronic disease is the breakdown of structure and/or function of a body system
- its origin is usually multifactorial
  - genes
  - environment
    - ✓ nutrition
    - ✓ infection
    - ✓ toxins
    - ✓ injury

low vitamin D status impairs this protective/ reparative activity

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VITAMIN D IN NATURE

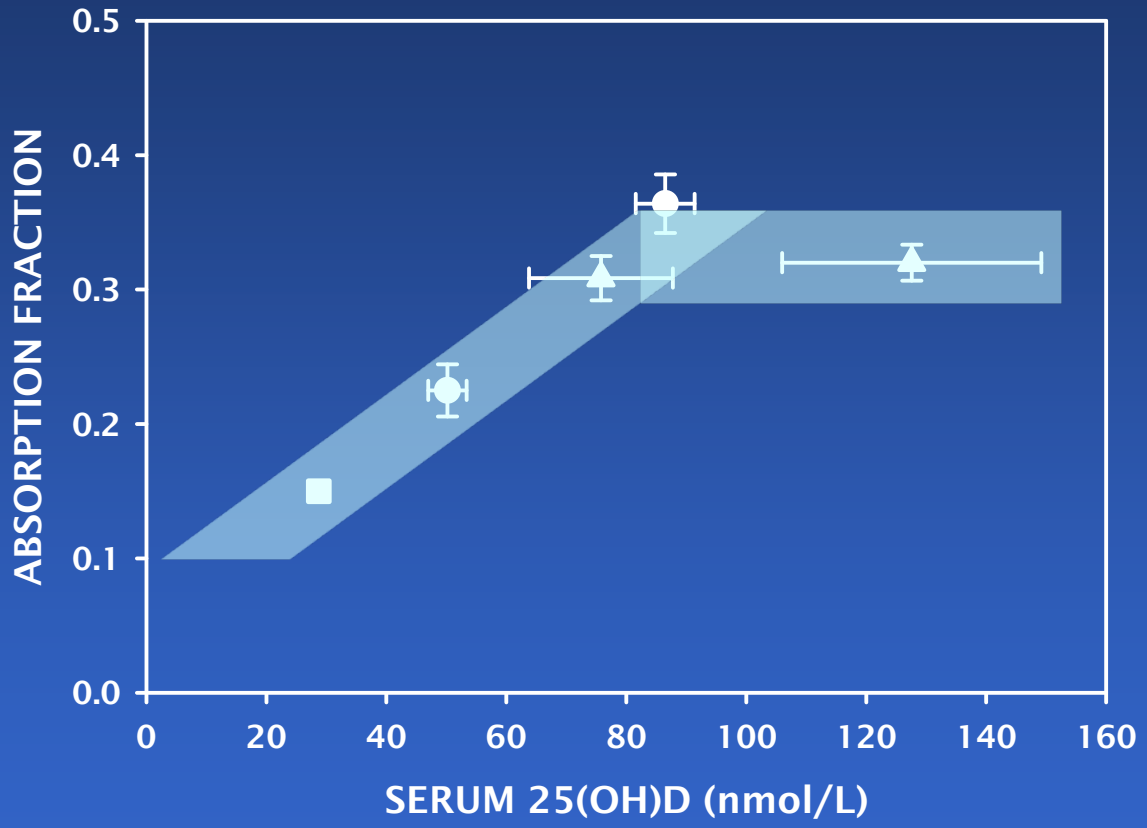
- vitamin D exists in two chemically distinct forms:
  - vitamin D2 – ergocalciferol
  - vitamin D3 – cholecalciferol
- cholecalciferol is the natural form in animals; it is what we make in our skins on exposure to UV-B light

VITAMIN D IN NATURE

- serum 25(OH)D is the way vitamin D status is evaluated
- lower end of acceptable range for serum 25(OH)D:
  75–80 nmol/L
  (30–32 ng/mL)

- There has been a gradually growing acceptance of 30–32 ng/mL (75–80 nmol/L) as the lower end of the "normal" range.
- What is the basis for this figure?
- Will it hold?

A VITAMIN D THRESHOLD



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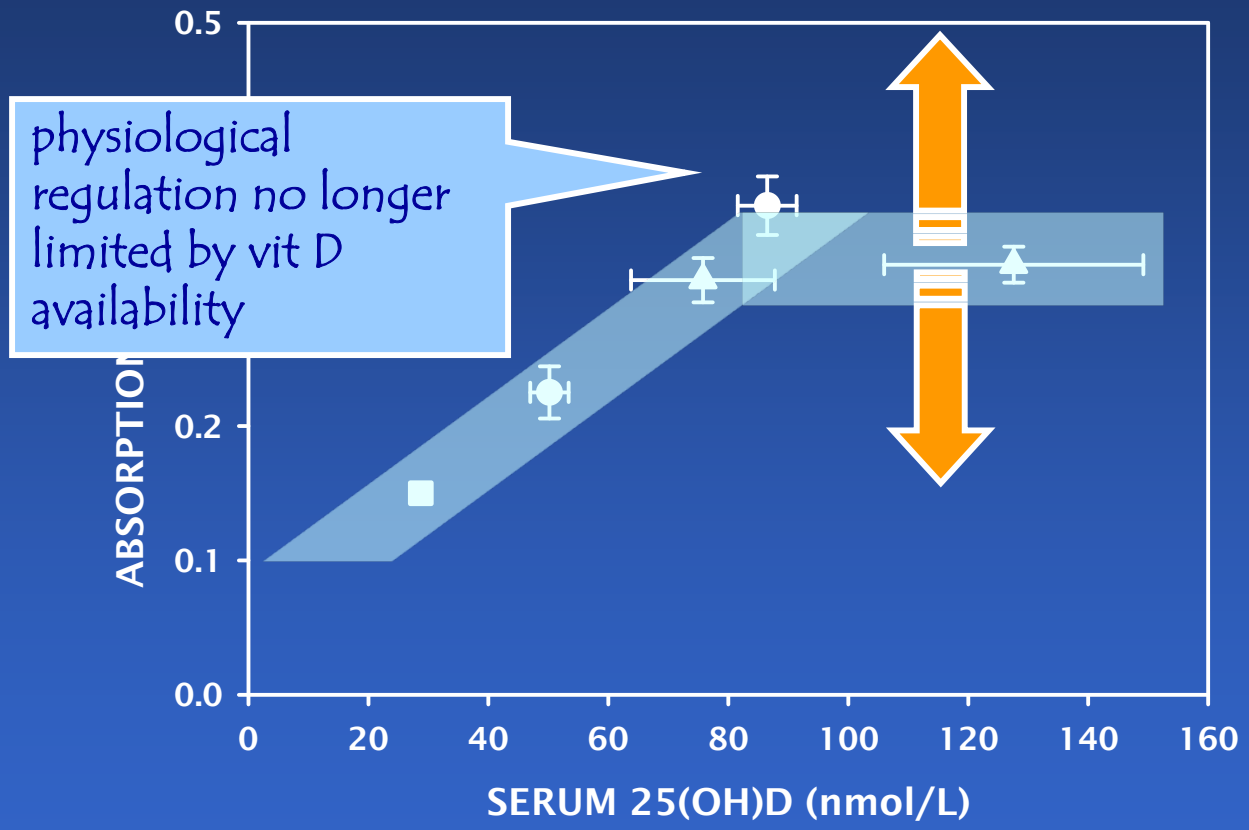

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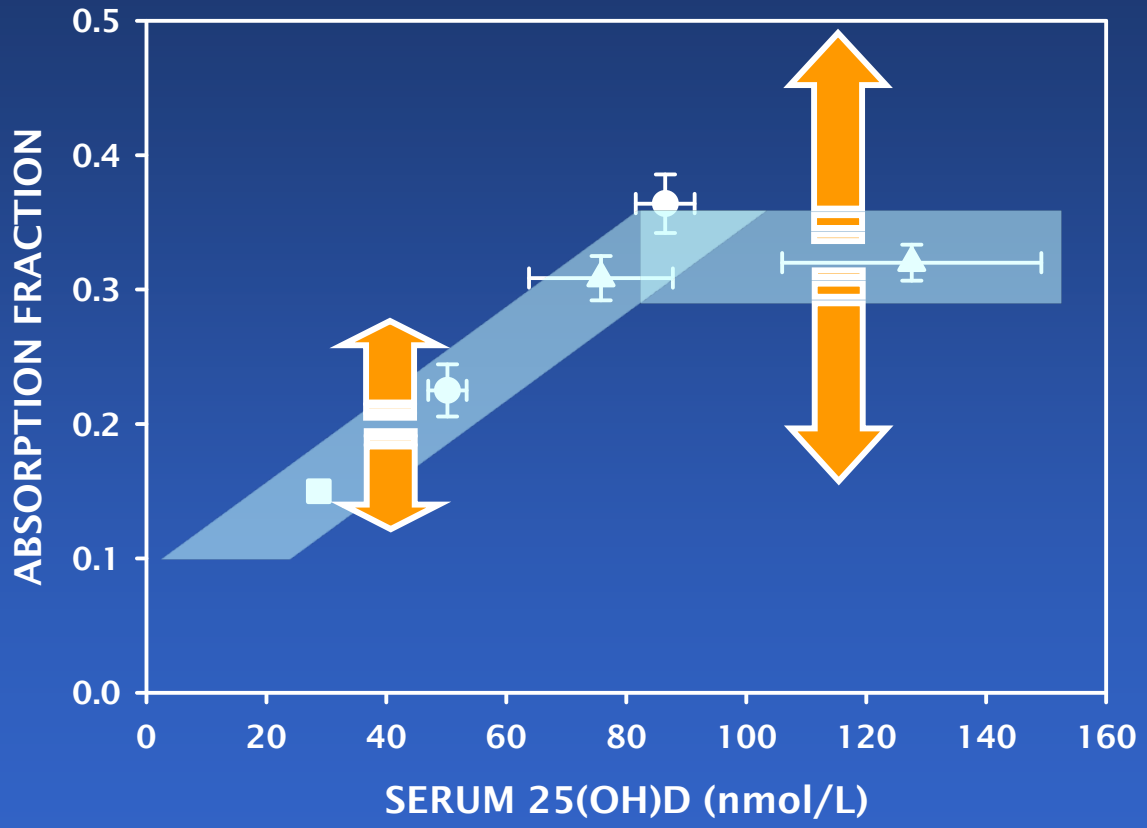

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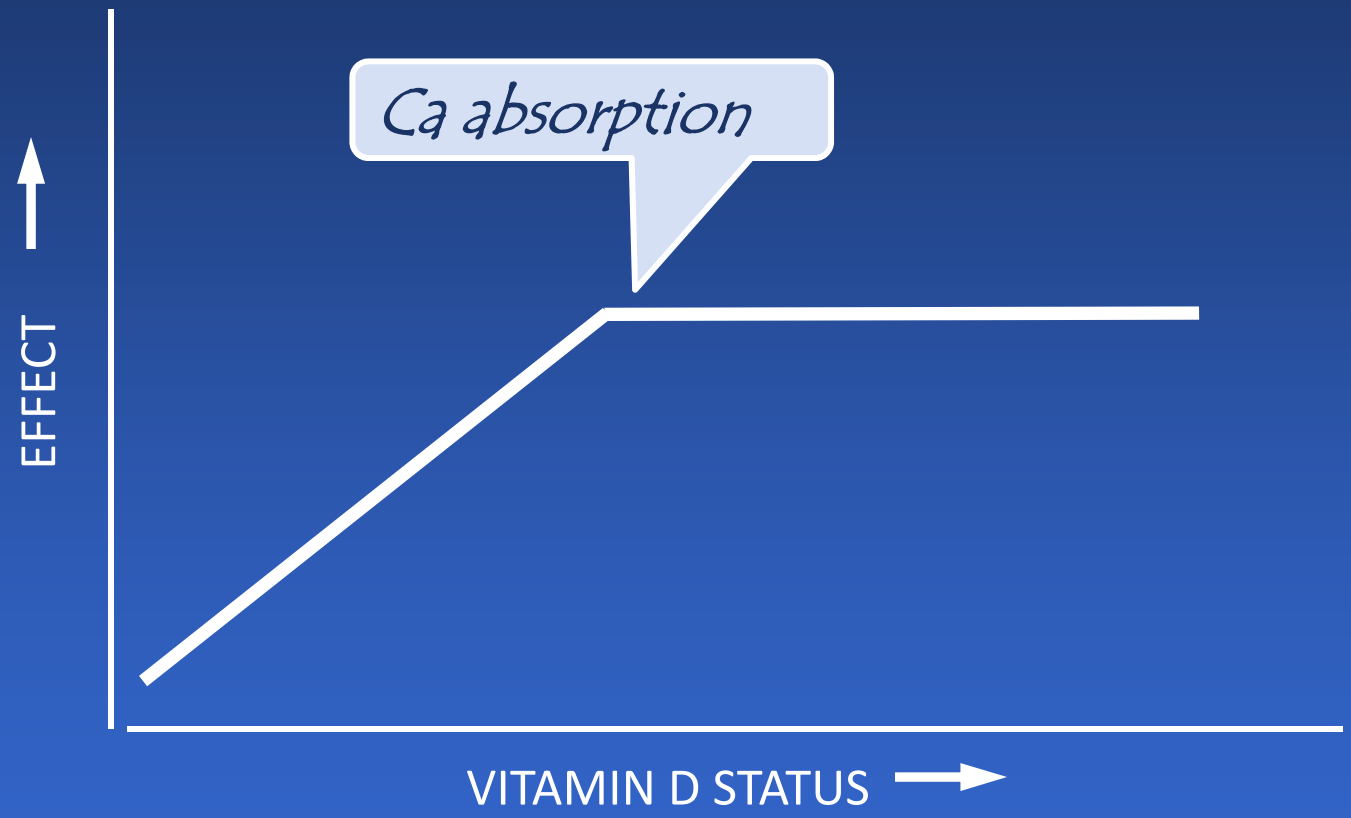
THE RESPONSE THRESHOLD



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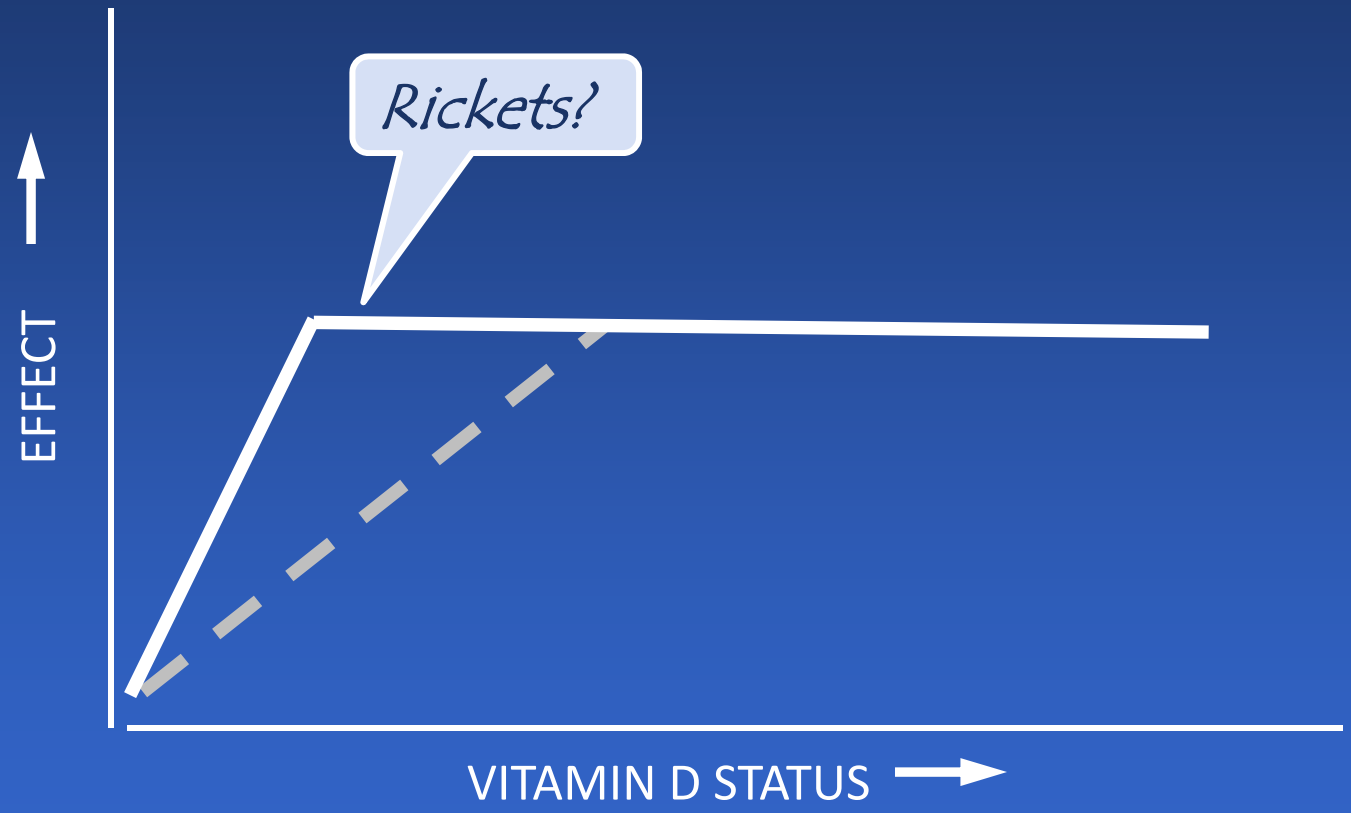
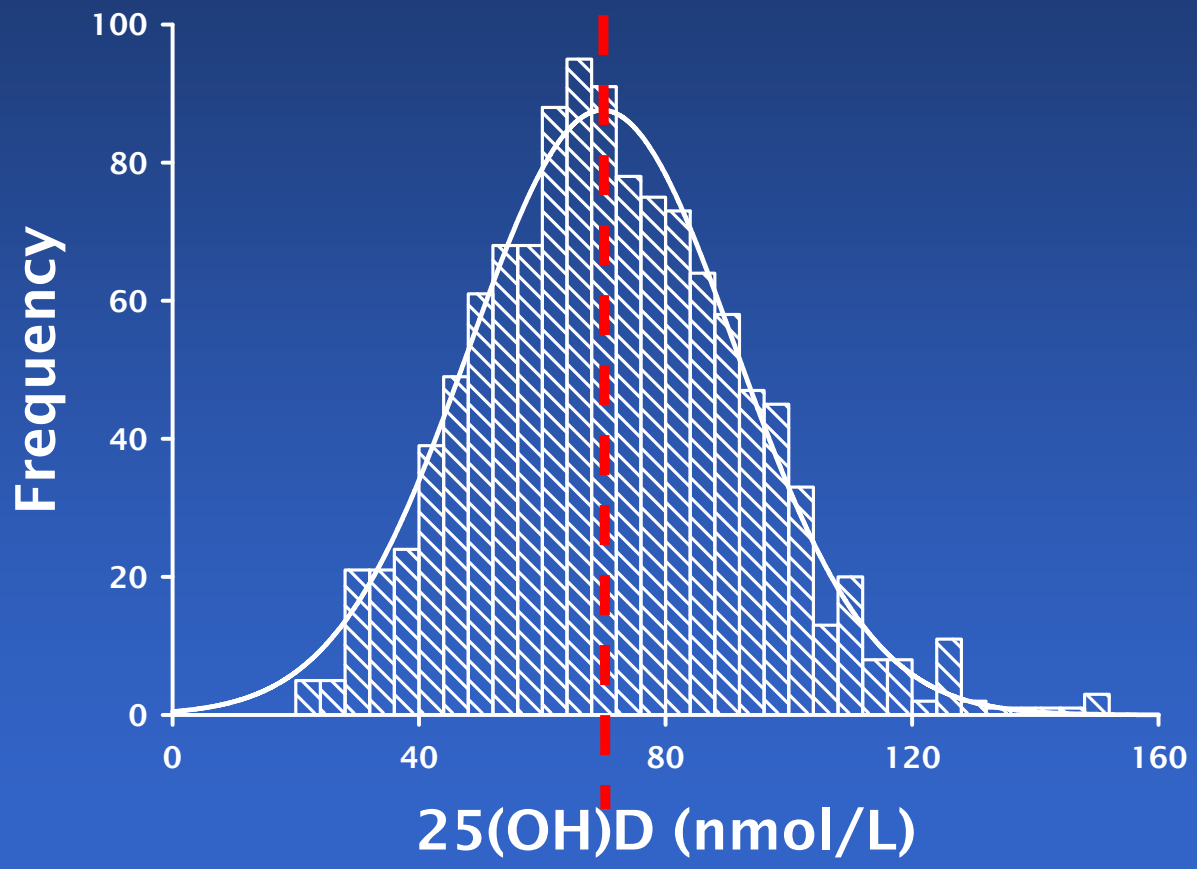


