

WHAT'S A VITAMIN D DEFICIENCY?

OVERVIEW, ACTIONS

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DISCLOSURES

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

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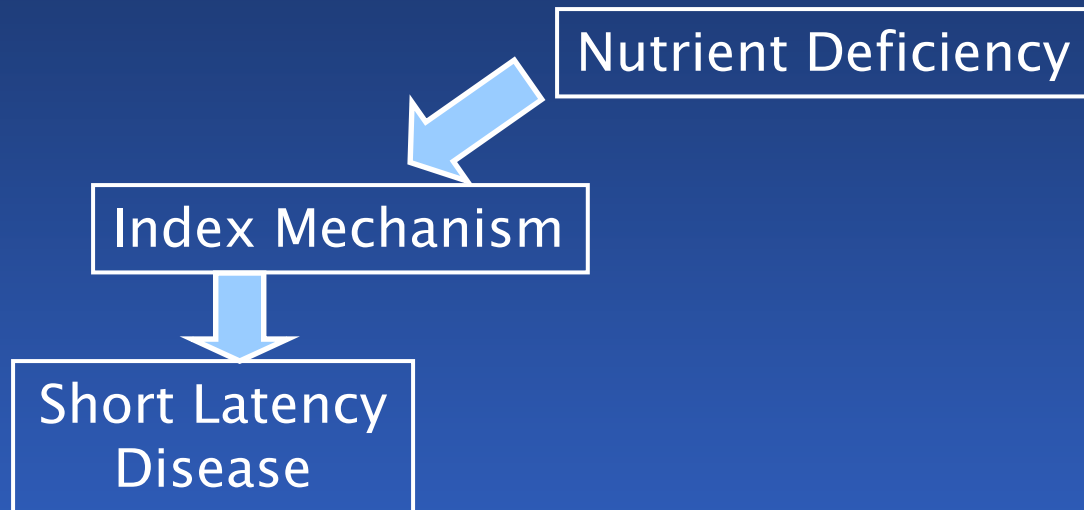
OBJECTIVES

- define nutrient deficiency
- define how vitamin D status is assessed
- define the low end of the vitamin D sufficiency range
- describe how vitamin D can work in so many different tissues & organ systems

Working definition:

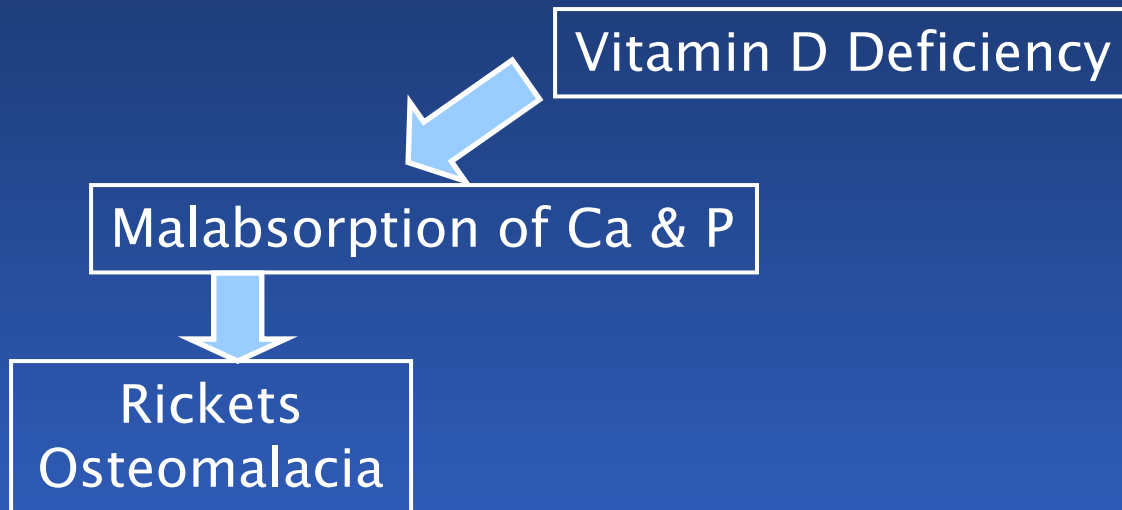
- a deficiency is any condition in which inadequate intake of a nutrient results in significant dysfunction or disease
- conversely, nutrient adequacy is the situation in which further increases in intake produce no further reduction in dysfunction or disease