25(OH)D IN OLDER WOMEN*

- 1168 women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU



*Lappe et al., JACN 2006

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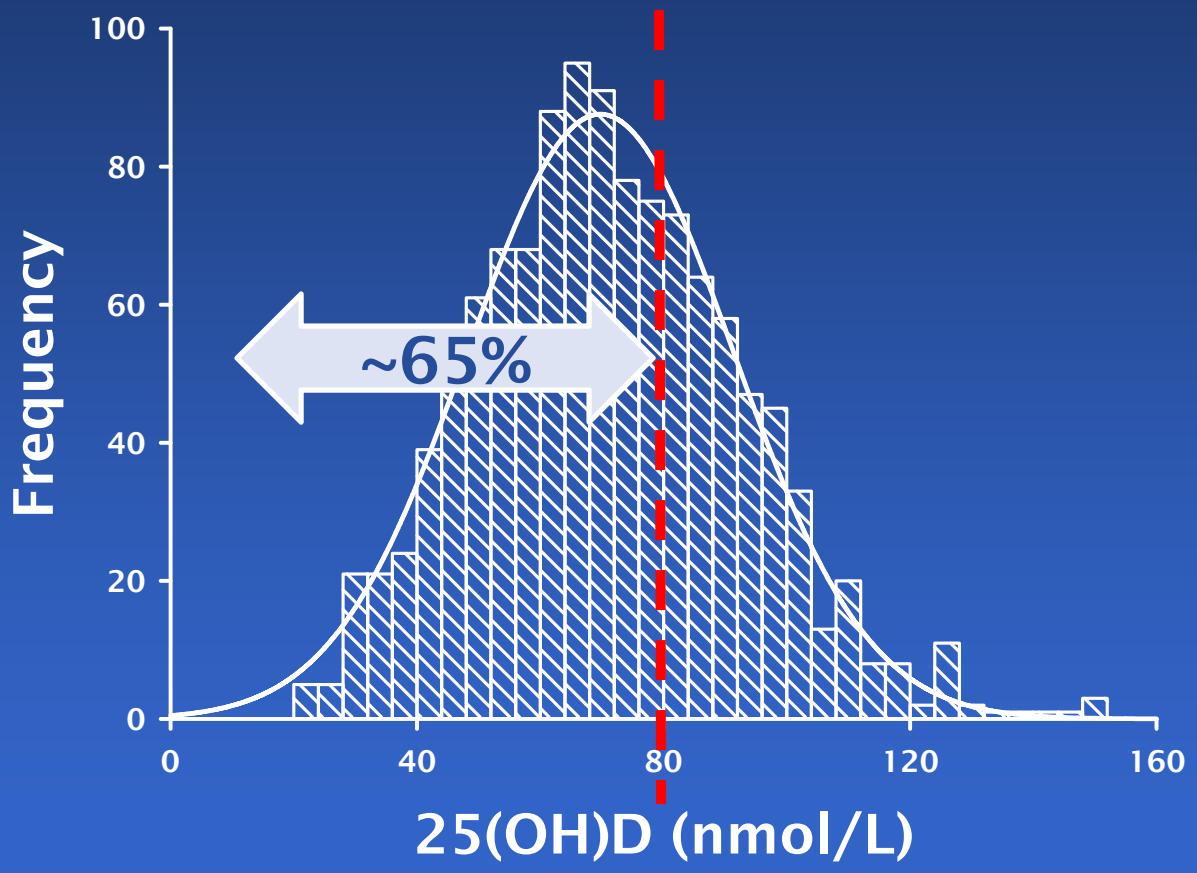
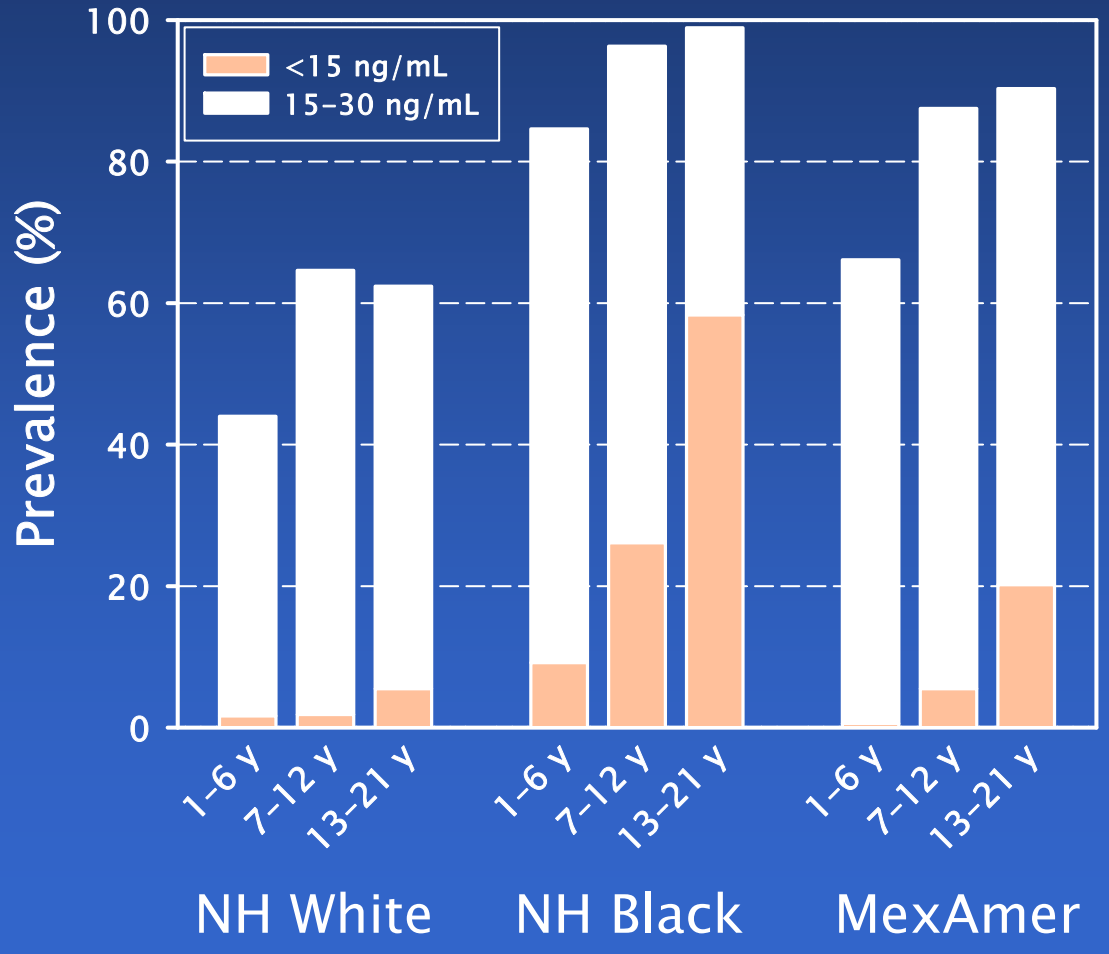


*Lappe et al., JACN 2006

VIT D DEFICIENCY IN CHILDREN

- NHANES 2001–2004
- girls
- n=3012
- Kumar et al. Pediatrics 2009



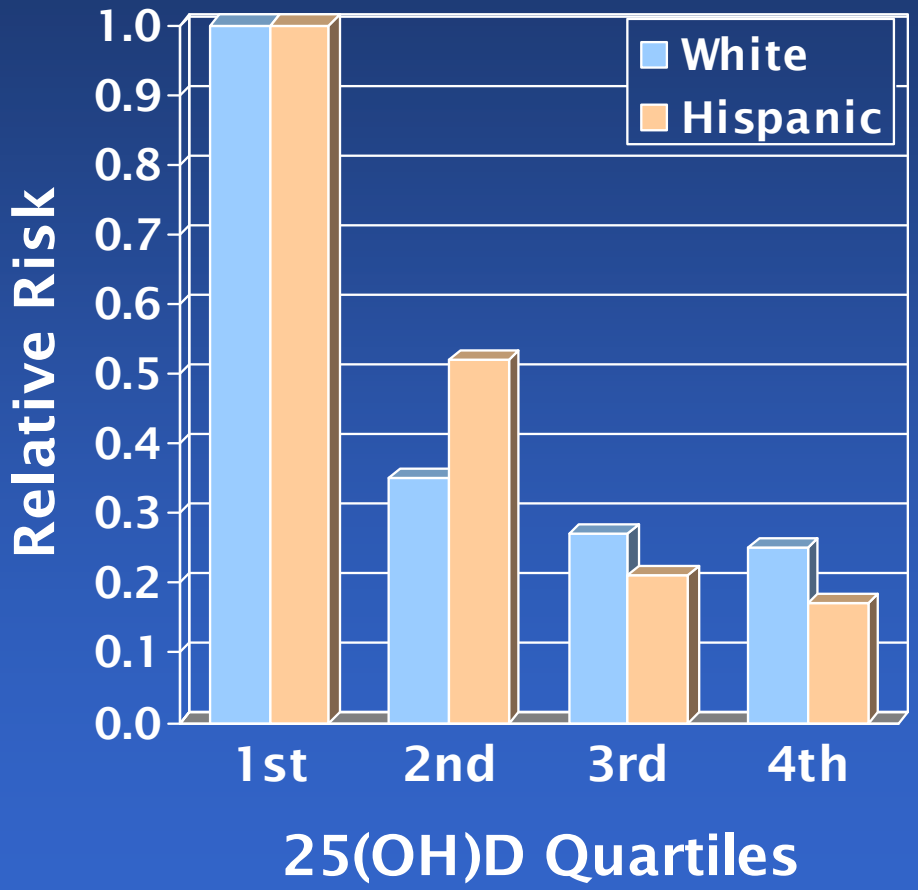
All studies, in virtually all nations, irrespective of latitude, show that the majority of the world's population has inadequate vitamin D status.

WHAT ARE THE CONSEQUENCES?

- bone diseases, falls, & fractures
- hypertension
- ↑ risk of cardiac disease & death
- prematurity, low birth weight, & ↑ Caesareans
- diabetes & metabolic syndrome
- periodontal disease
- decreased resistance to infection
- various cancers
- ↑ risk of multiple sclerosis

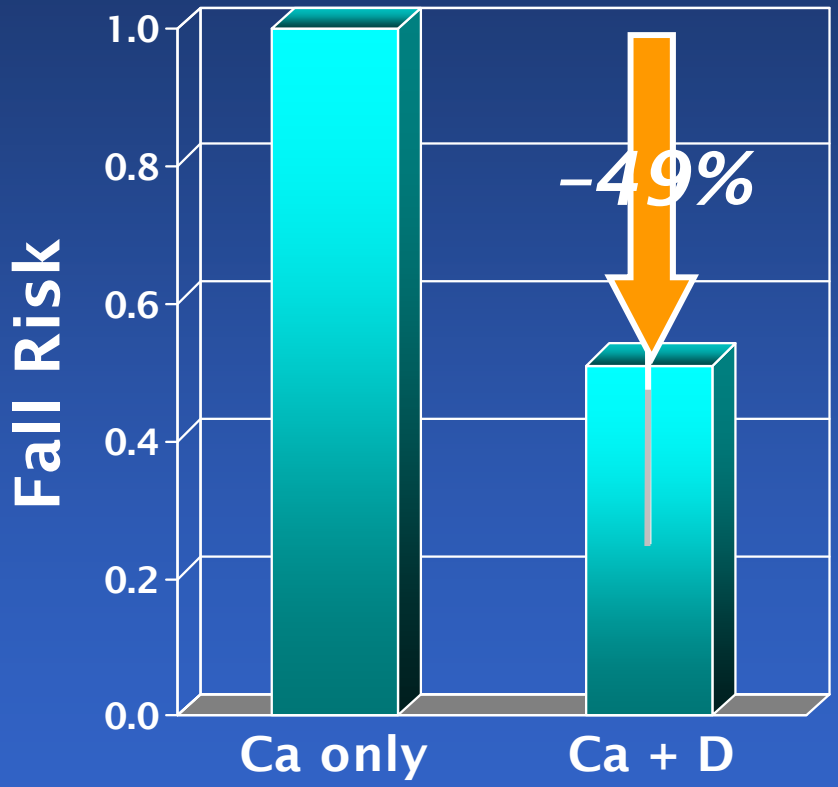
DIABETES & 25(OH)D

- Scragg et al., 2004 Diabetes Care 27:2813-18
- NHANES-III
- 6,228 adults
- plasma glucose independently predicted by BMI & serum 25OHD (fasting and 2 hr post load)



VITAMIN D & RISK OF FALLING*

- 122 women
- Age: 63–99
- DB-RCT
  - Ca 1,200 mg/d
  - Ca + 800 IU Vit D
- 12 week duration
- 25(OH)D 12 ng/mL at baseline



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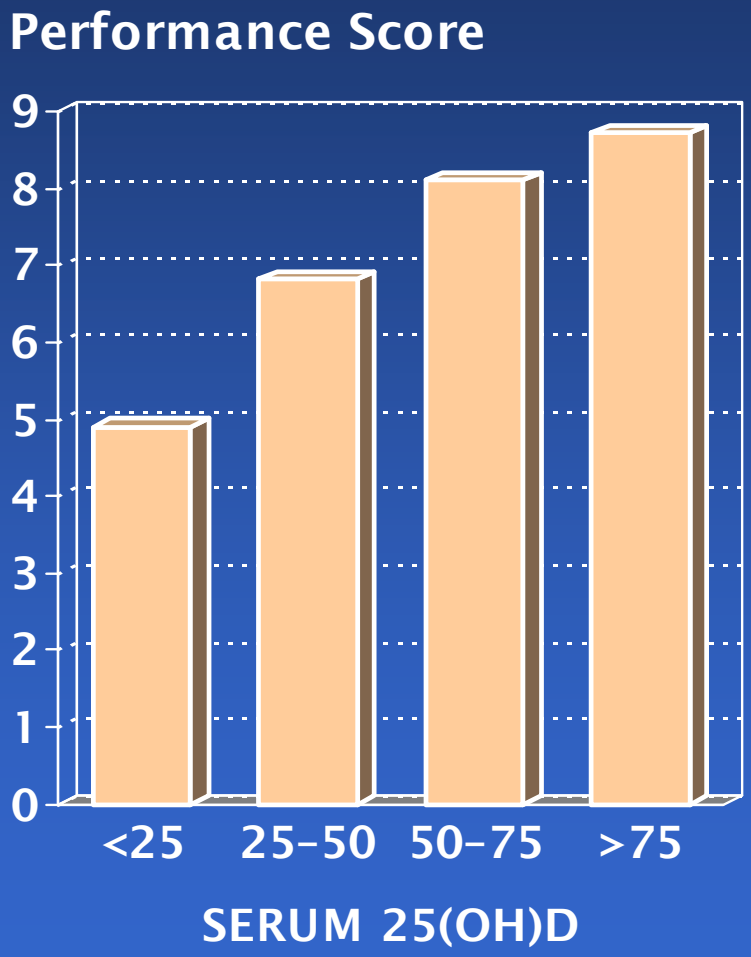
*Bischoff et al. *JBMR*. 2003;18:343–351.

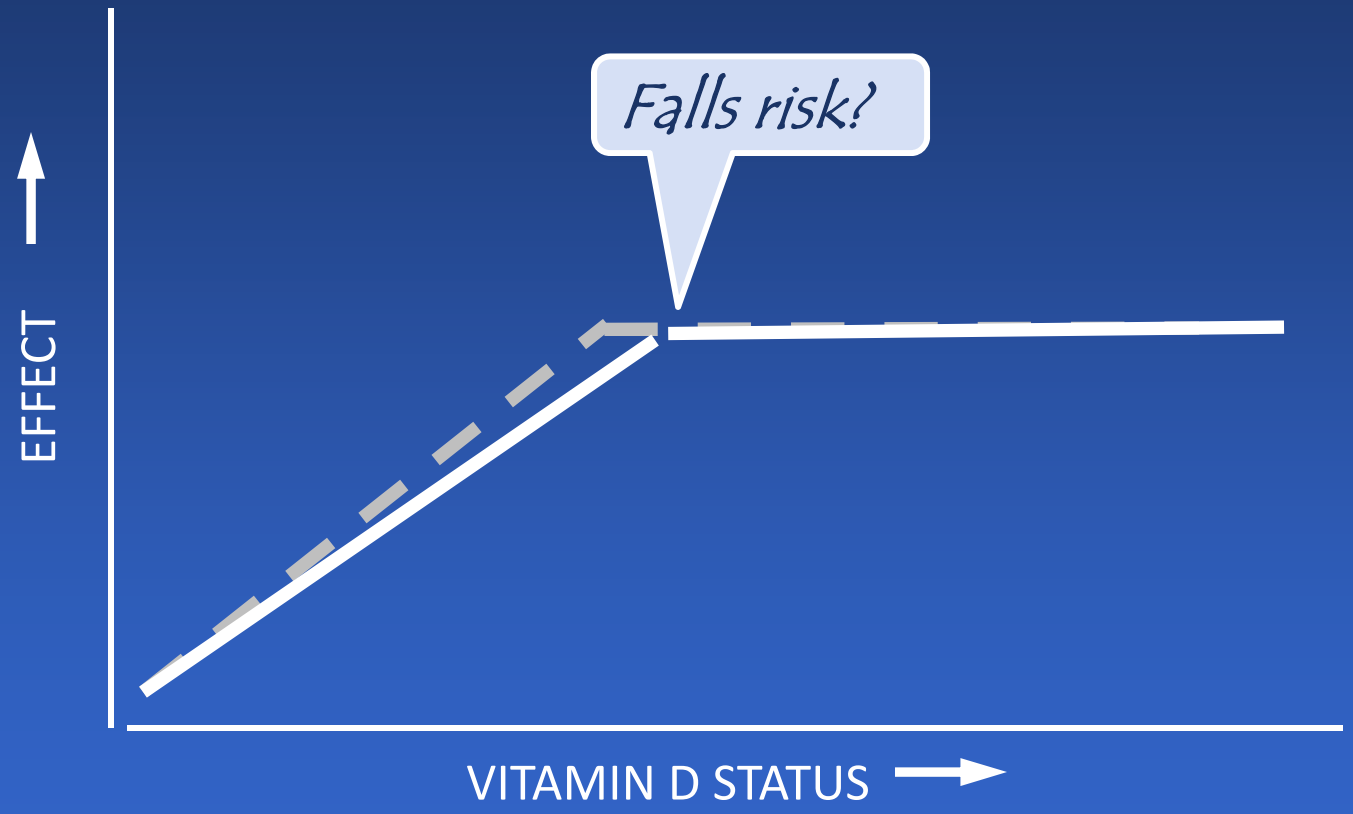
VIT D & NEUROMUSCULAR FUNCTION*

- 1359 men & women; mean age 75.5
- Amsterdam longitud. aging study
- neuromuscular performance measured on a scale of 0 to 12 (higher is better)
- each step statistically significant



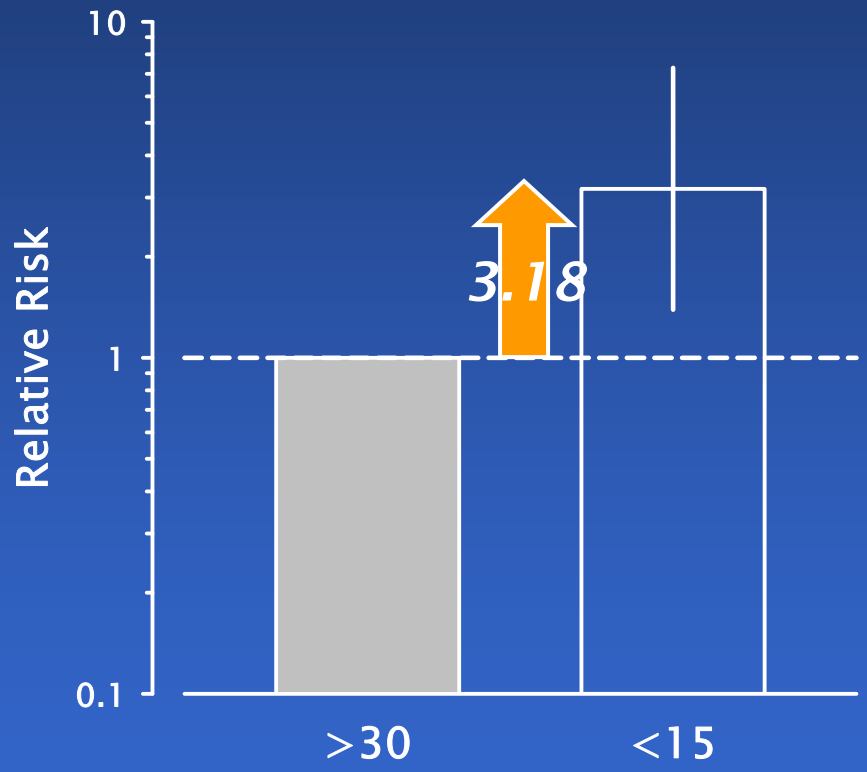
*Wicherts et al. *JBMR*. 2005.

THE RESPONSE THRESHOLD



VIT D & BLOOD PRESSURE*

- 1811 men & women with measured 25(OH)D levels**
- 4 yrs' observation
- 97 cases of incident hypertension
- RR computed for 25(OH)D <15ng/mL vs. >30 ng/mL

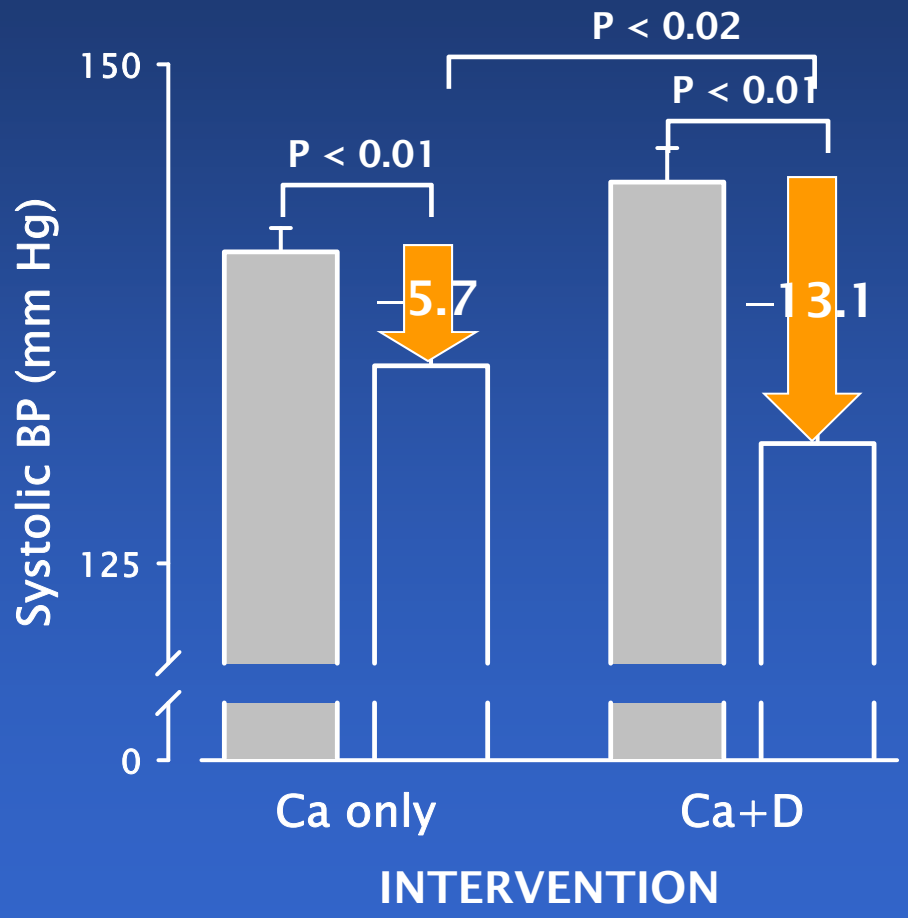


*Forman at al., 2007;Hypertension 49:1063

** Health Profs Follow-up Study & Nurses Health Study

VIT D & BLOOD PRESSURE*

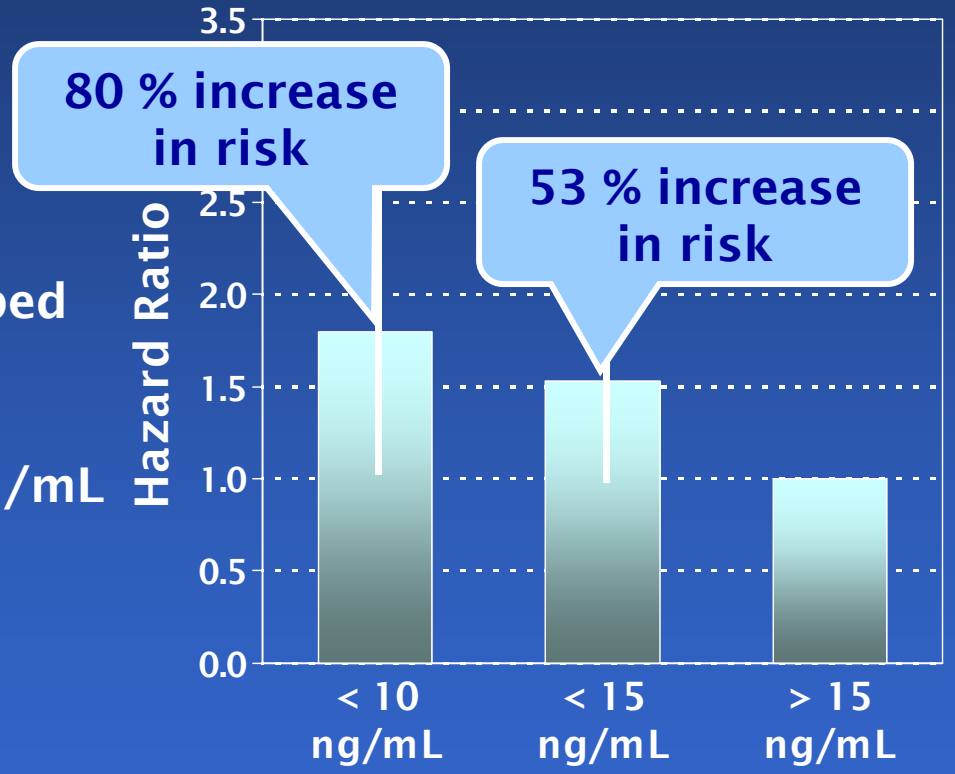
- 148 women, aged 74 ± 1
- DB-RCT
- baseline 25(OH)D < 50 nmol/L
- treated for 8 wks with:
  Ca 1200 mg/d or
  Ca + 800 IU vit D/d



*Pfeifer et al., JCEM 2001; 86:1633–37

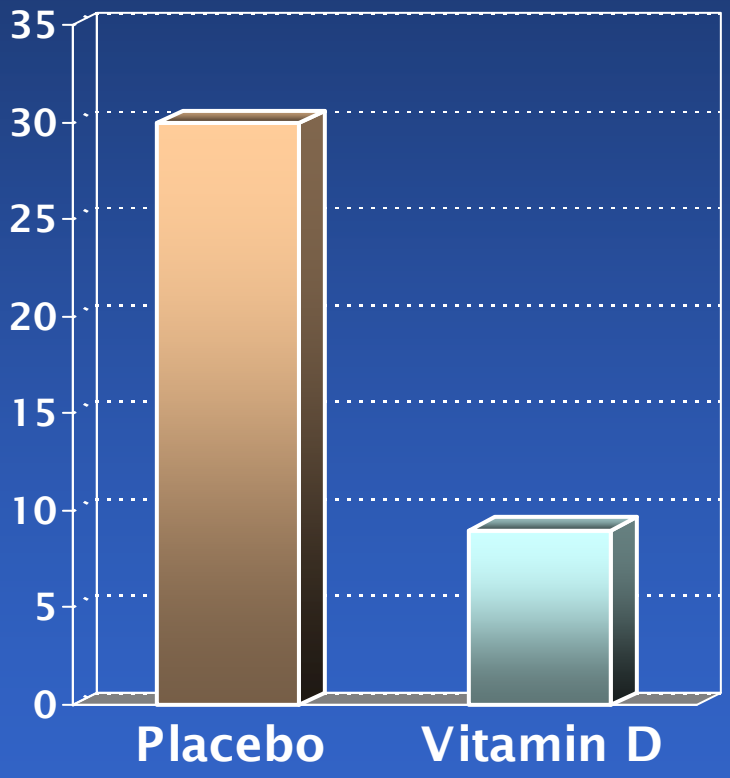
VIT D & CARDIOVASCULAR DISEASE

- 1739 Framingham Offspring members
- age: 59 yrs
- follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL
- *Wang et al. Circulation 2008*



VITAMIN D & INFLUENZA*

- 208 African-American, postmenopausal women
- 3 yr DB-RCT
- placebo or vit D_3
  - 800 IU/d – 2 yrs
  - 2000 IU/d – 3rd yr
- basal 25(OH)D: 18.8 ± 7.5
- P < 0.002

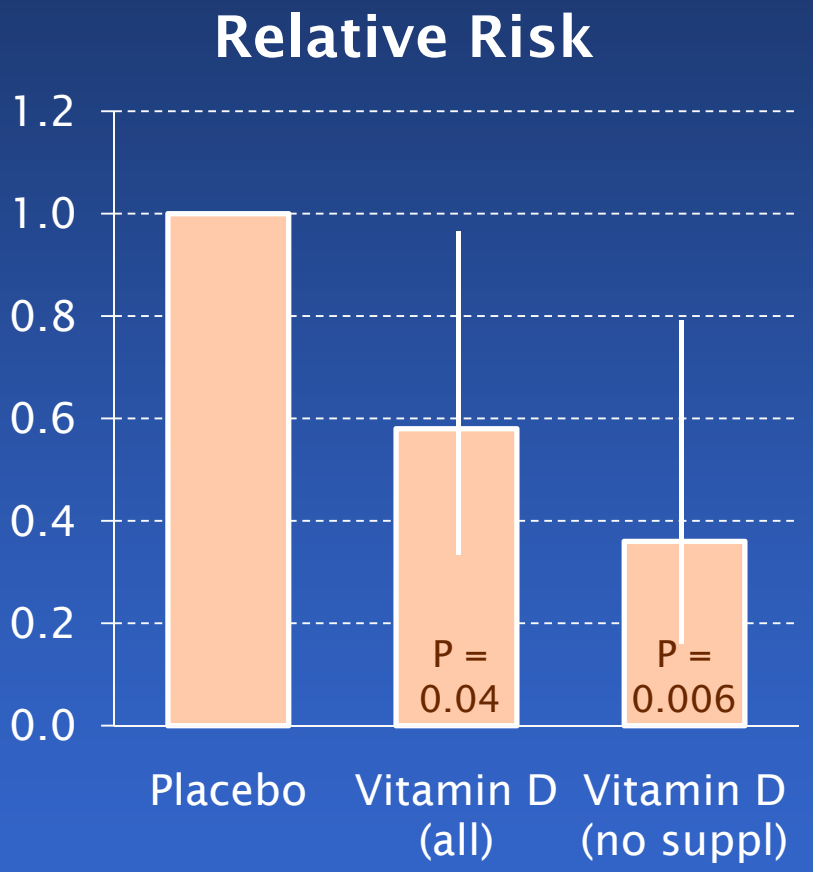


CU ORC

*Aloia & U-Ng (2007) Epidemiol & Infect

VITAMIN D & INFLUENZA*

- DB-RCT
- winter 2008–2009
- 334 Japanese school children, aged 6–15
- mean wt: 35.5 kg
- 1200 IU D_3/d in addition to self-supplementation



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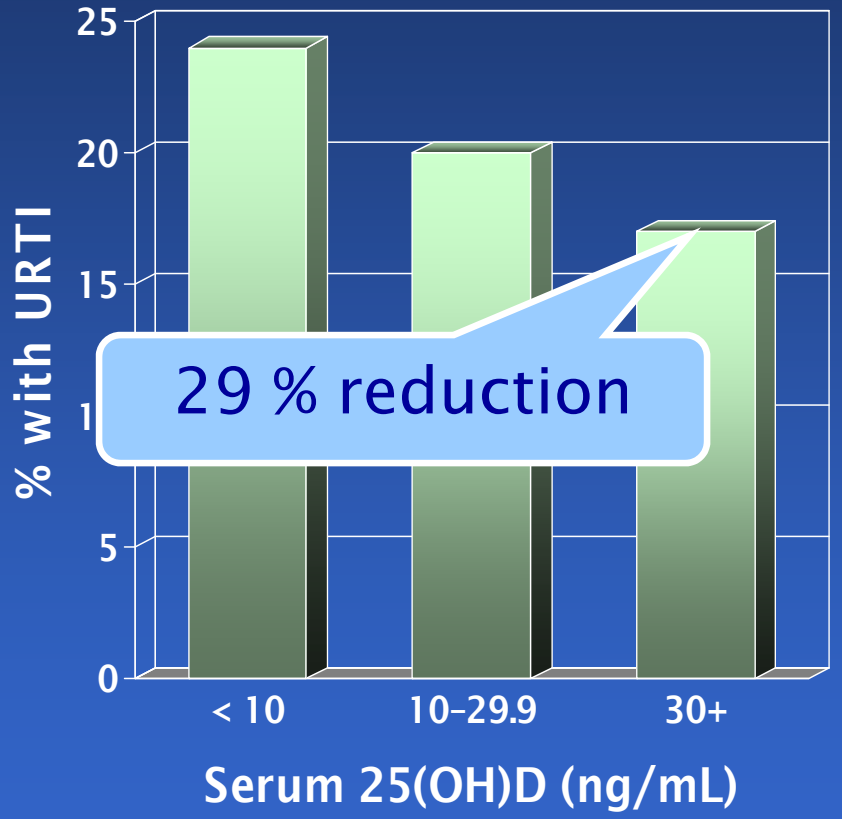
*Urashima et al., AJCN 2010

VITAMIN D & THE COMMON COLD*

- 18,883 individuals in NHANES-III
- tested association between serum 25(OH)D & recent URTI
- P < 0.001
- association stronger for those with asthma & COPD

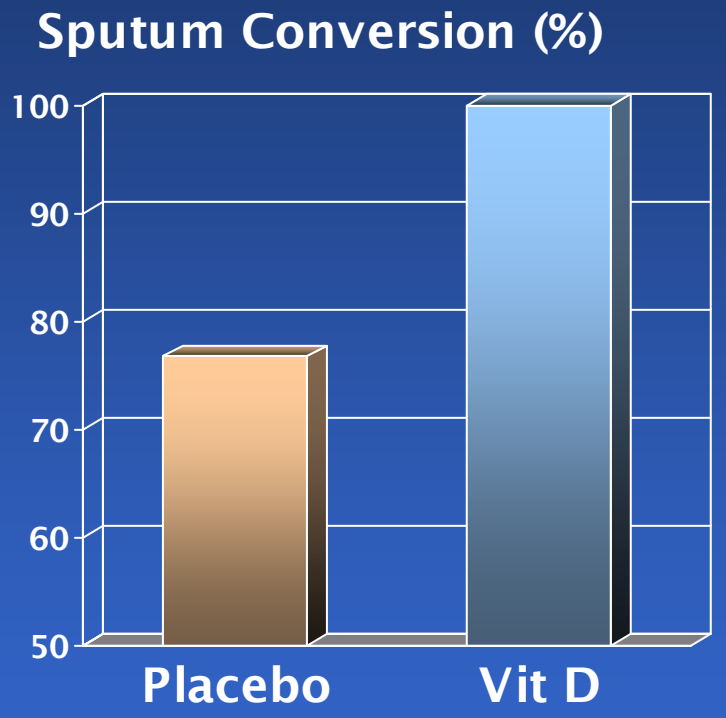


CU ORC

Ginde et al., Arch Int Med 2009 169:

VITAMIN D & TUBERCULOSIS*

- 67 pts with pulmonary TB
- standard treatment for all
- in addition, randomized to either vit D 10,000 IU/d or placebo
- P = 0.002



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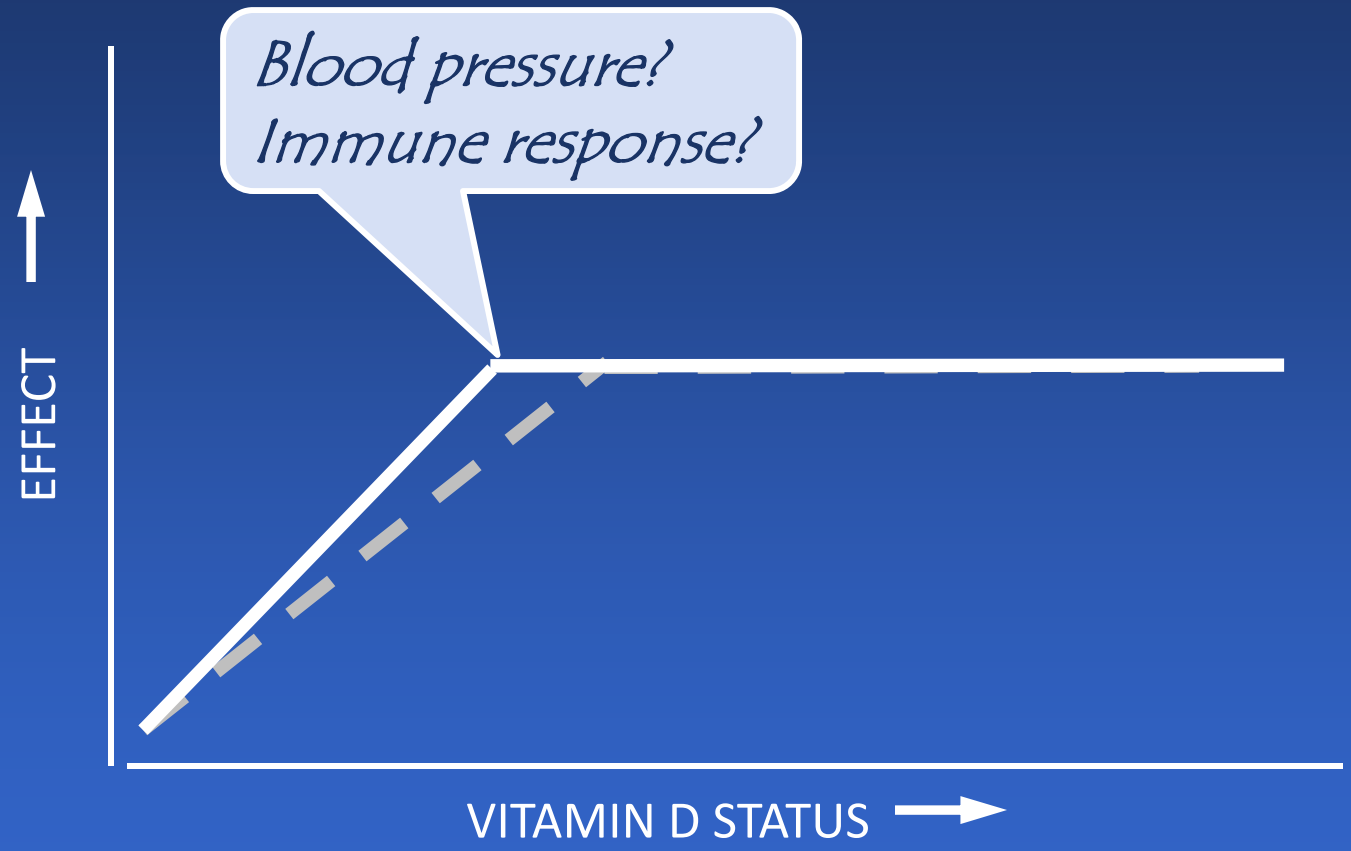
*Nursyam et al., Acta Med Indones 2006


things go
better
with
Vitamin D

THE RESPONSE THRESHOLD

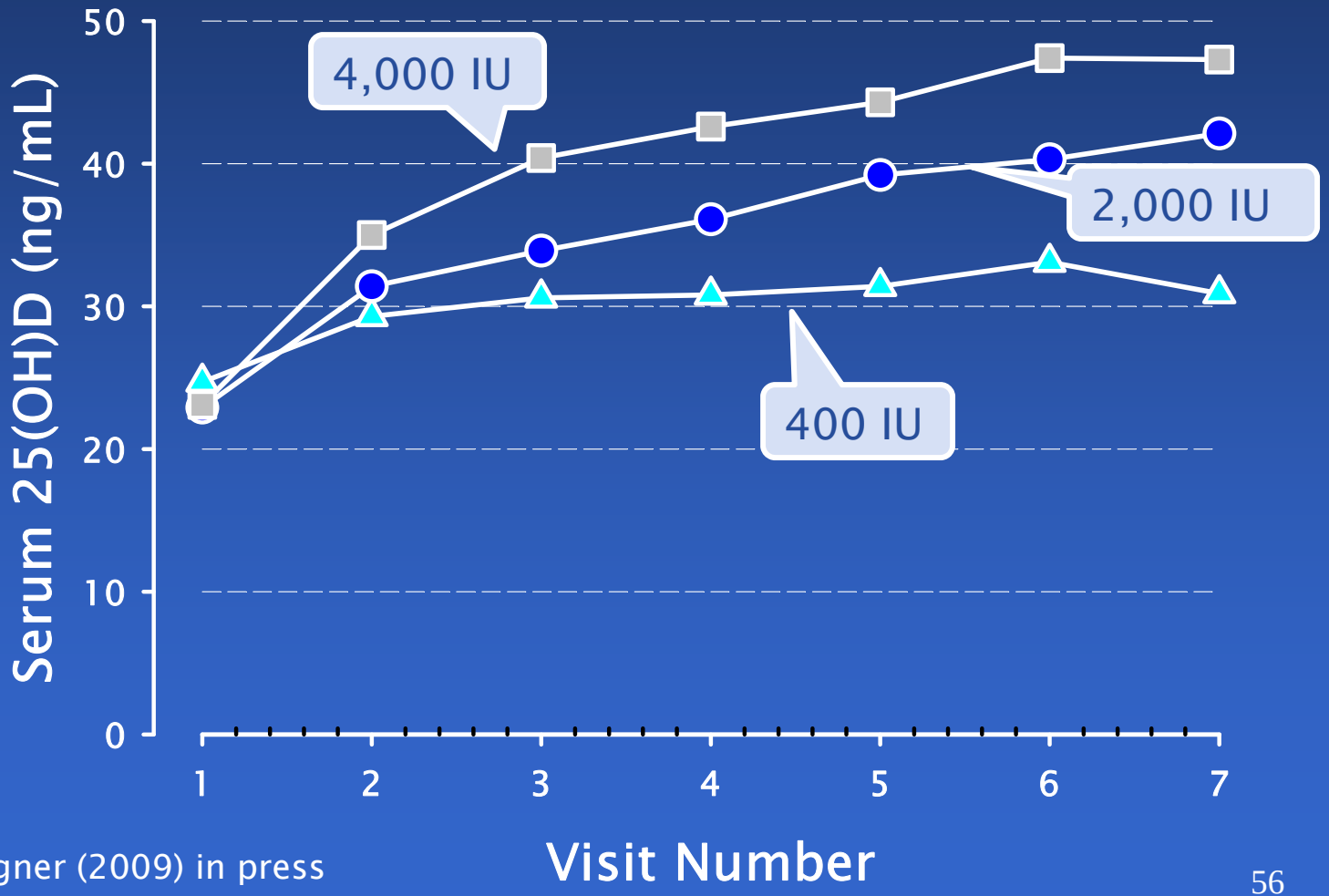


VIT D & PREGNANCY OUTCOMES*

- DB-RCT; N = 690 pregnant women
- dosed with 400, 2000, & 4000 IU/d from wk 12 to delivery

*Hollis & Wagner (2009) in press

VIT D & PREGNANCY OUTCOMES*



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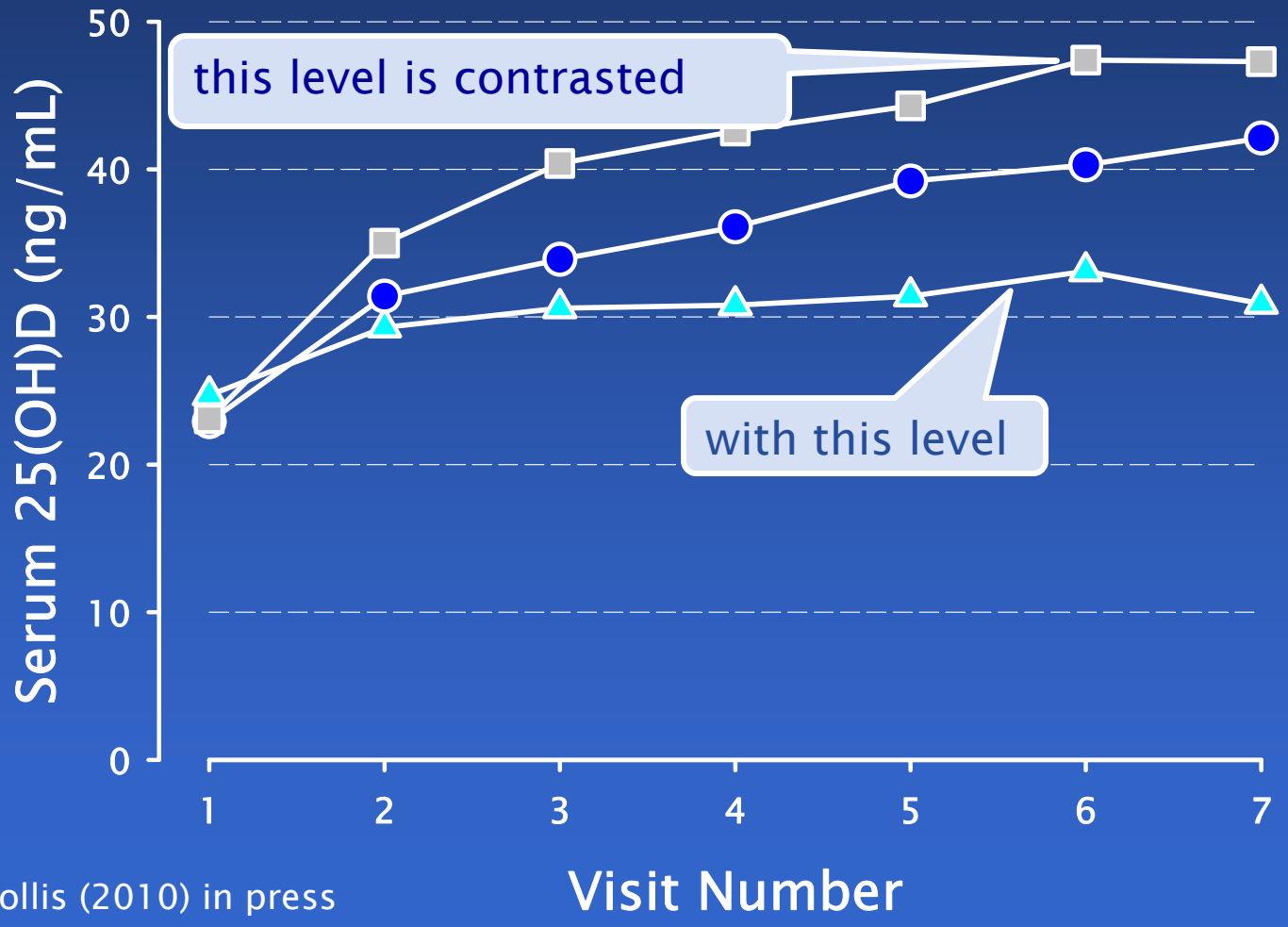