RETHINKING DEFICIENCY DISEASE

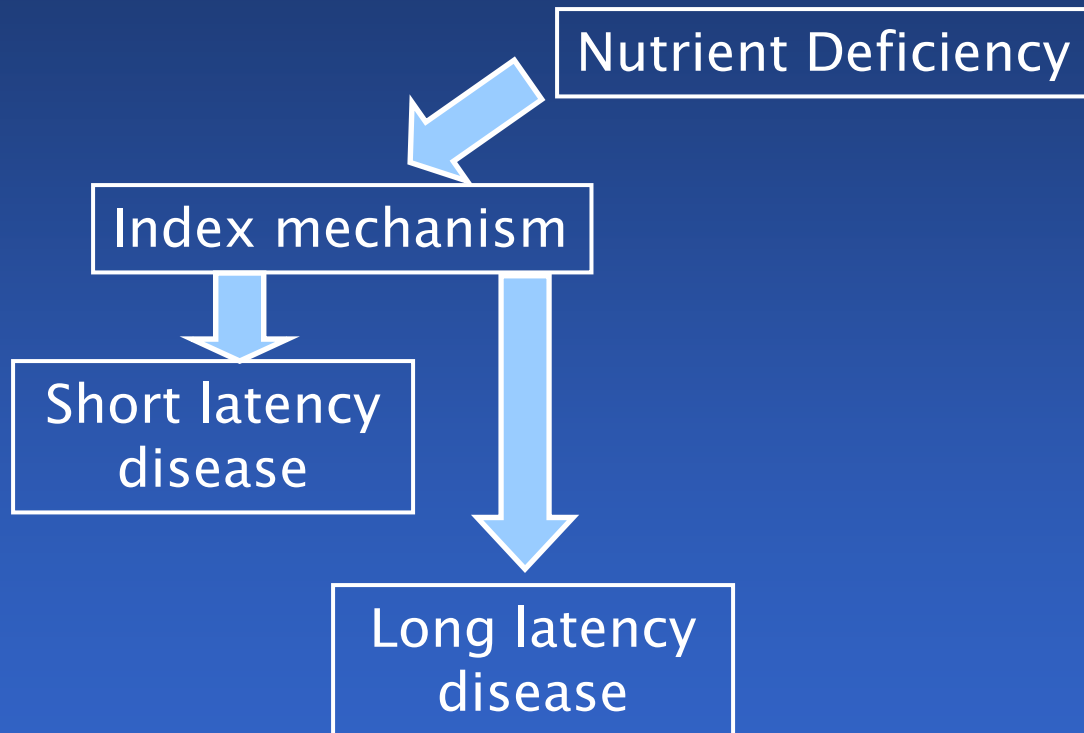


In the early days of nutrition as a science, short latency of the disease/dysfunction was necessary in order to recognize the connection between cause and effect.