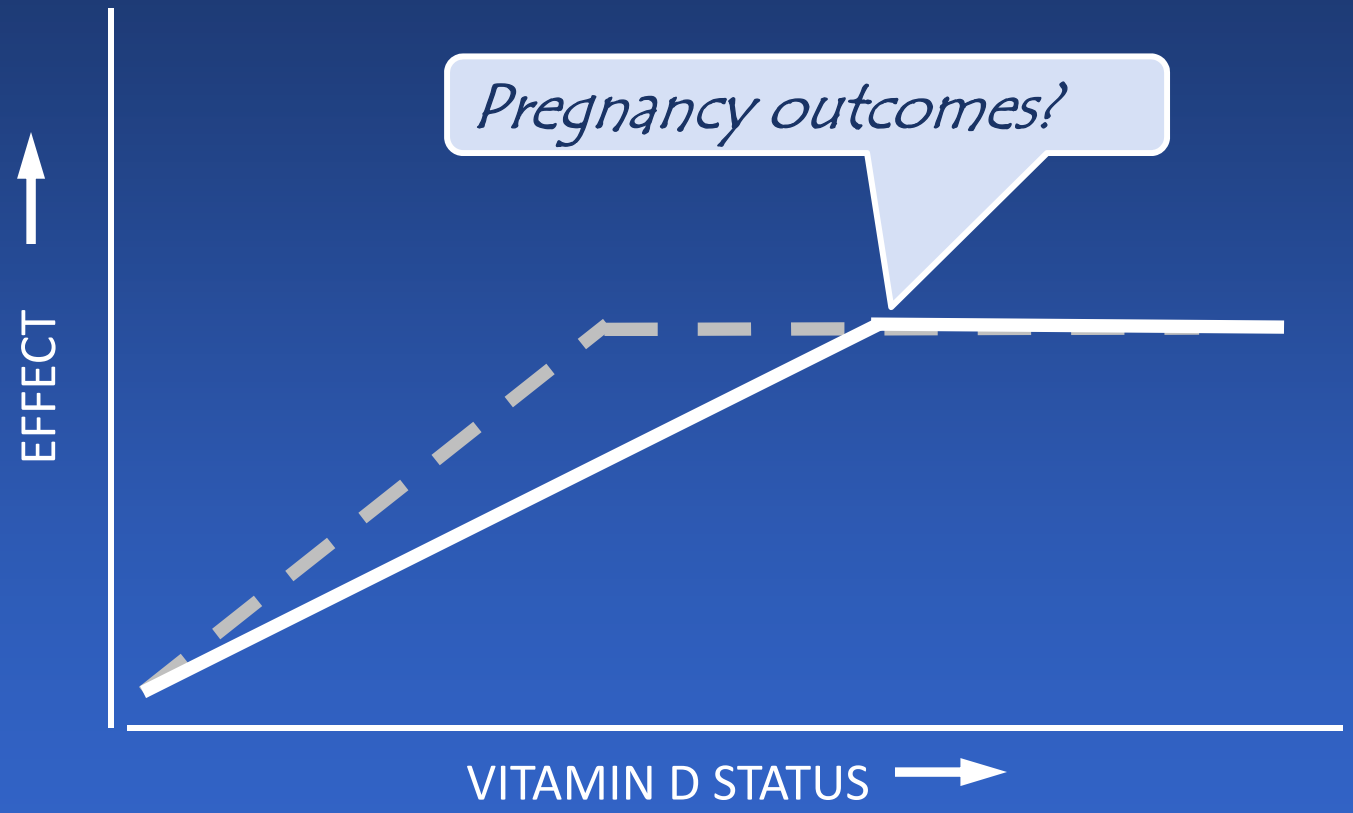
*Wagner & Hollis (2010) in press

VIT D & PREGNANCY OUTCOMES*

- DB-RCT; N = 690 pregnant women
- dosed with 400, 2000, & 4000 IU/d from wk 12 to delivery
- risk of untoward outcomes reduced by half:
  - pre-term delivery (P < 0.01)
  - gestational diabetes, pre-eclampsia, hypertension (P < 0.01)
  - periodontal disease (P < 0.05)
  - neonatal infection (P < 0.05)

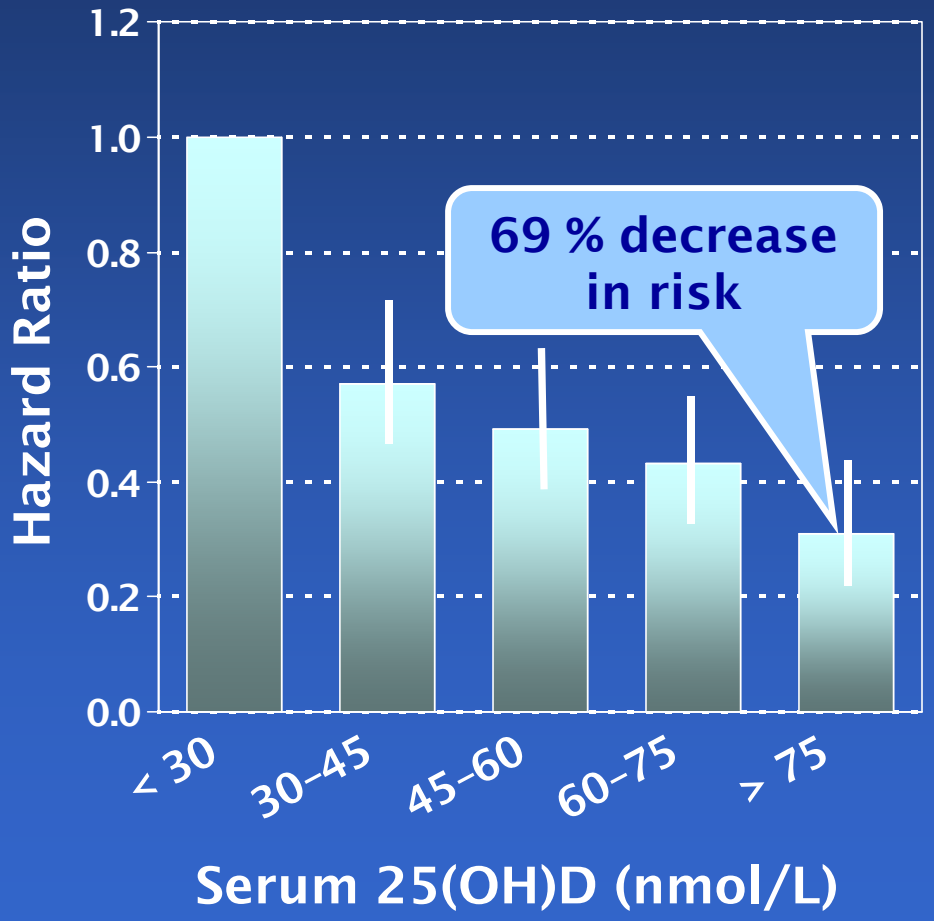
*Wagner & Hollis (2010) in press

THE RESPONSE THRESHOLD



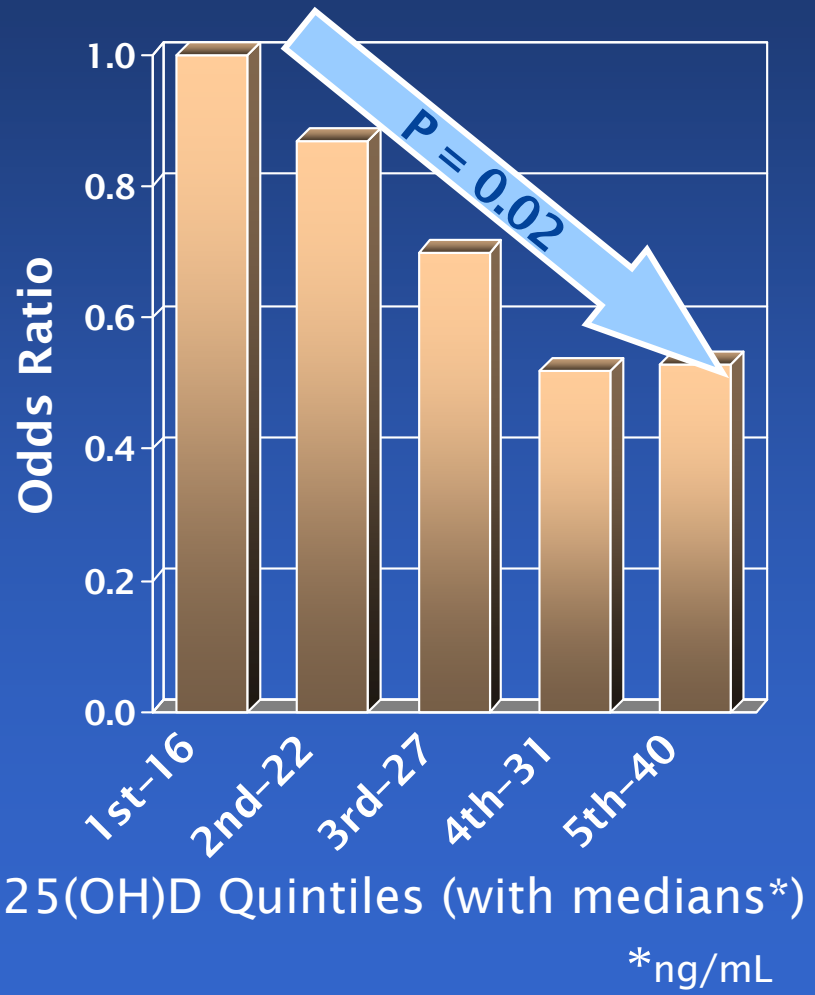
BREAST CANCER RISK

- Case-control study
  - 1394 cases
  - 1365 controls
- Odds ratio for CA inversely associated with vit D status [25(OH)D]
- *Abbas et al., Carcinogenesis (2008) 29:93–99*



COLORECTAL CANCER

- Nurses' Health Study
- ages 46–78
- nested case-control study
- 193 incident cases
- 25(OH)D measured twice, prior to diagnosis
- Feskanich et al., Cancer Epidemiol Biomarkers Prev 2004 13:1502–08



VITAMIN D & CANCER*

- 1179 healthy women
- aged 66.7 ± 7.3
- four year trial
- 1032 finished (87.5%)
- baseline 25(OH)D: 28 ng/mL ± 8
- three treatment groups:
  - control
  - Ca (1400–1500 mg/d)
  - Ca plus D_3 (1100 IU/d)
- achieved 25(OH)D: 38 ng/mL ± 9

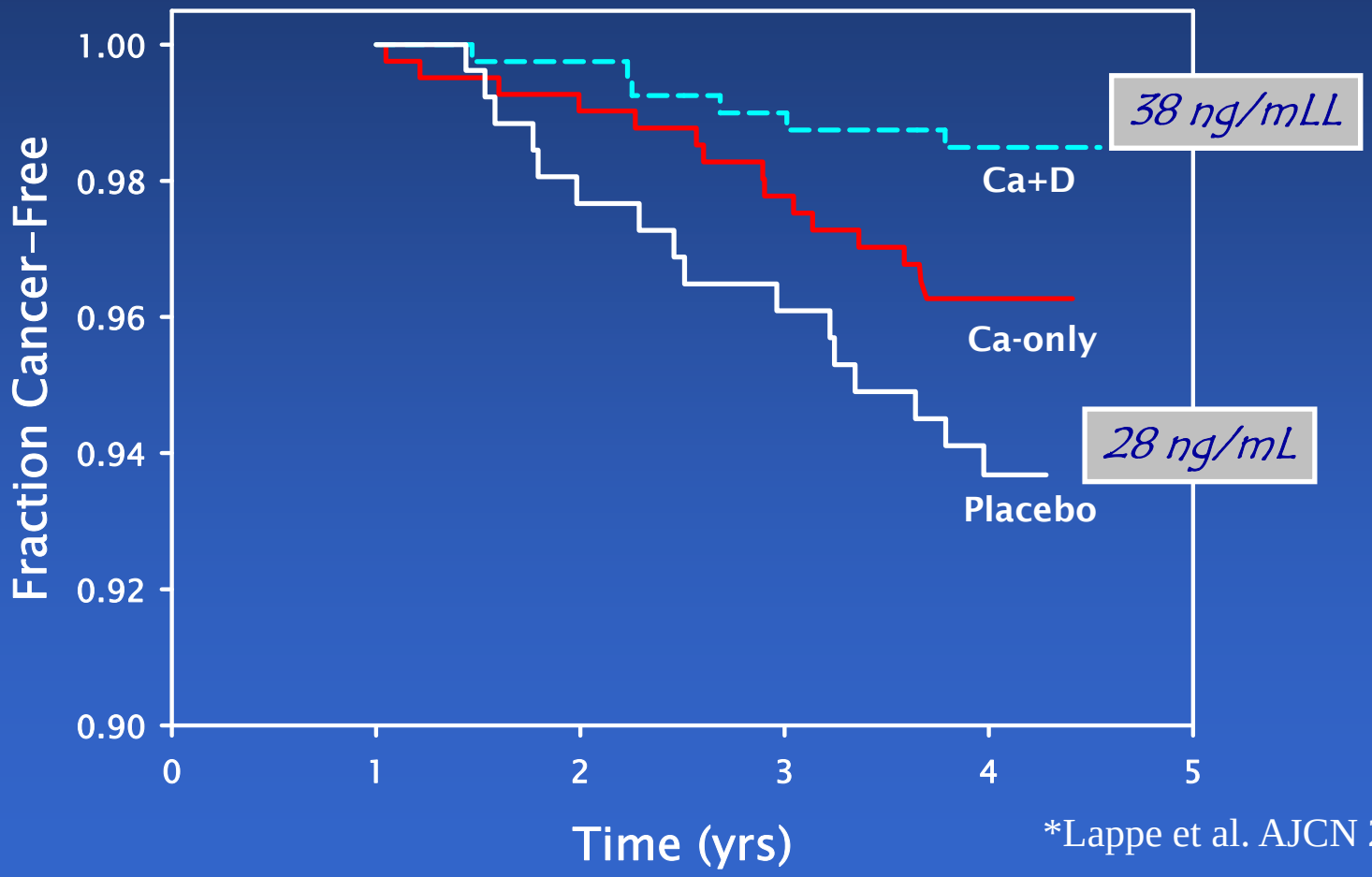
*Lappe et al. AJCN 2007

CANCERS BY TREATMENT (YRS 2–4)

Site	Placebo (n=266)	Ca+D (n = 403)
Breast	7 (2.6%)	4 (1.0%)
Colon	2 (0.7%)	0 (0.0%)
Lung	3 (1.1%)	1 (0.2%)
Marrow/Lymphoma	4 (1.5%)	2(0.5%)
Other	2 (0.7%)	1 (0.2%)
Total	18 (6.8%)	8 (2.0%)*

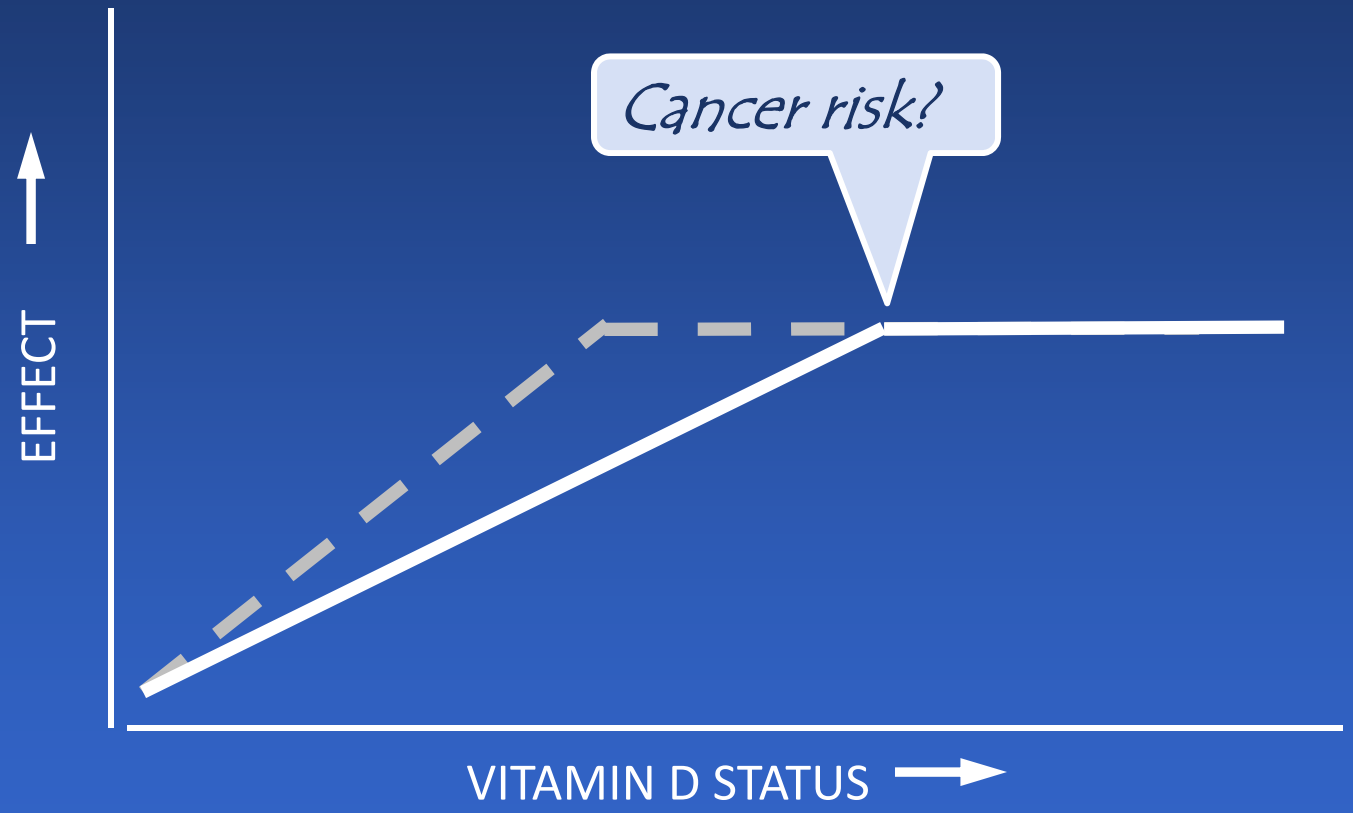
* $P < 0.05$

VITAMIN D & CANCER*

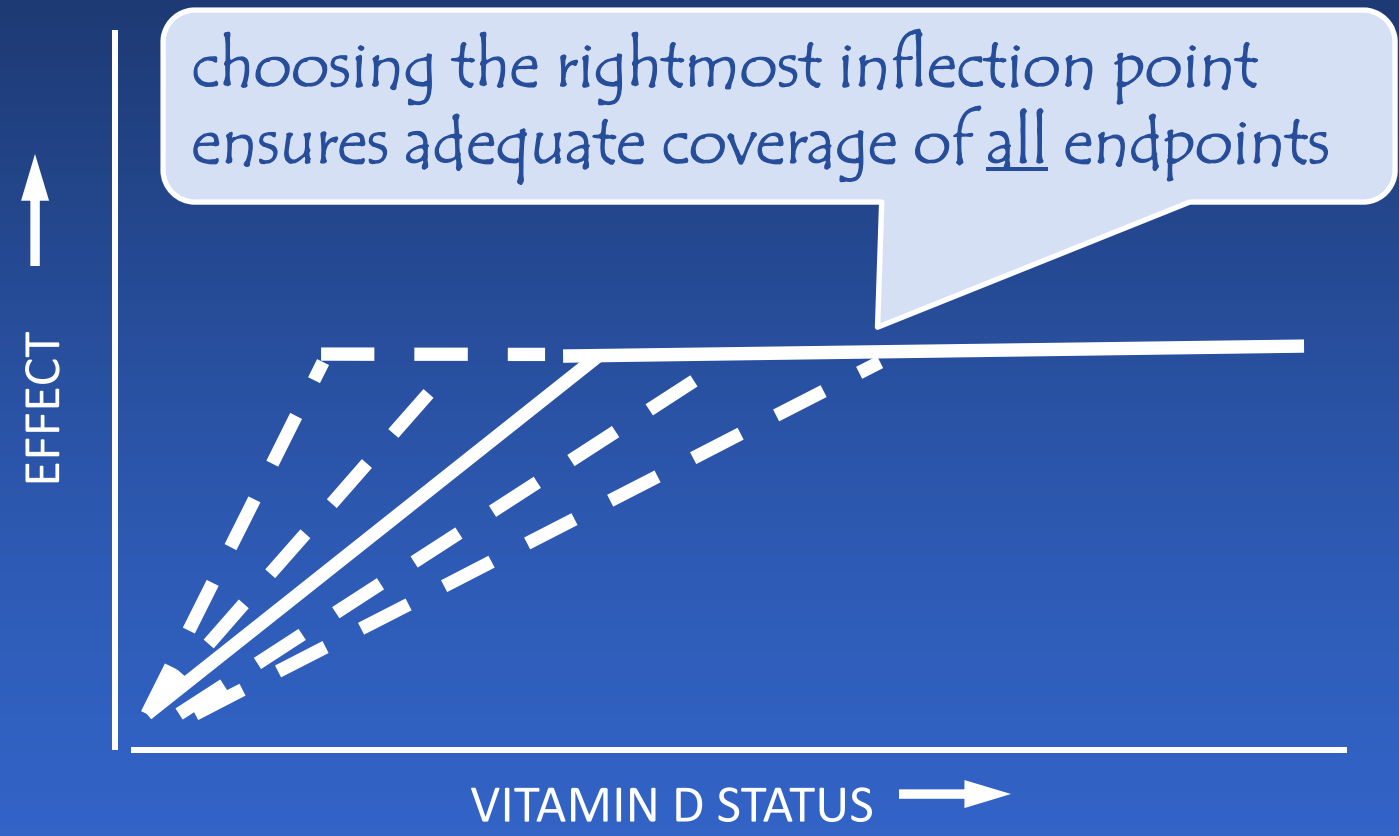


*Lappe et al. AJCN 2007

THE RESPONSE THRESHOLD



THE RESPONSE THRESHOLD



How is it that a single nutrient could have such diverse effects in such a wide range of tissues & systems?