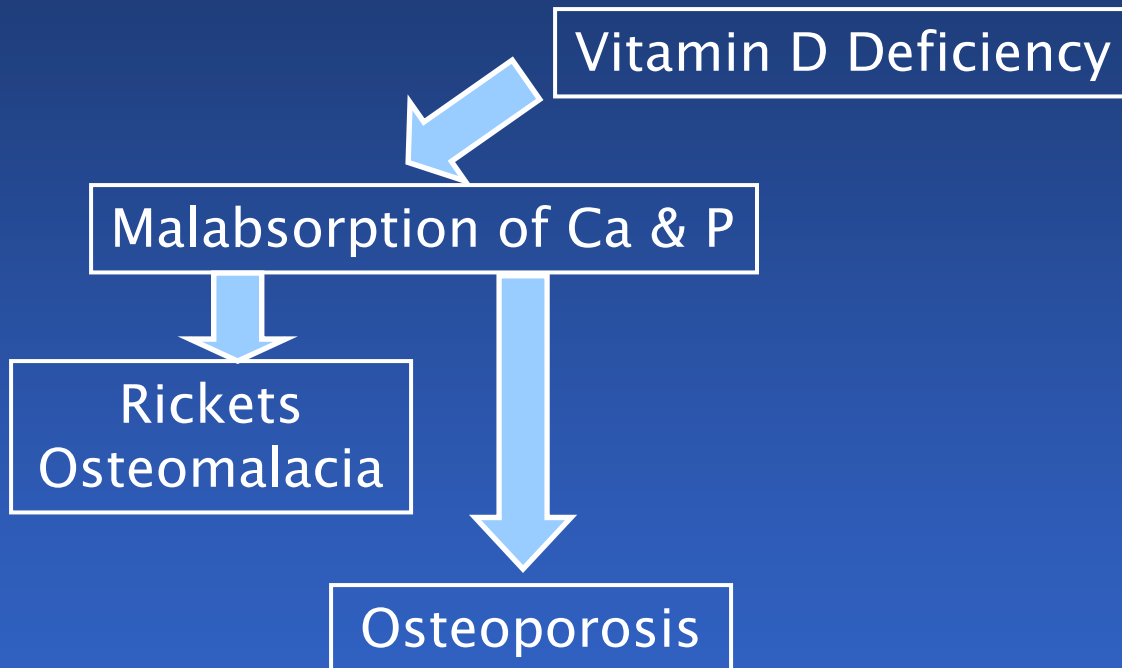
RETHINKING DEFICIENCY DISEASE



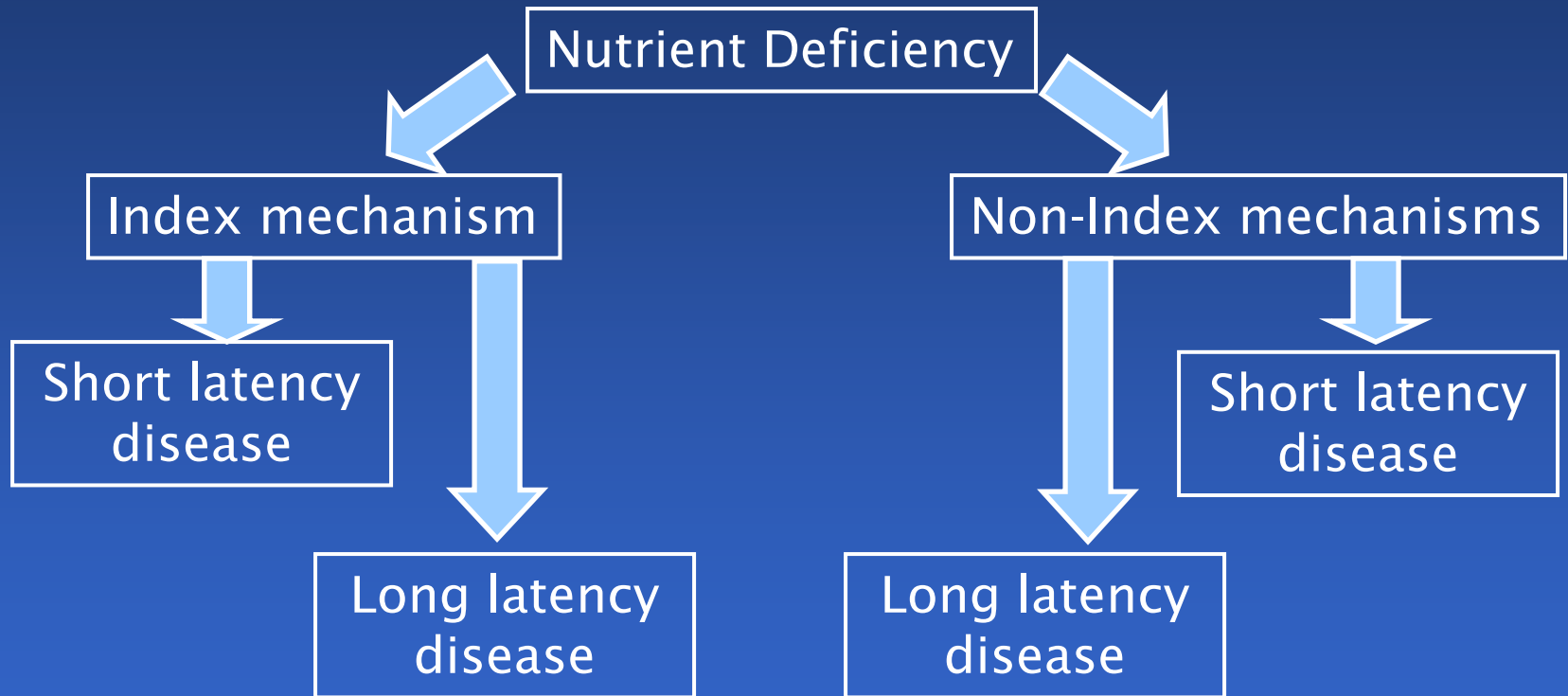
RETHINKING DEFICIENCY DISEASE



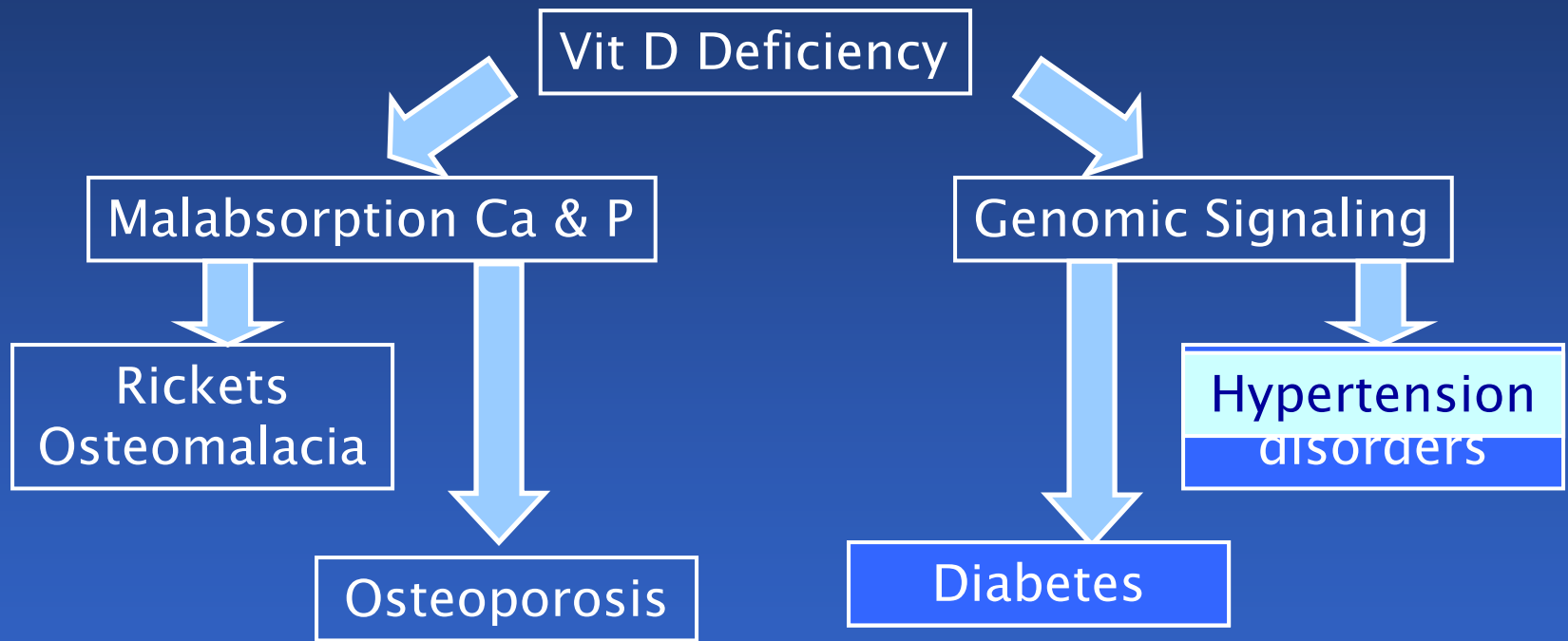
RETHINKING DEFICIENCY DISEASE



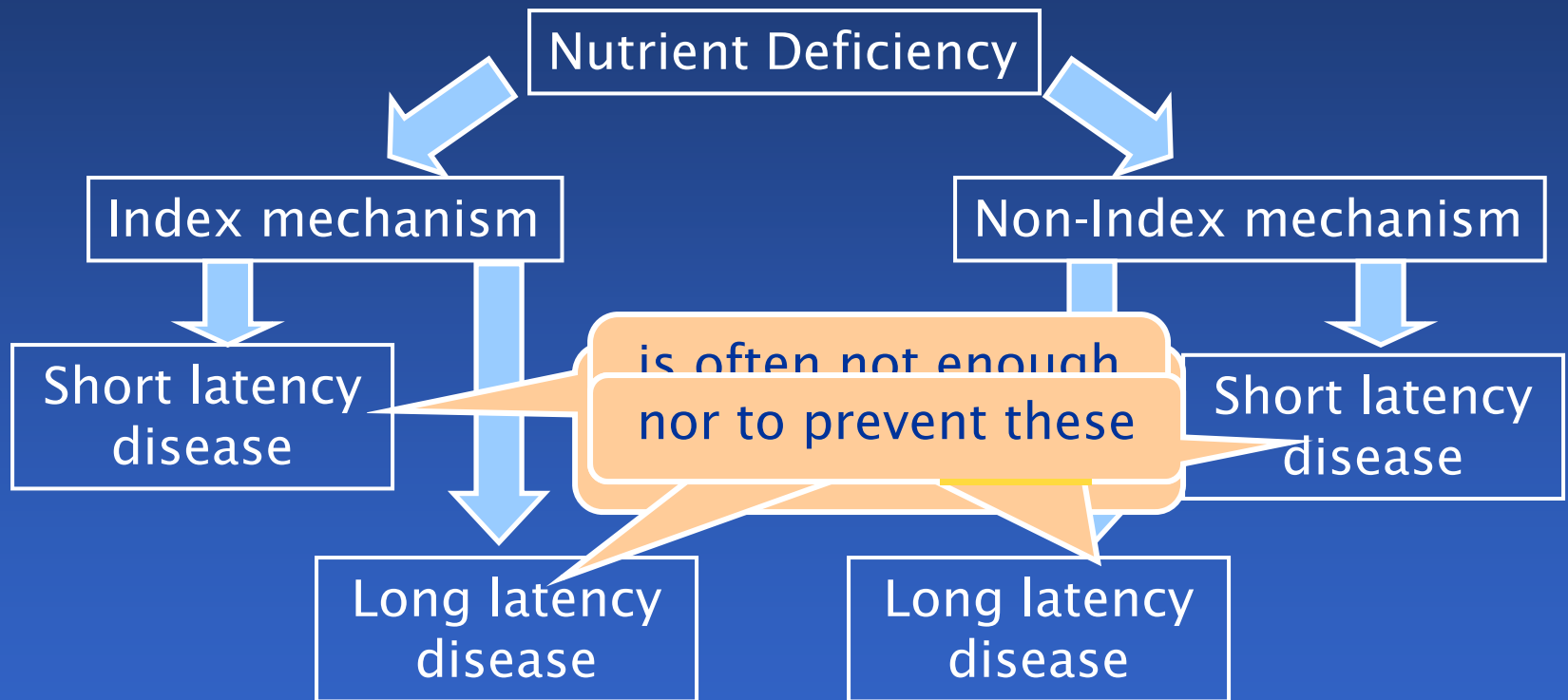