VIT D – CANONICAL SCHEME

skin liver kidney gut

- the functional indicator of vit D status
- a principal storage form of the vitamin

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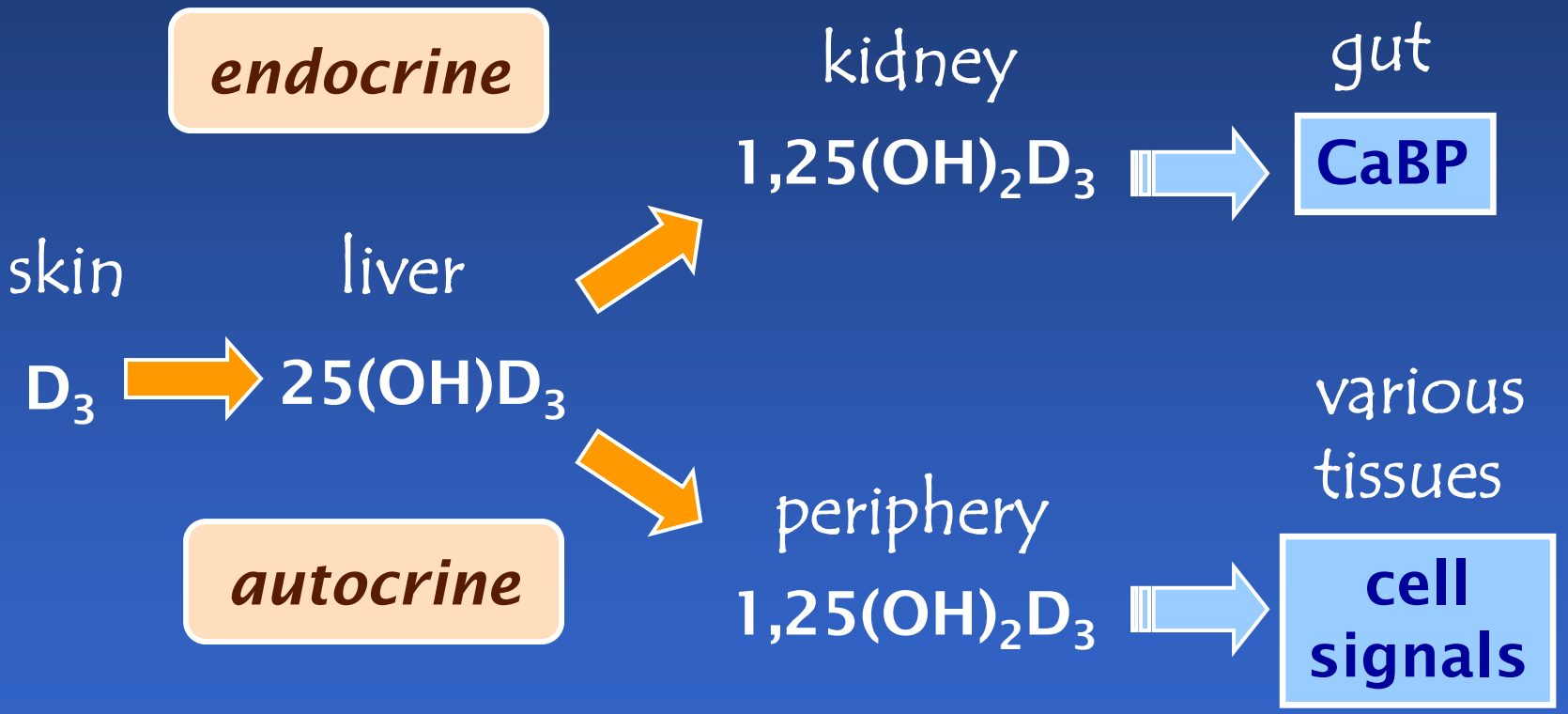
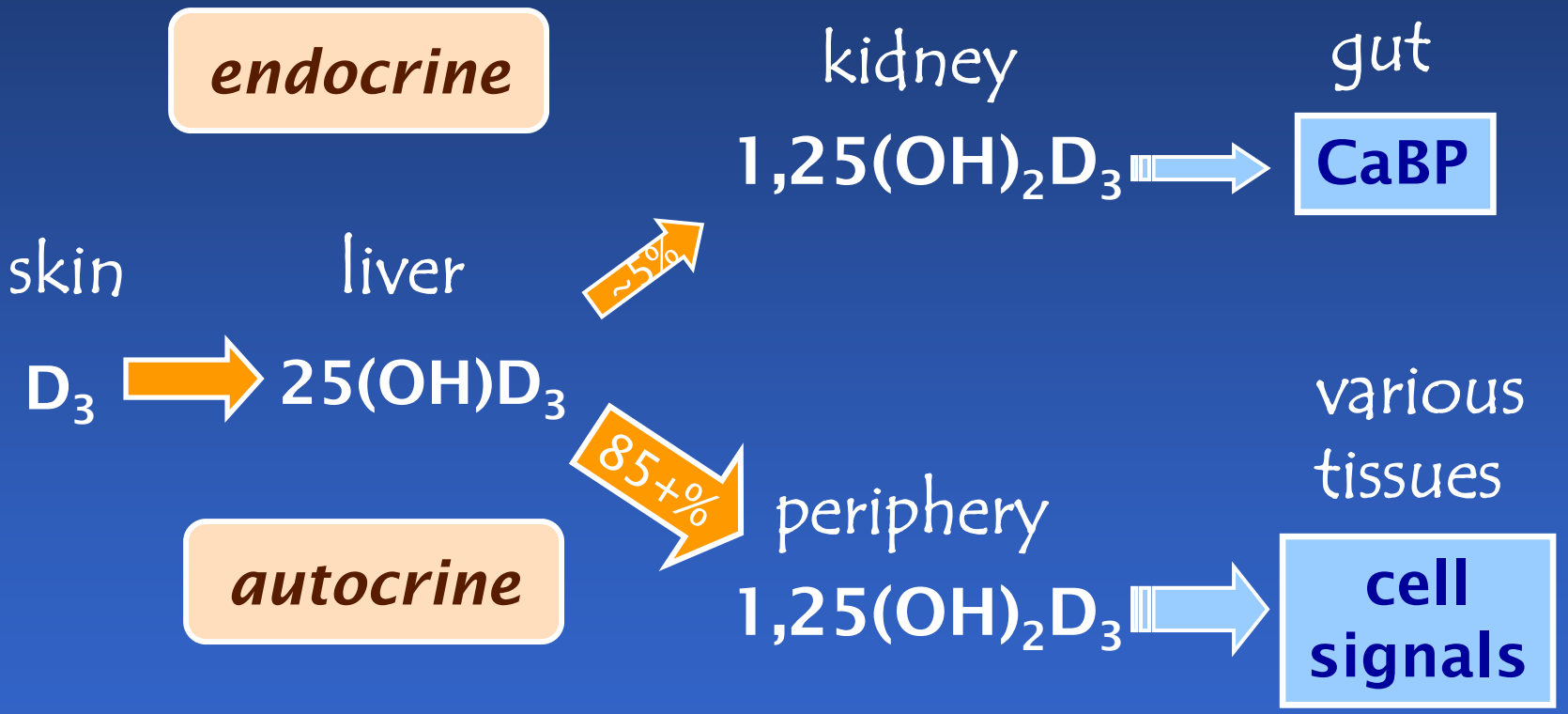
OLD
VIT D – ΛCANONICAL SCHEME

skin liver kidney gut

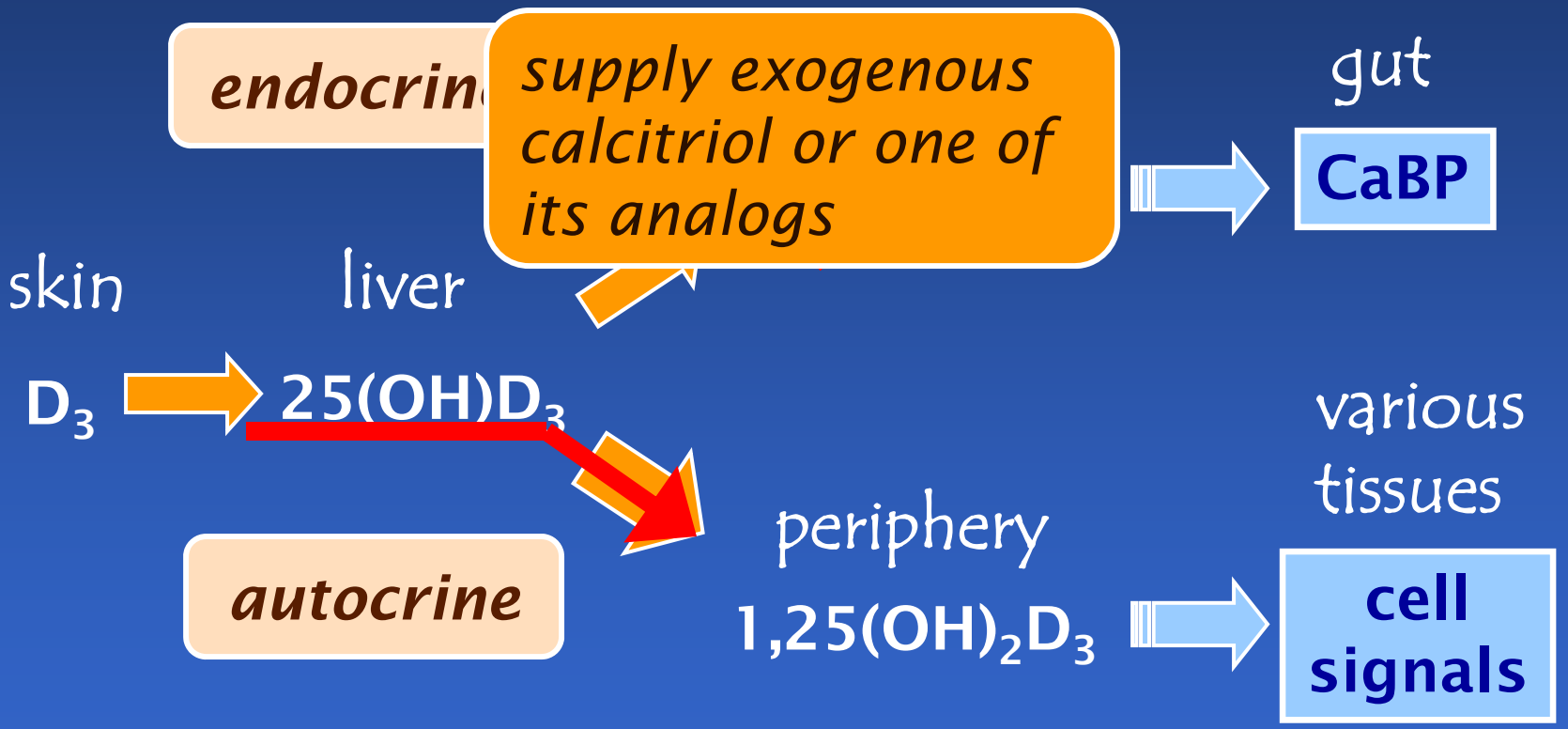
VIT D – EXPANDED SCHEME



VIT D – EXPANDED SCHEME



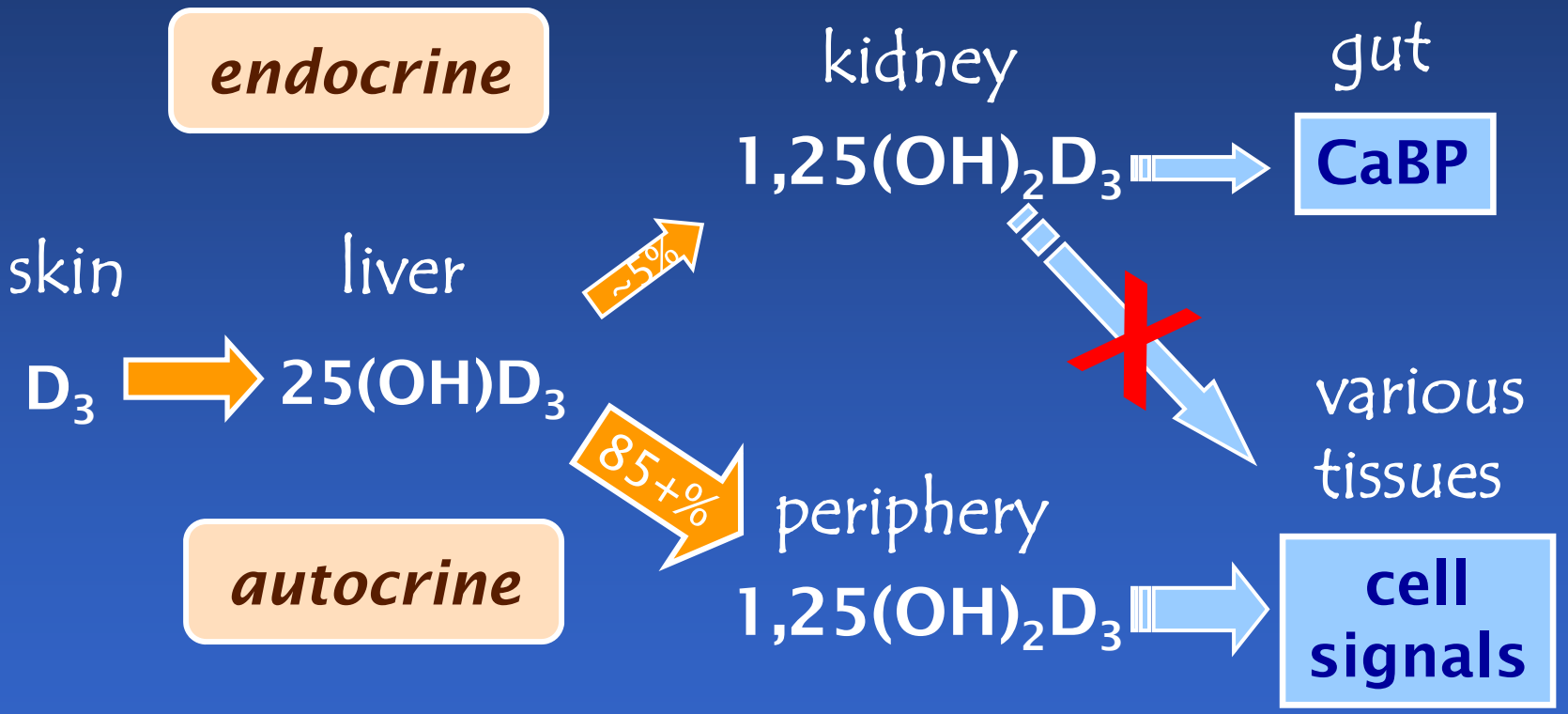
VIT D – EXPANDED SCHEME



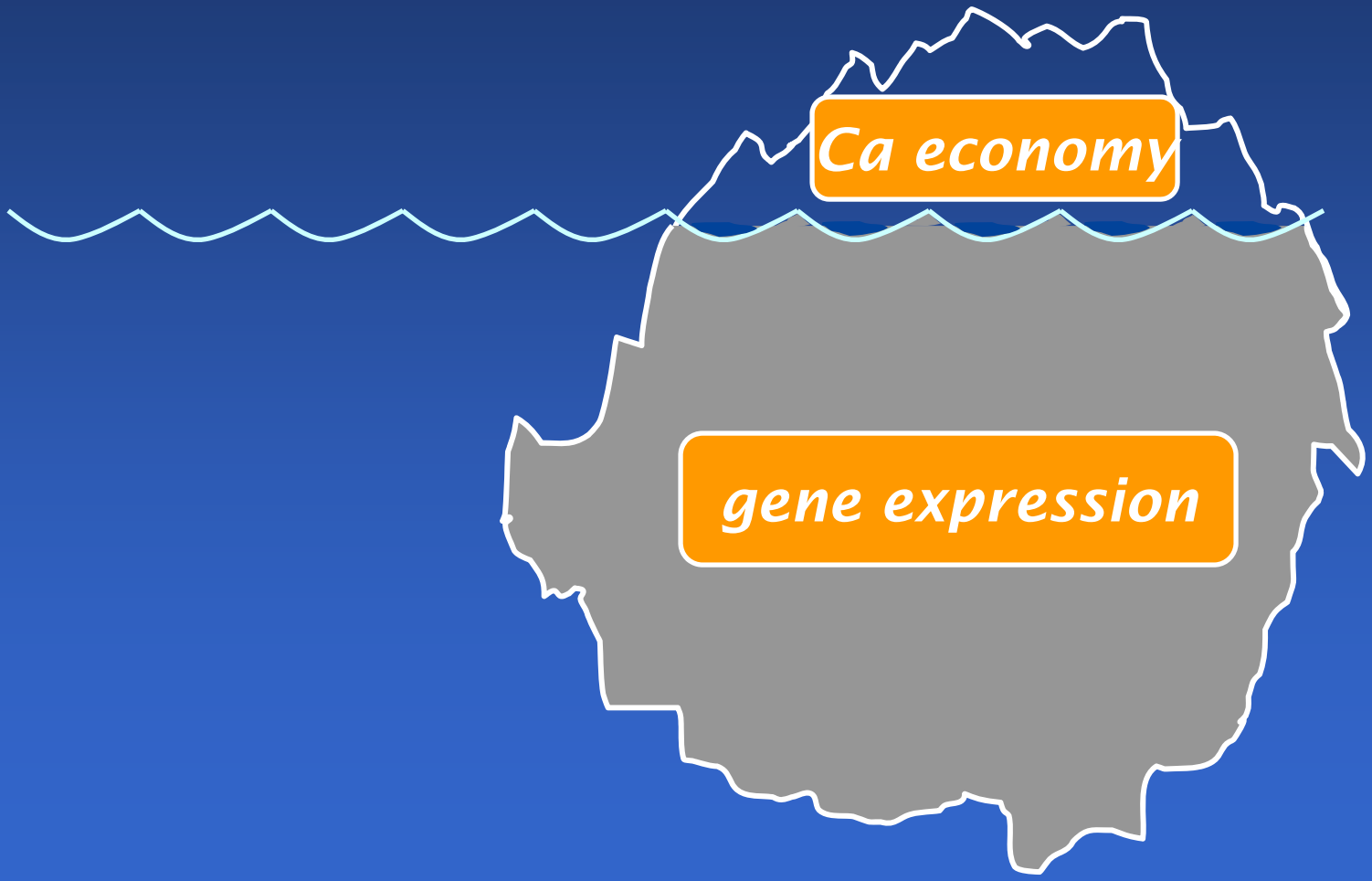
Won't calcitriol meet the body's need for vitamin D?

NO!

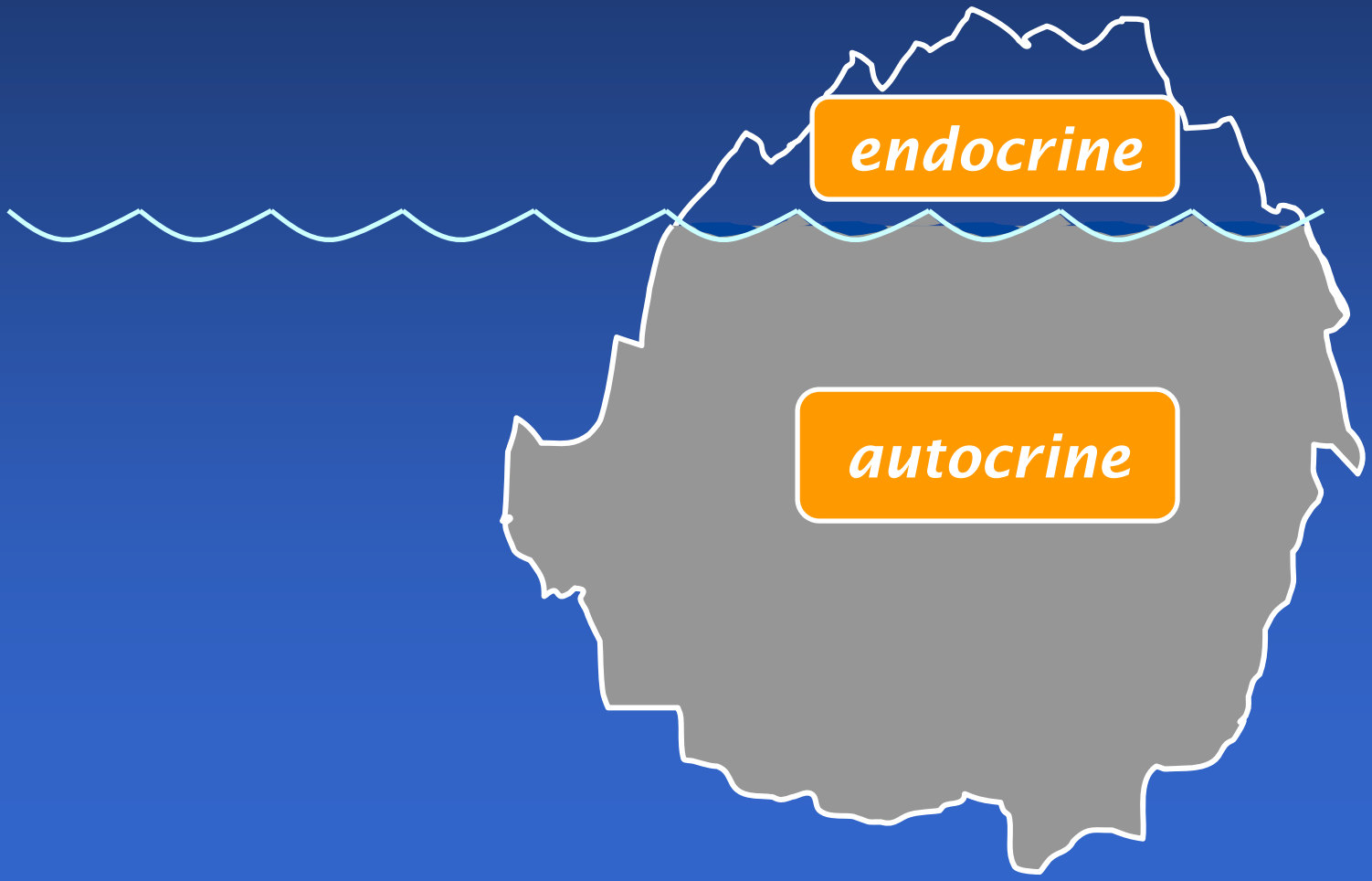
VIT D – EXPANDED SCHEME



THE VITAMIN D ICEBERG

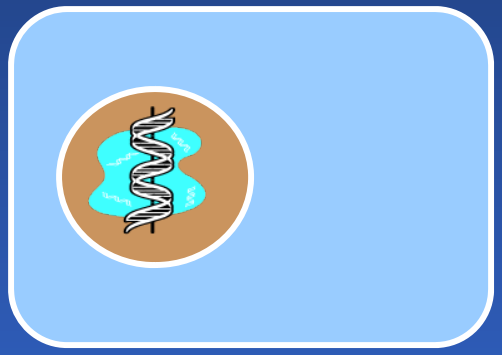


THE VITAMIN D ICEBERG



CELL MODELS

old:



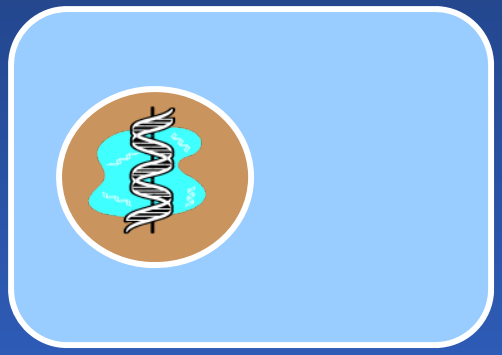
DNA in somatic cells functions mainly to make faithful copies for tissue repair or replacement

new:

DNA functions constantly in synthesis of needed cellular apparatus

CELL MODELS

old:

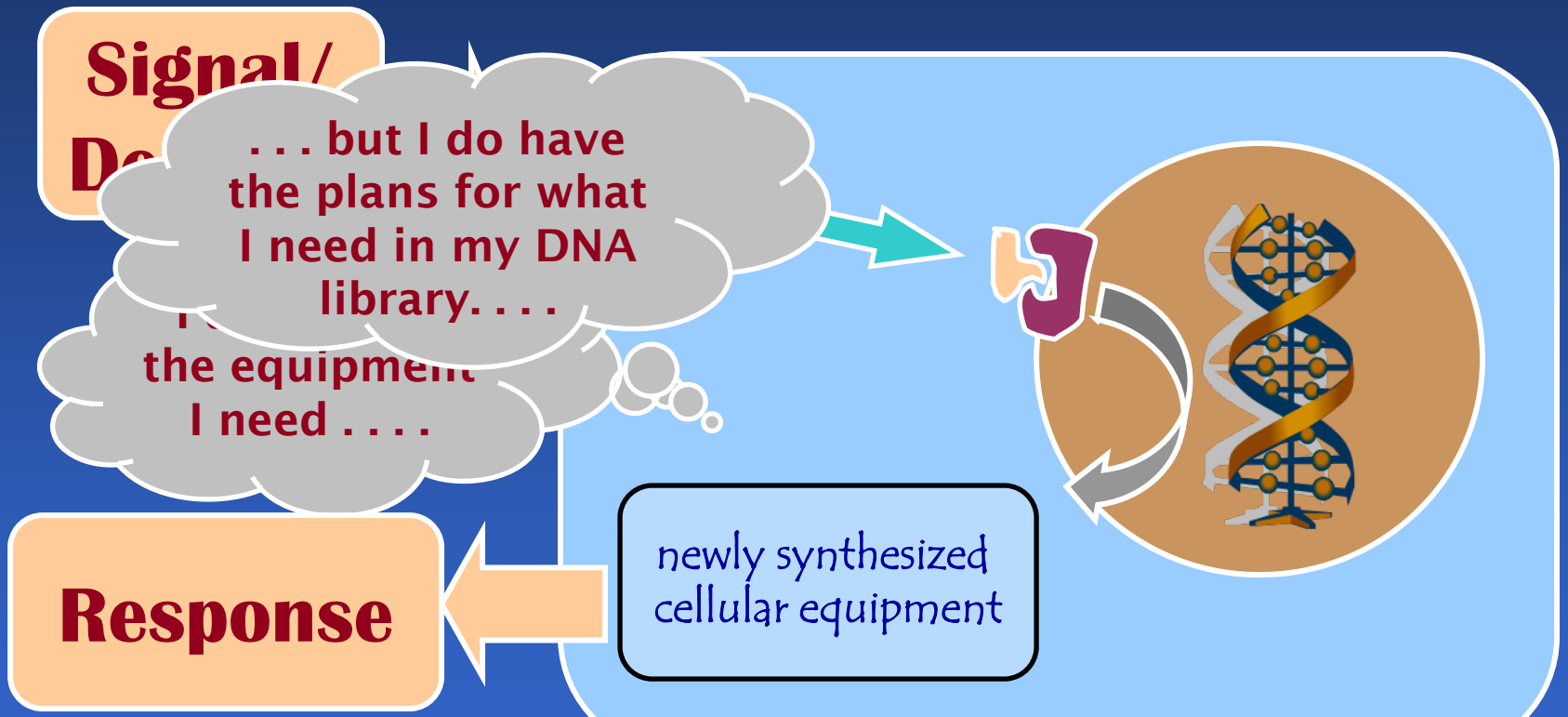


cell/tissue differentiation meant that each cell type contained different cytoplasmic apparatus

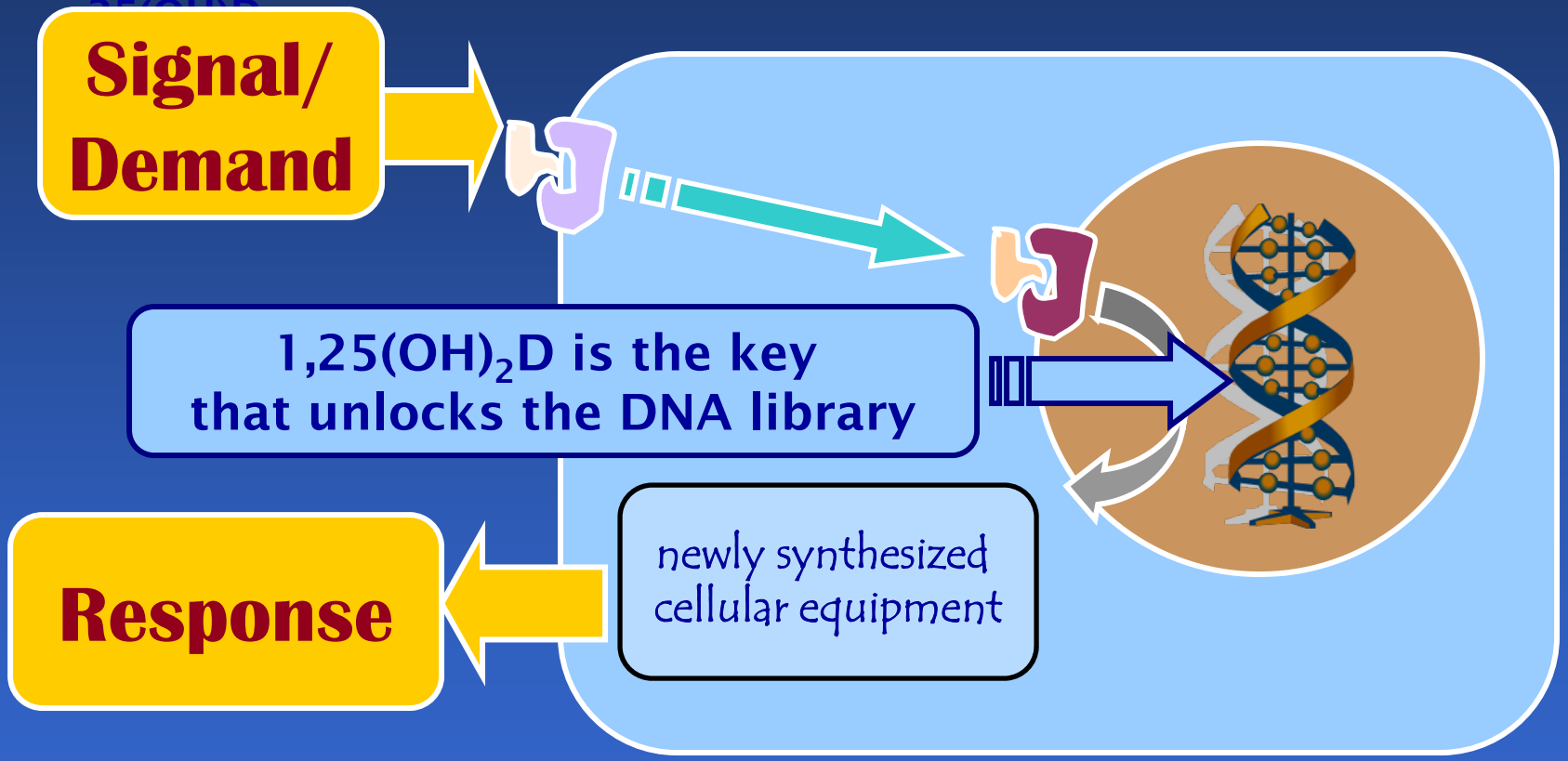
new:

cell/tissue differentiation meant that only certain genes can be accessed in each tissue

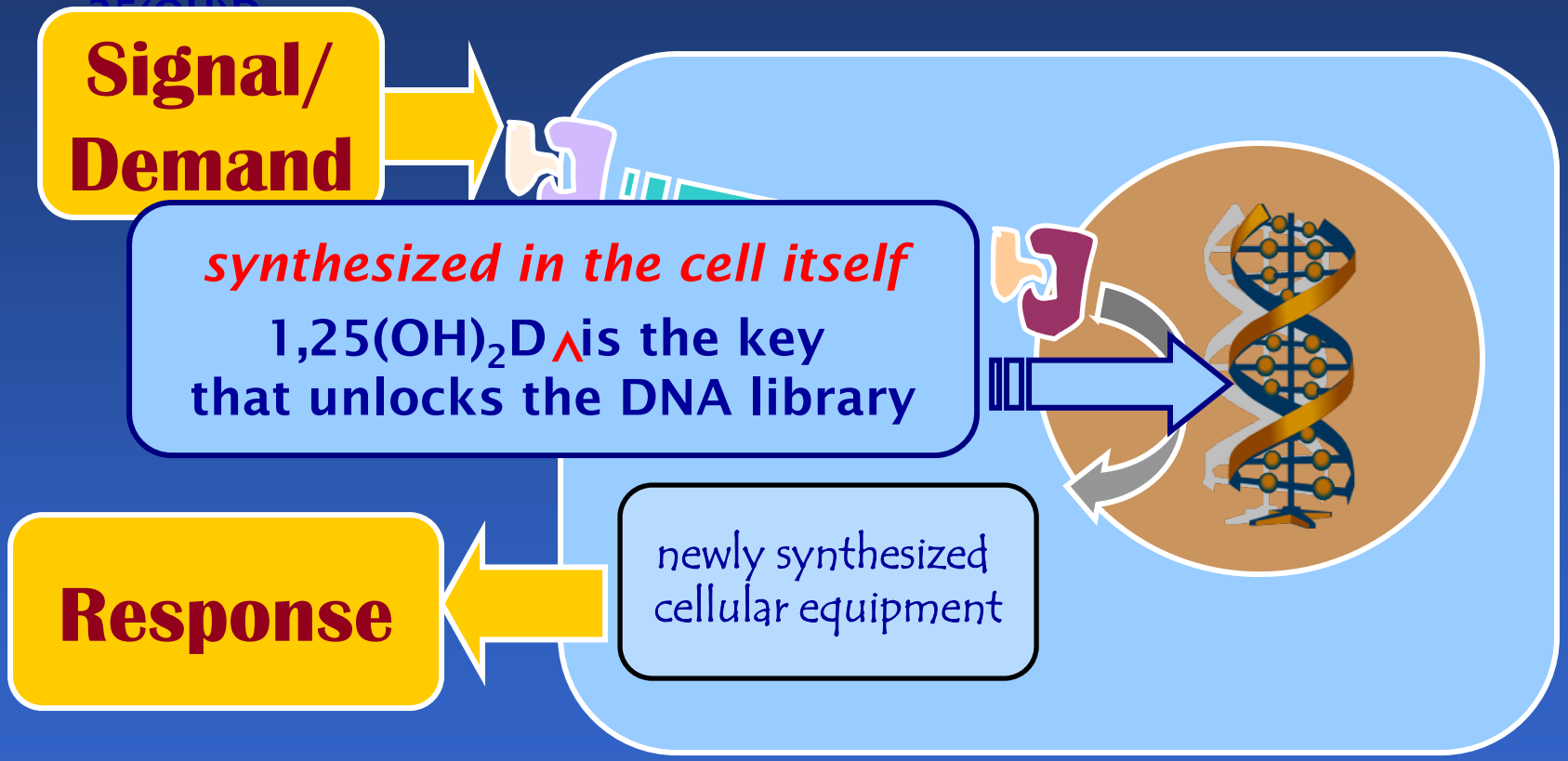
HOW A CELL RESPONDS



HOW A CELL RESPONDS

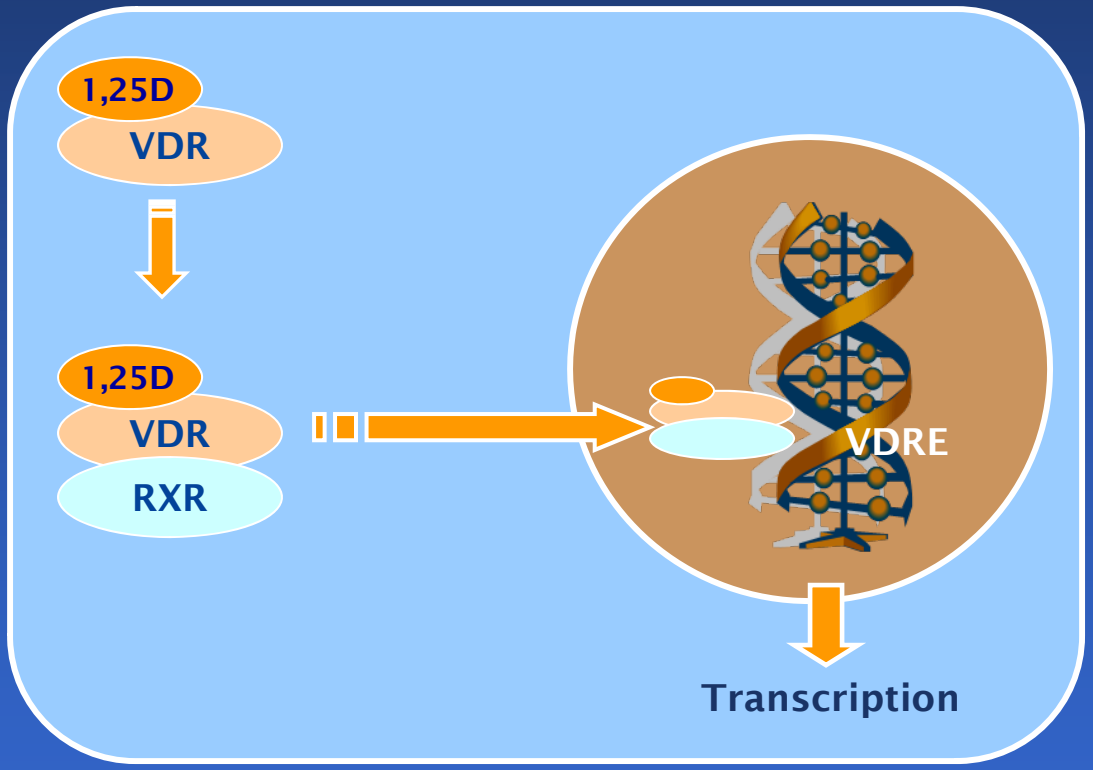


HOW A CELL RESPONDS



AUTOCRINE ACTION

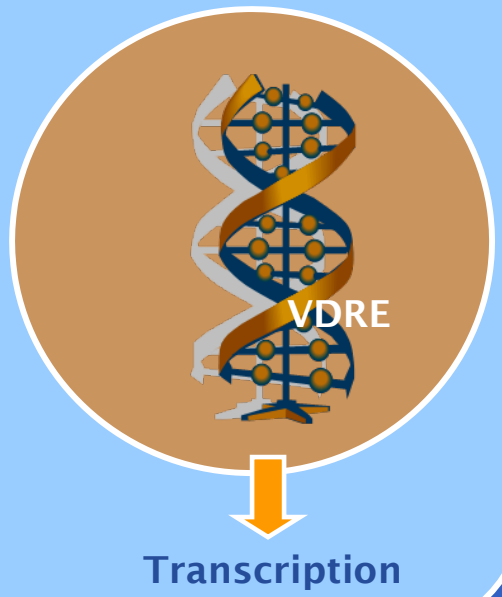
25(OH)D



AUTOCRINE ACTION

25(OH)D

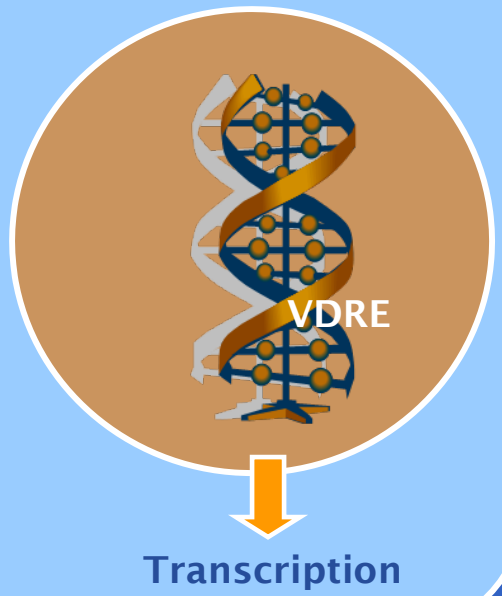
- cell proliferation
- cell differentiation
- apoptosis
- immune response
- 24-hydroxylase