RETHINKING DEFICIENCY DISEASE



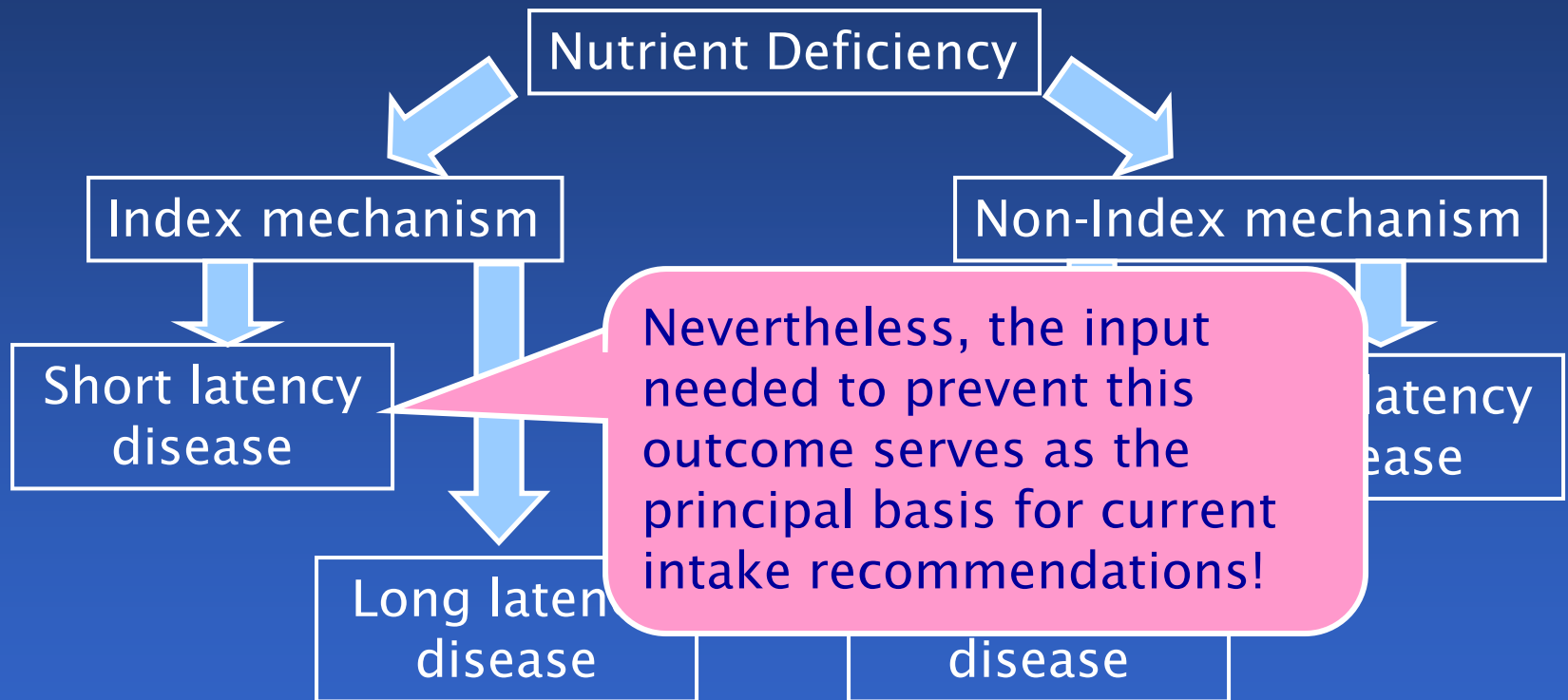
RETHINKING DEFICIENCY DISEASE



RETHINKING DEFICIENCY DISEASE



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

Nutrition Facts

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