AUTOCRINE ACTION

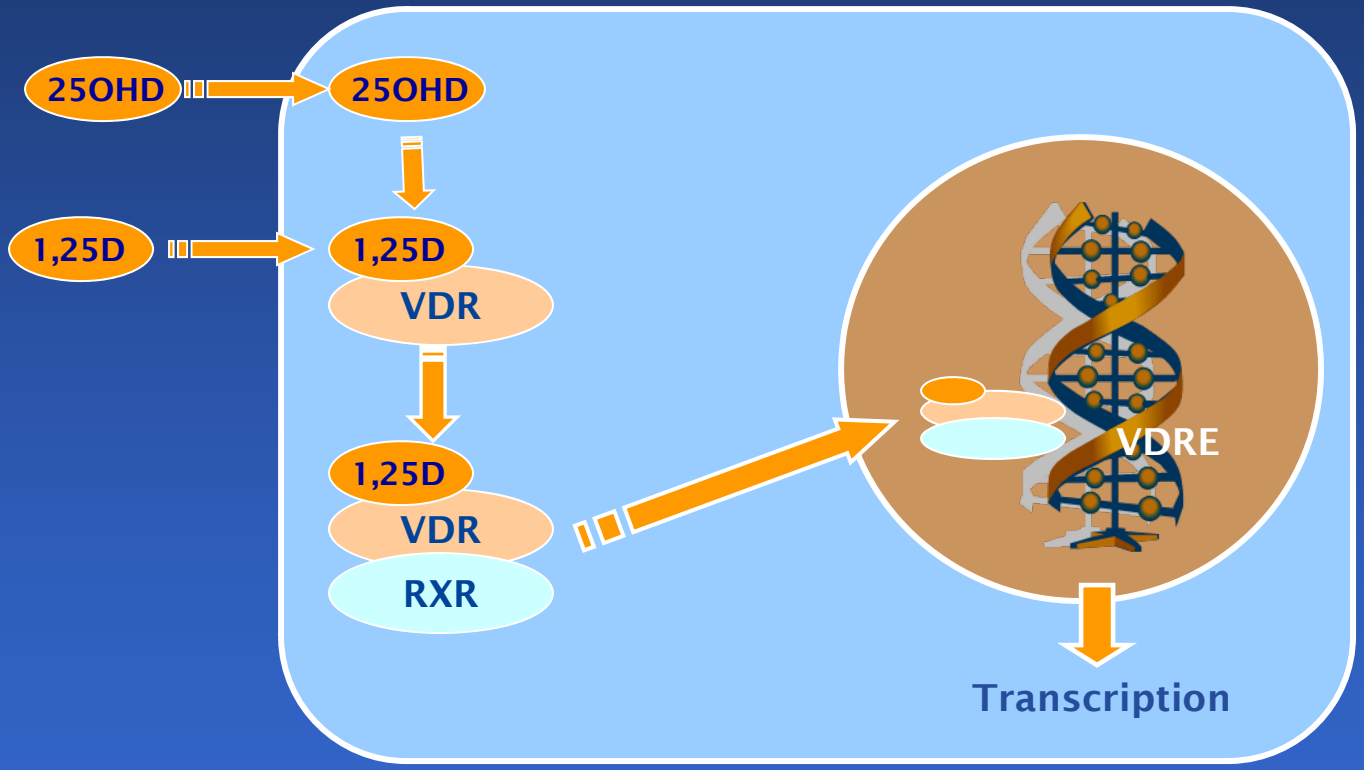
25(OH)D

> 1000 genes have VDREs



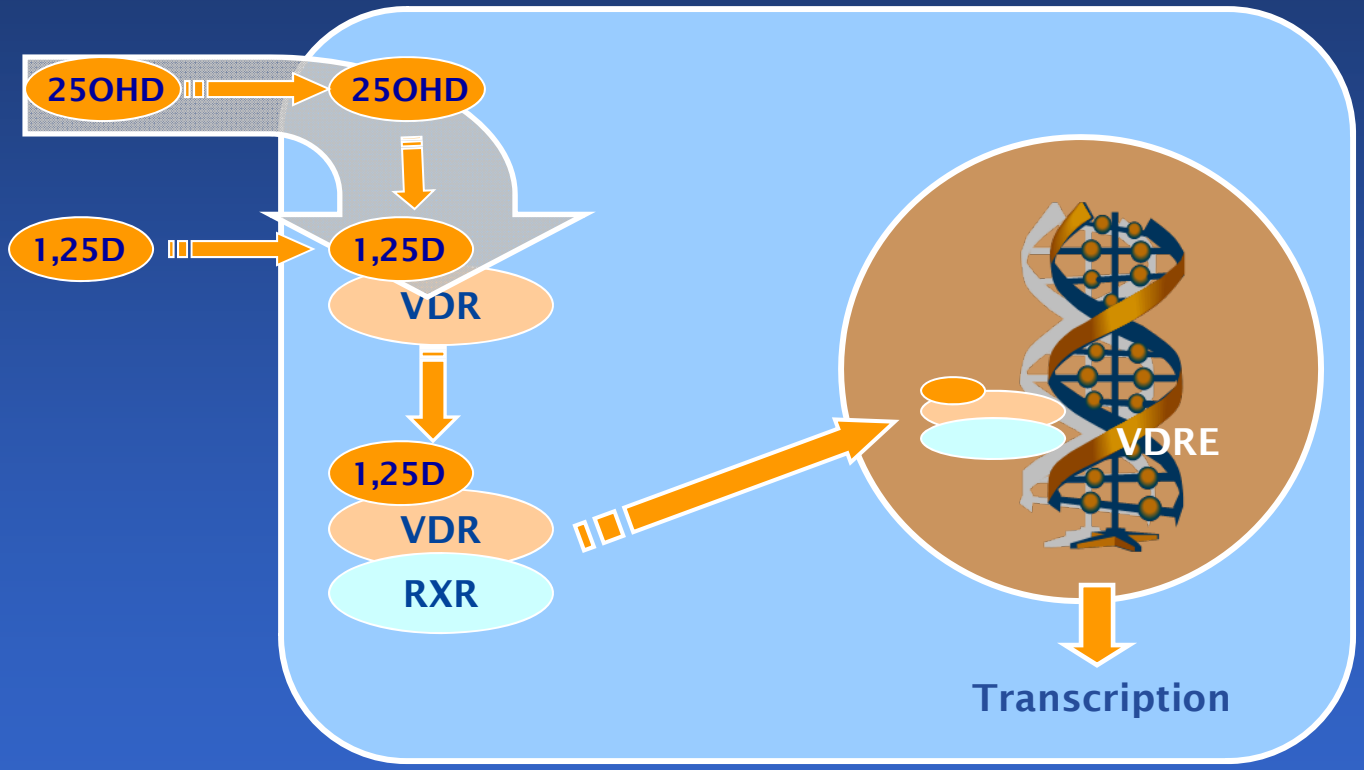
AUTOCRINE ACTION

25(OH)D



AUTOCRINE ACTION

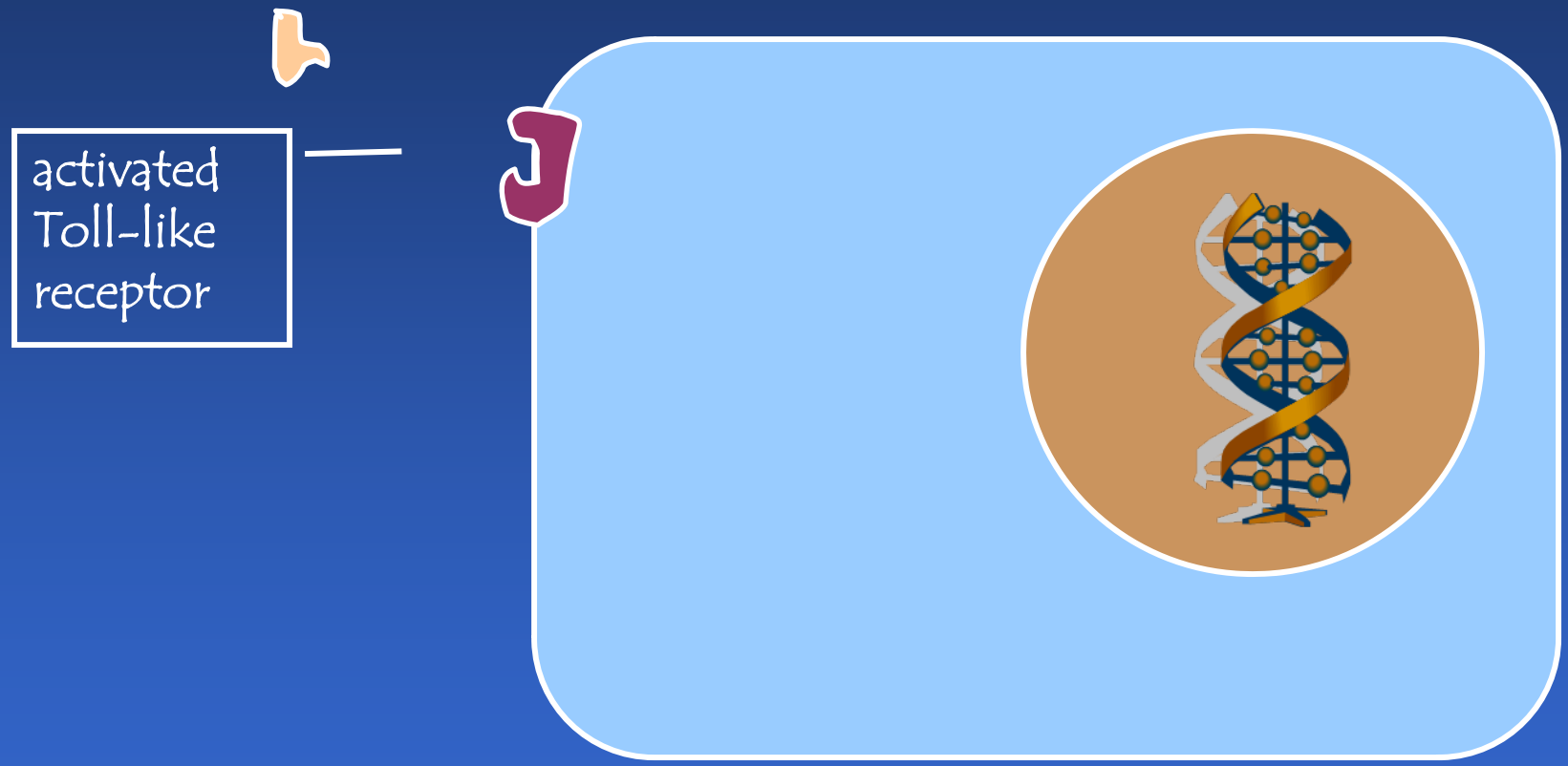
25(OH)D



This scheme means that each tissue

- has the amount of $1,25(OH)_2D$ it needs
- when it needs it
- and is not dependent upon a "one-size-fits all" systemic level of circulating $1,25(OH)_2D$

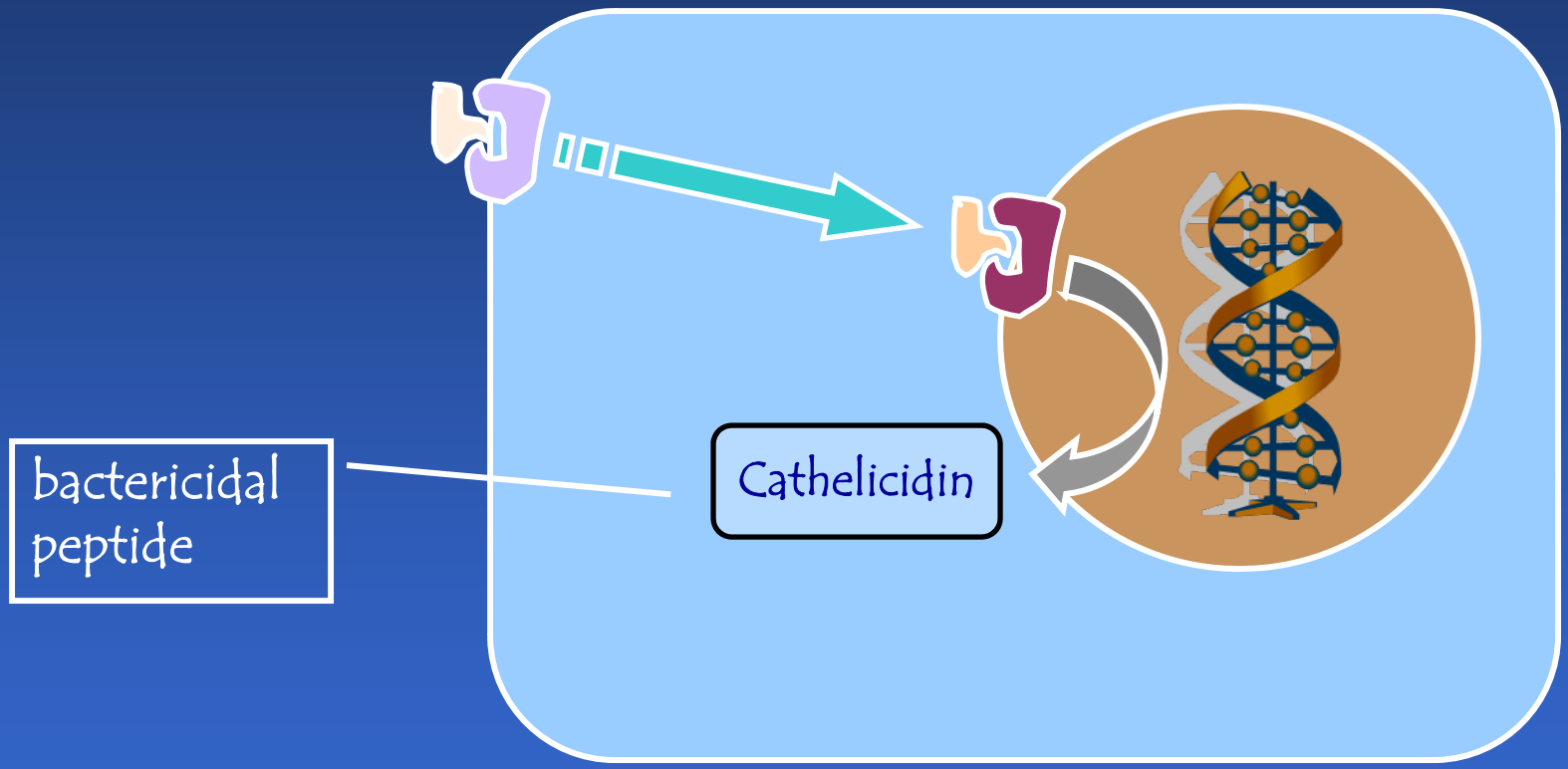
VITAMIN D & INNATE IMMUNITY*



*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D



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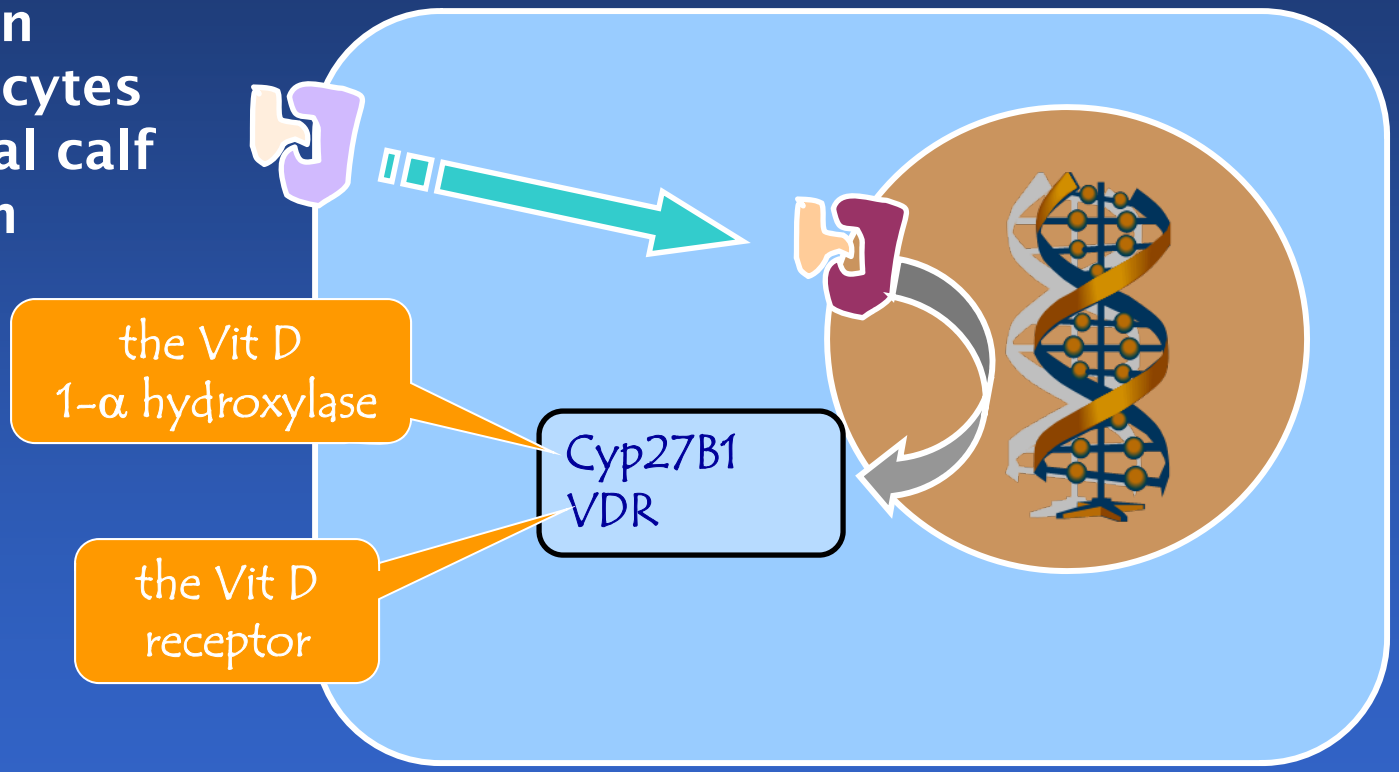
*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum



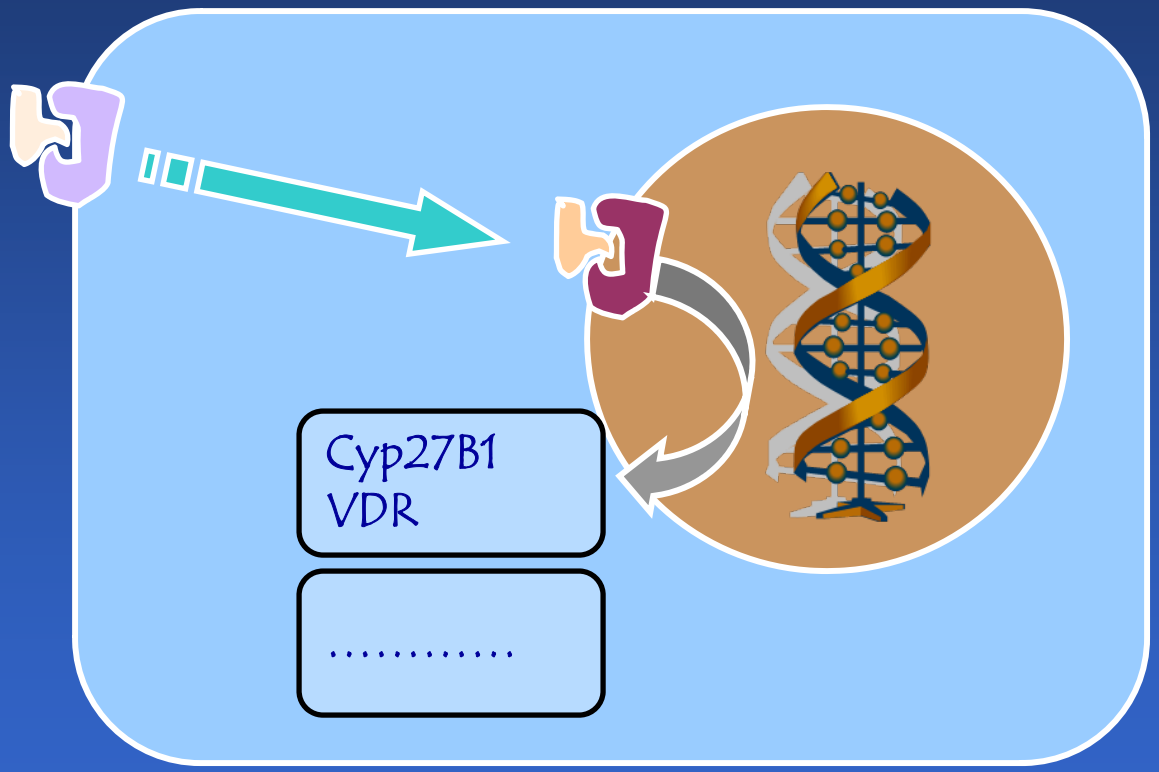
CU ORC

*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum
- fetal calf serum is low in both 25(OH)D & $1,25(OH)_2D$



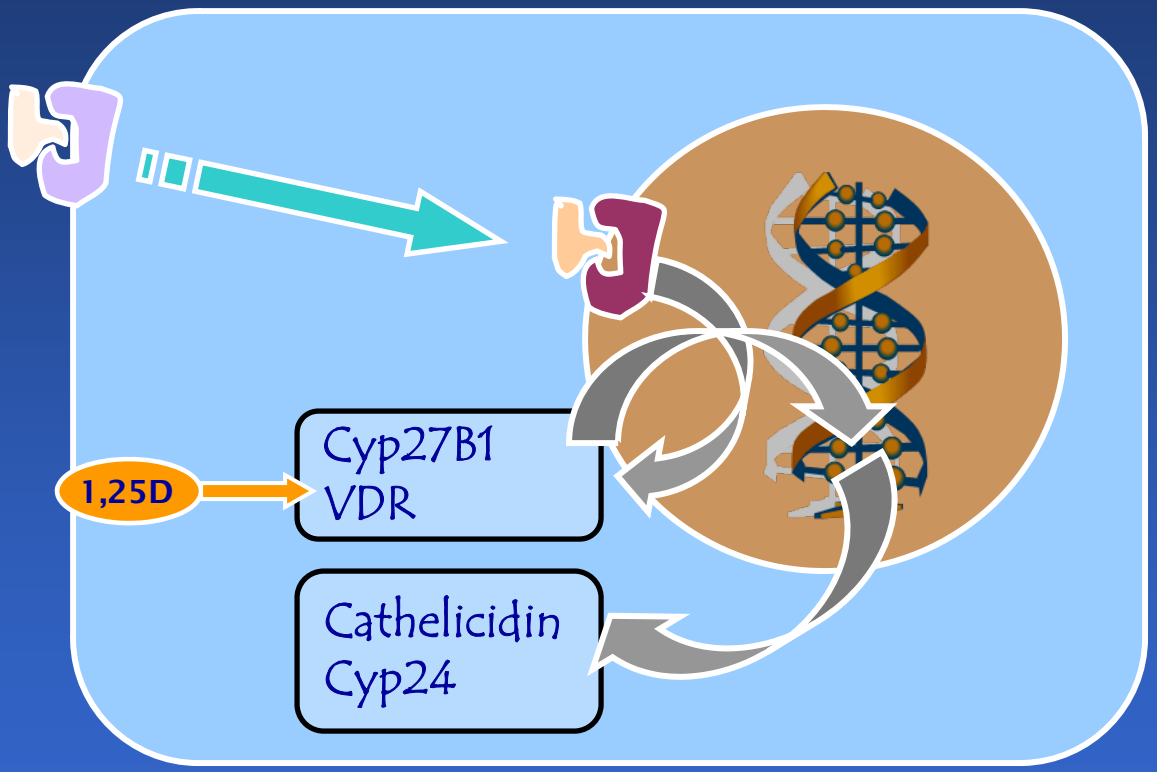
CU ORC

*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum
- add $1,25(OH)_2D$ to the system



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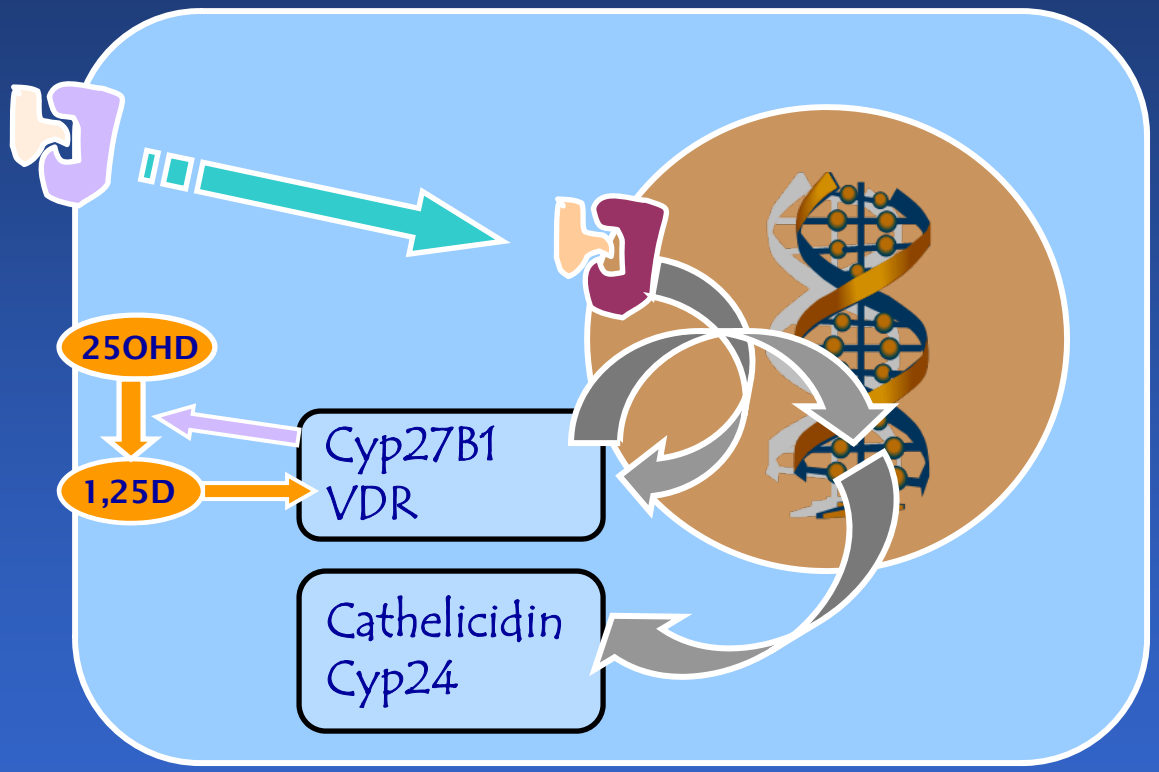
*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum
- add 25(OH) D to the system

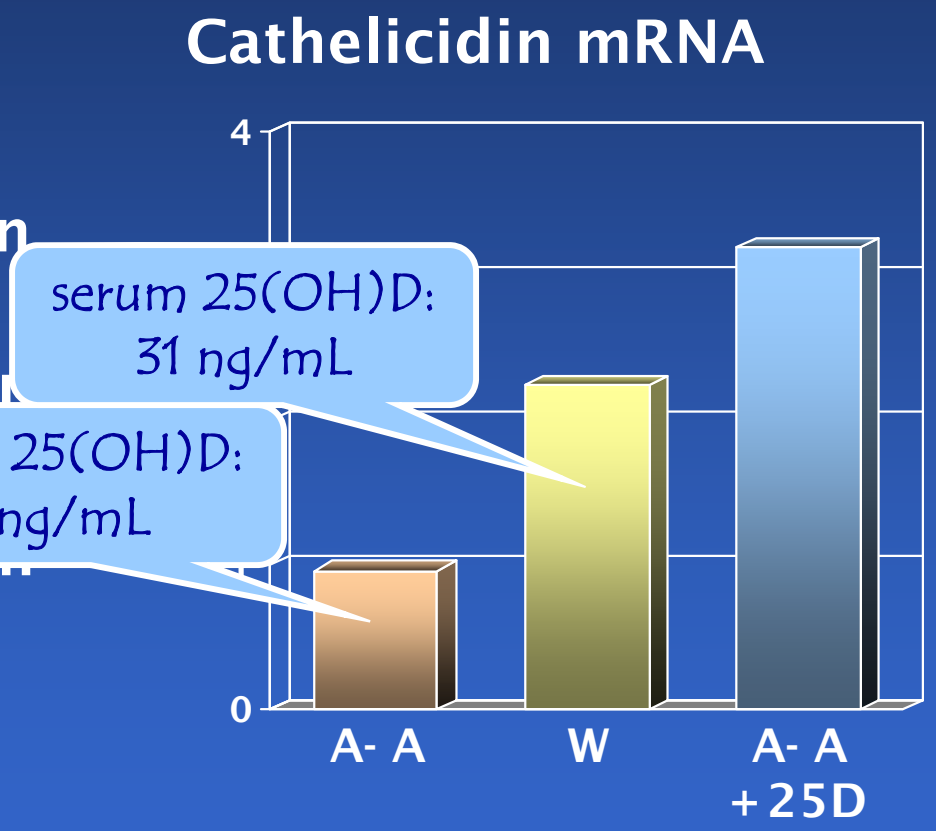


CU ORC

*Liu et al., Science 2006

VITAMIN D & TUBERCULOSIS

- human monocytes activated with *M. Tuberculosis* and incubated in human serum
  - African-American
  - White
  - African-American with added 25(OH)D



CU ORC

*Liu et al., Science 2006

VITAMIN D & TUBERCULOSIS

these experiments show that:

- vit D is an essential mediator in the innate immune response
- serum 25(OH)D is the critical variable
- at least some of the increased sensitivity to infection in vit D-deficiency is due to reduction in response to infectious agents because 25(OH)D is rate-limiting
- the greater tuberculosis susceptibility of blacks is due in part to their low vit D status

ASSESSING VITAMIN D DEFICIENCY

- serum *total* 25(OH)D is the: –
  - functional indicator for vit D status
  - an important storage form of vit D at typical inputs
- serum 25(OH)D_2 is of no value unless the MD is following treatment with vit D_2
- serum 1,25$(OH)_2$D does not measure vit D status (instead, it measures Ca need)

MANAGEMENT

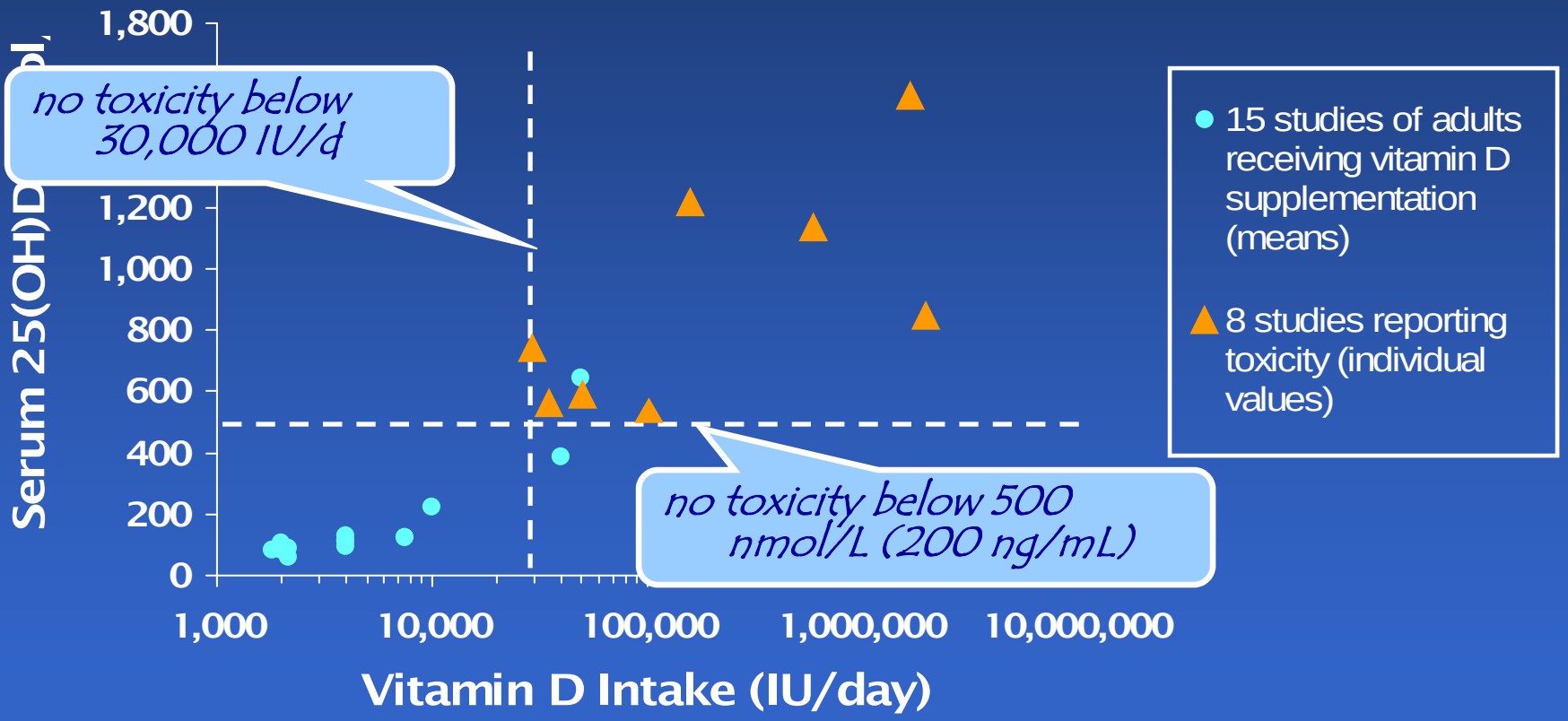
- all-source requirement ≅75 IU/kg/d
- most adults will need 1000–3000 IU/d in addition to all other inputs
- 25(OH)D response varies widely
- it is the serum 25(OH)D concentration that must be optimized, not the oral dose
- the correct oral dose is the one that produces and maintains a desired 25(OH)D level

HOW MUCH IS ENOUGH?

▪ rickets & osteomalacia	▪ 10 ng/mL
▪ Ca absorption	▪ 32 ng/mL
▪ pregnancy outcomes	▪ 48 ng/mL
▪ cancer	▪ 40 ng/mL
▪ other	▪ ????

Safety

VITAMIN D INTAKE & TOXICITY*



* Hathcock JN et al. *Am J Clin Nutr*. 2007;85:6–18.

CONCLUSIONS – 1

- serum 25(OH)D levels below 80 nmol/L are not adequate for any body system
- levels of as high as 120 nmol/L may be closer to optimal
- inputs from all sources combined (needed to sustain 80 nmol/L) are in the range of ~4,000 IU/d and higher

CONCLUSIONS – 2

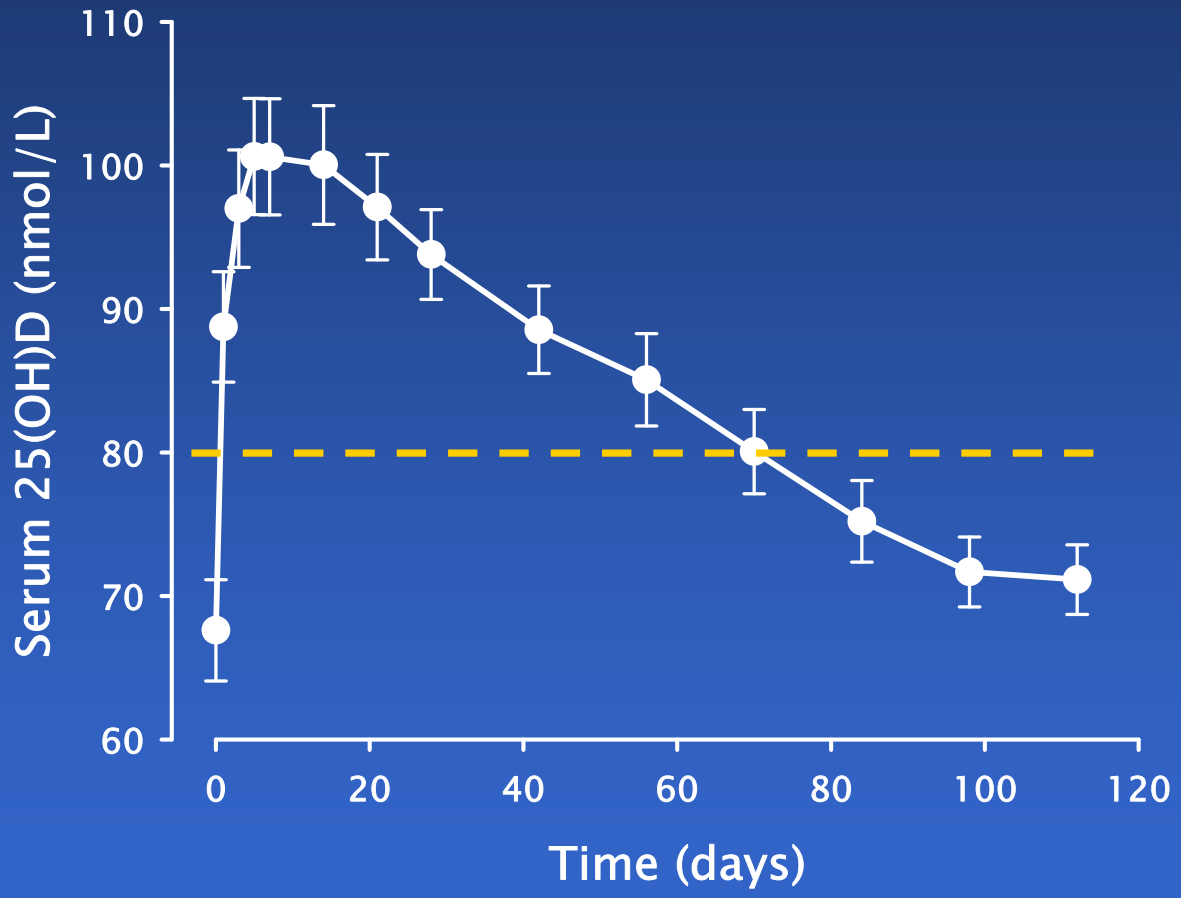
- vitamin D deficiency is widespread and mostly silent
- vitamin D deficiency impairs our patients' responses both to their illnesses and to whatever treatment we may be prescribing
- attention to vitamin D repletion should be a part of every therapeutic regimen

Thank you

Supplemental slides

25(OH)D RESPONSE TO LARGE DOSES*

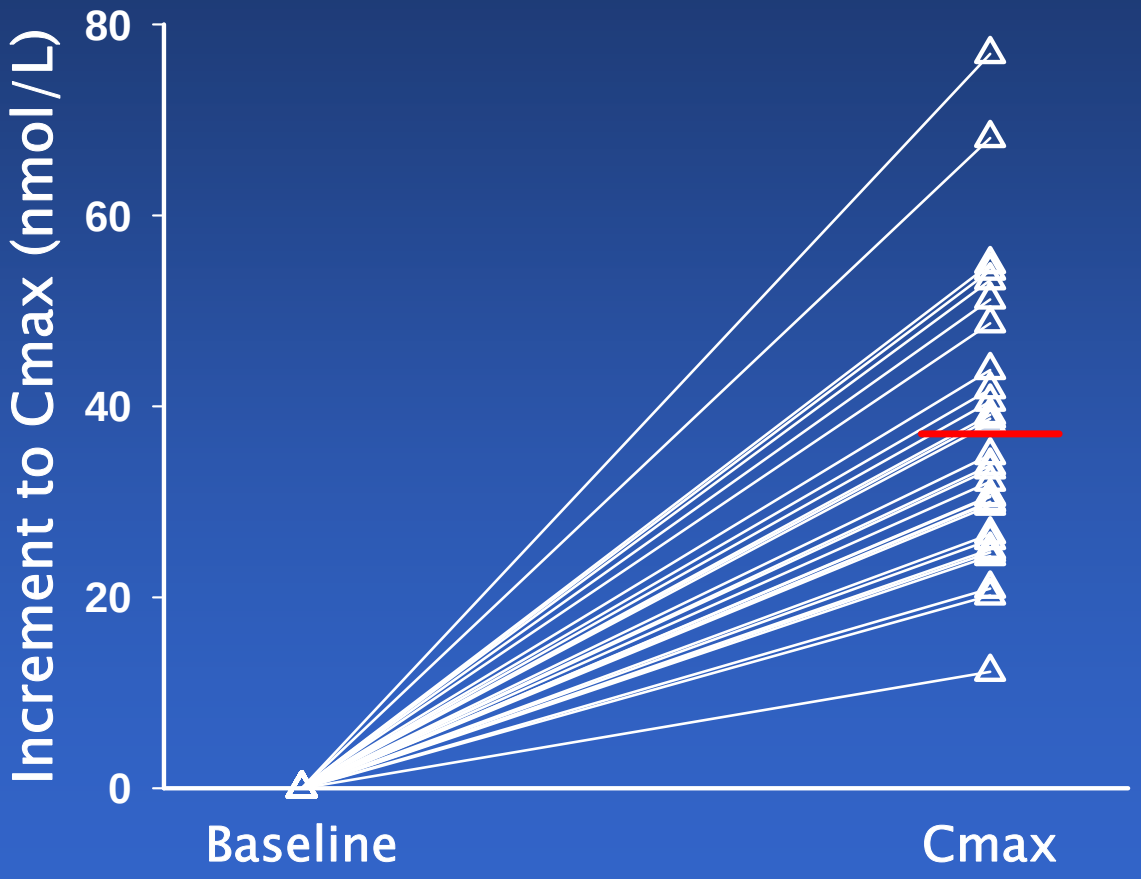
- 100,000 IU D_3, by mouth, once



*Ilahi, Armas, & Heaney (in press)

VARIABILITY OF 25(OH)D RESPONSE*

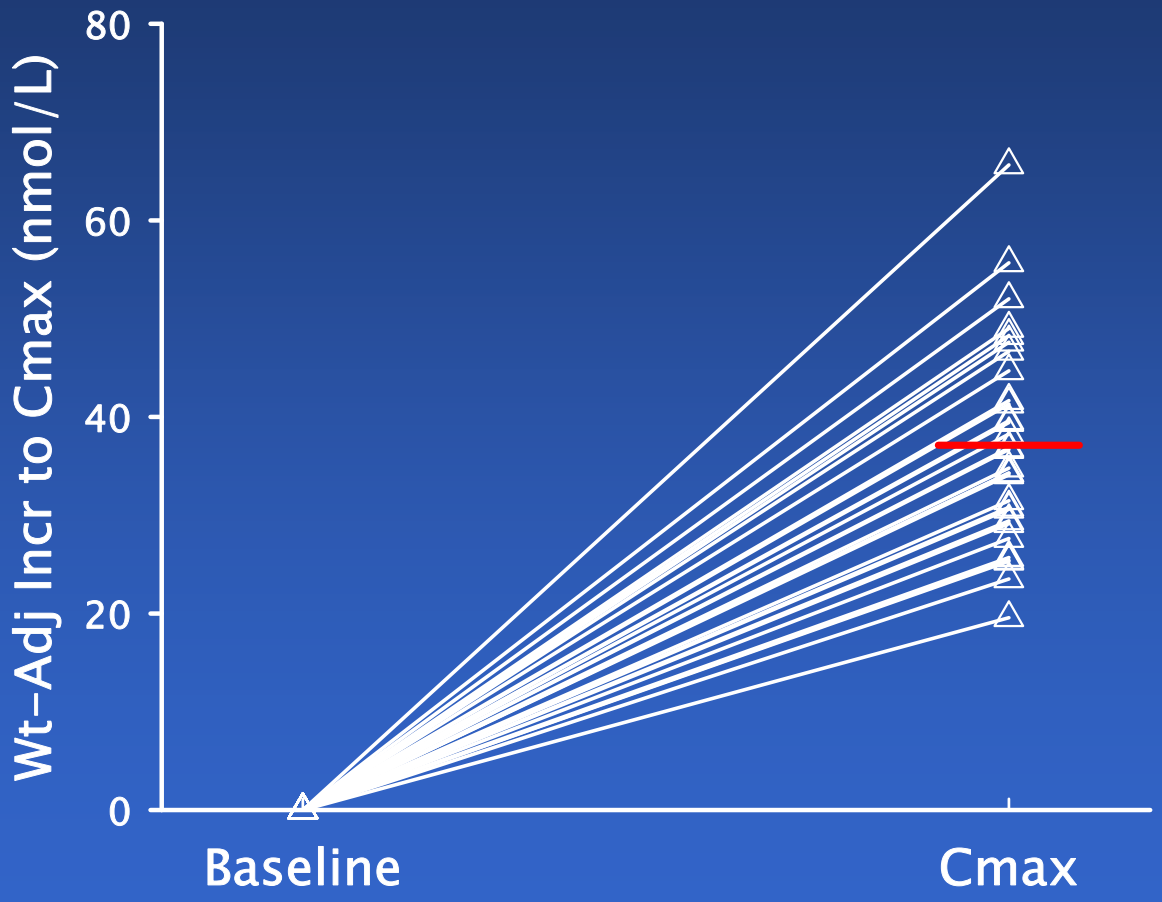
- Δ 25(OH)D to C_{max} ranged from +12 nmol/L to +76 nmol/L
- ~half of the variability due to body size



*Ilahi, Armas, & Heaney (AJCN 2008)

VARIABILITY OF 25(OH)D RESPONSE*

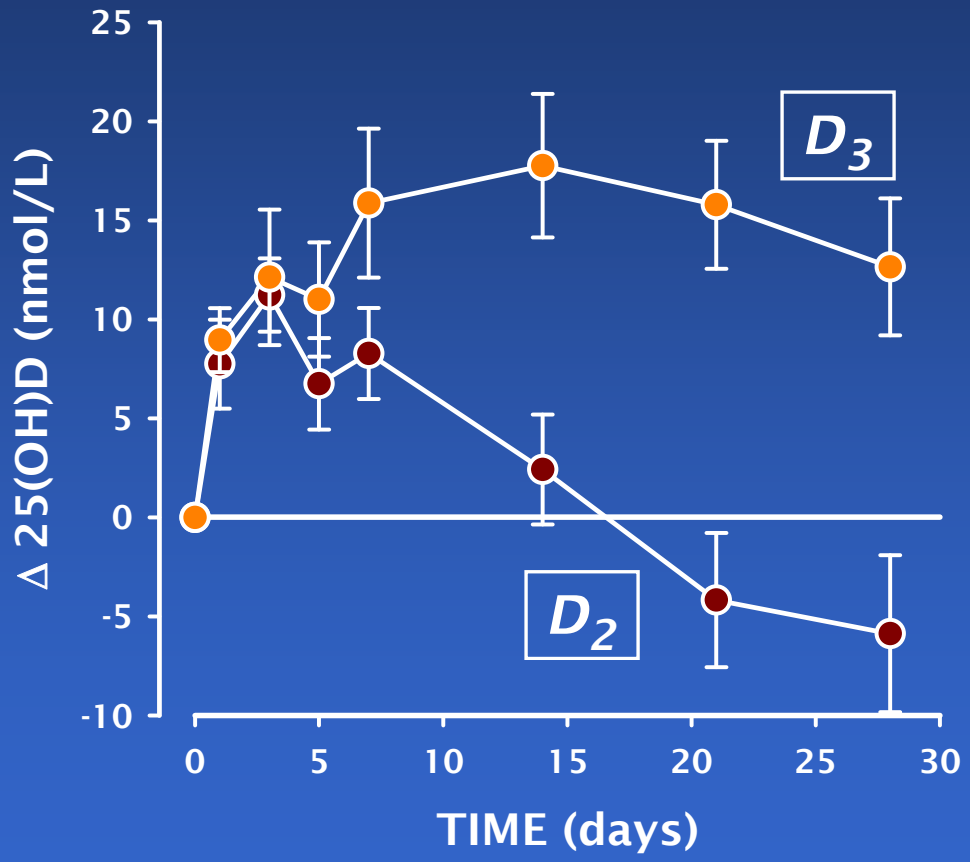
- **Wt-adjusted Δ 25(OH)D to C_{max} ranged from +20 nmol/L to +66 nmol/L**



*Ilahi, Armas, & Heaney (in press)

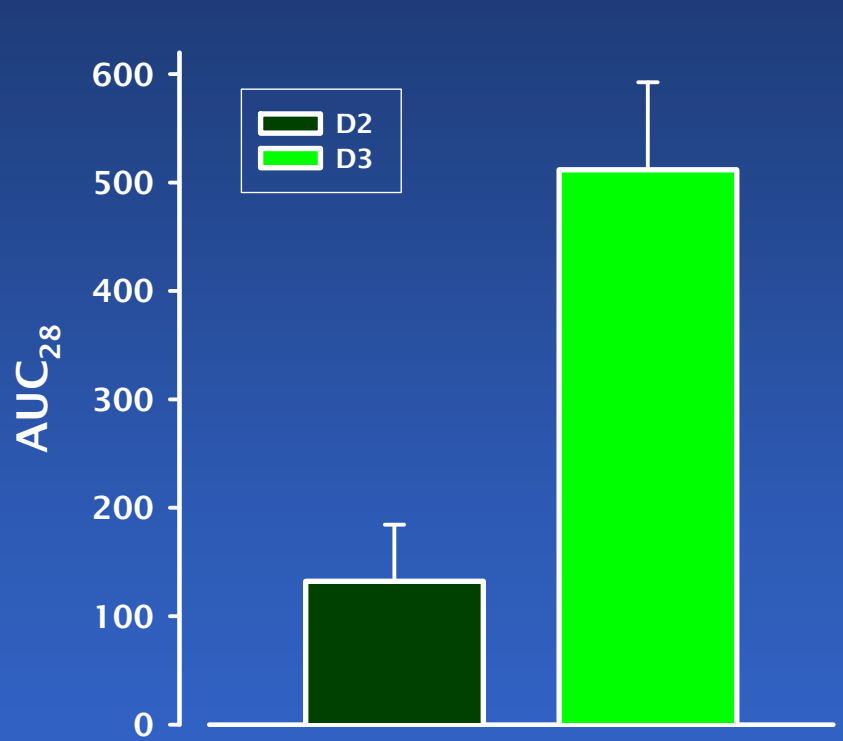
D_2 vs. D_3*

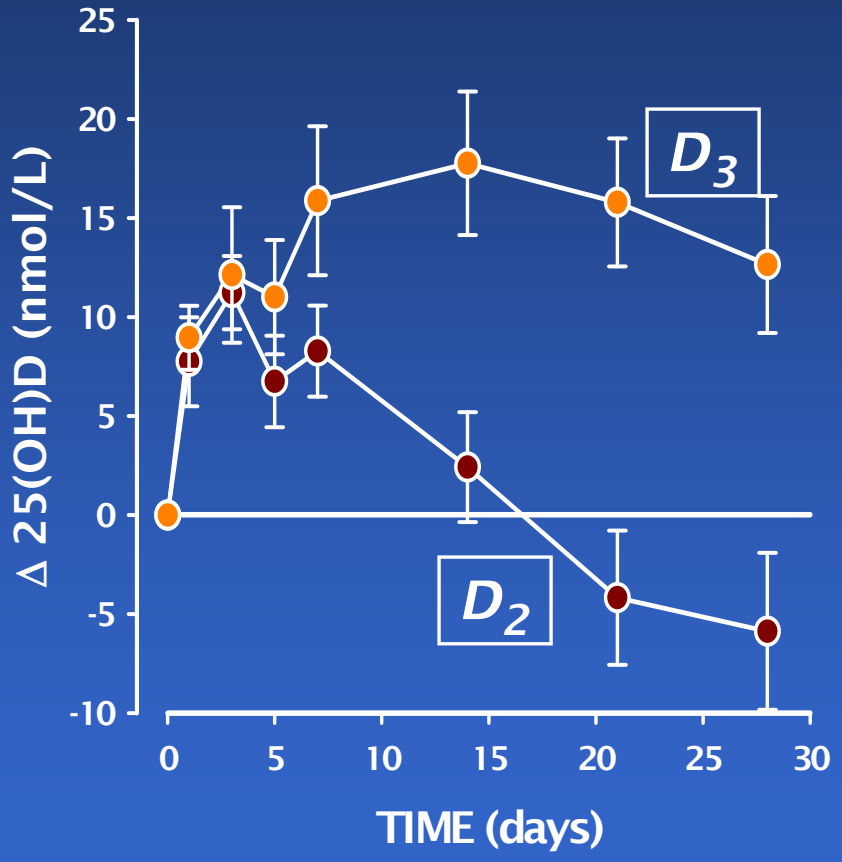
- single oral dose
- 50,000 IU
- D_2 or D_3
- n = 10 in each group



*Armas et al., 2004

D_2 vs. D_3* – AUC





*Armas et al., 2004