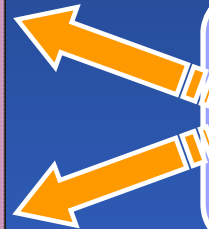
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Limit these nutrients



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 batters 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; and
- therefore, expression of nutrient deficiency will usually be pluriform – both between and within individuals

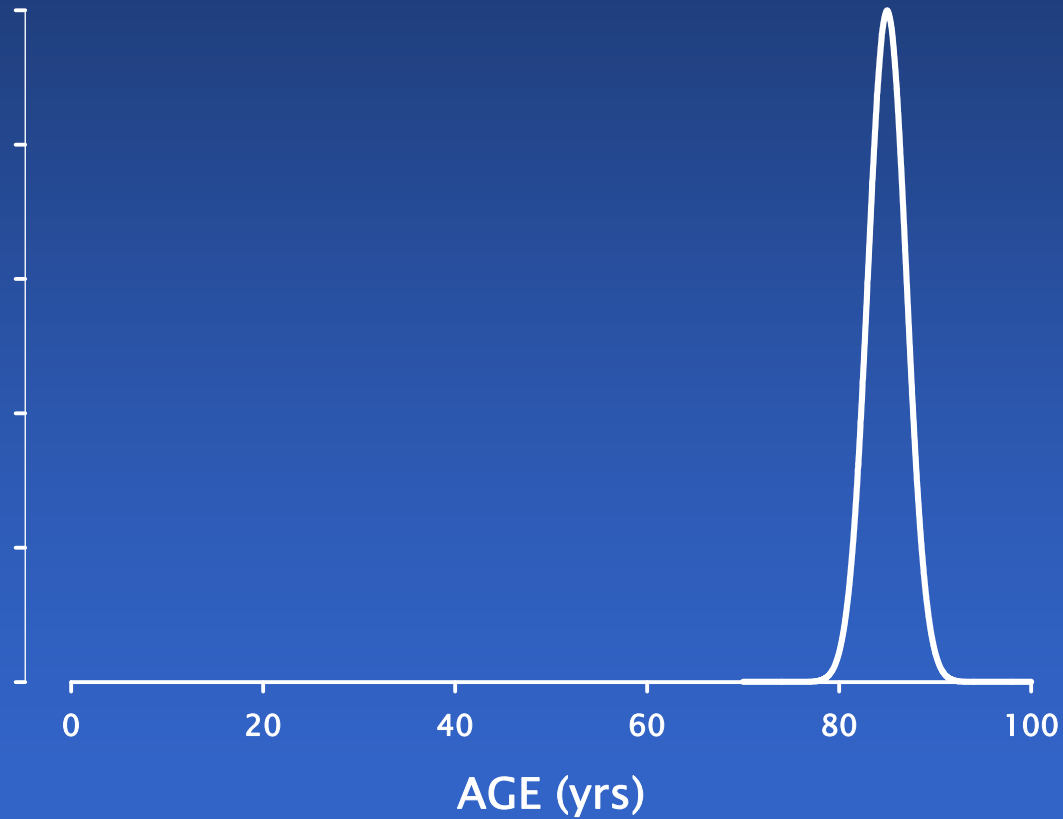
THE INTAKE REFERENT

- it is sometimes argued that primitive intakes may be ill-suited to modern conditions
- but lacking specific evidence to that effect, the presumption ought to tip toward the primitive intake
 - what is the justification for privileging the status quo?
- the burden of proof should fall on those who claim that primitive intakes are unsafe or that lower intakes are adequate

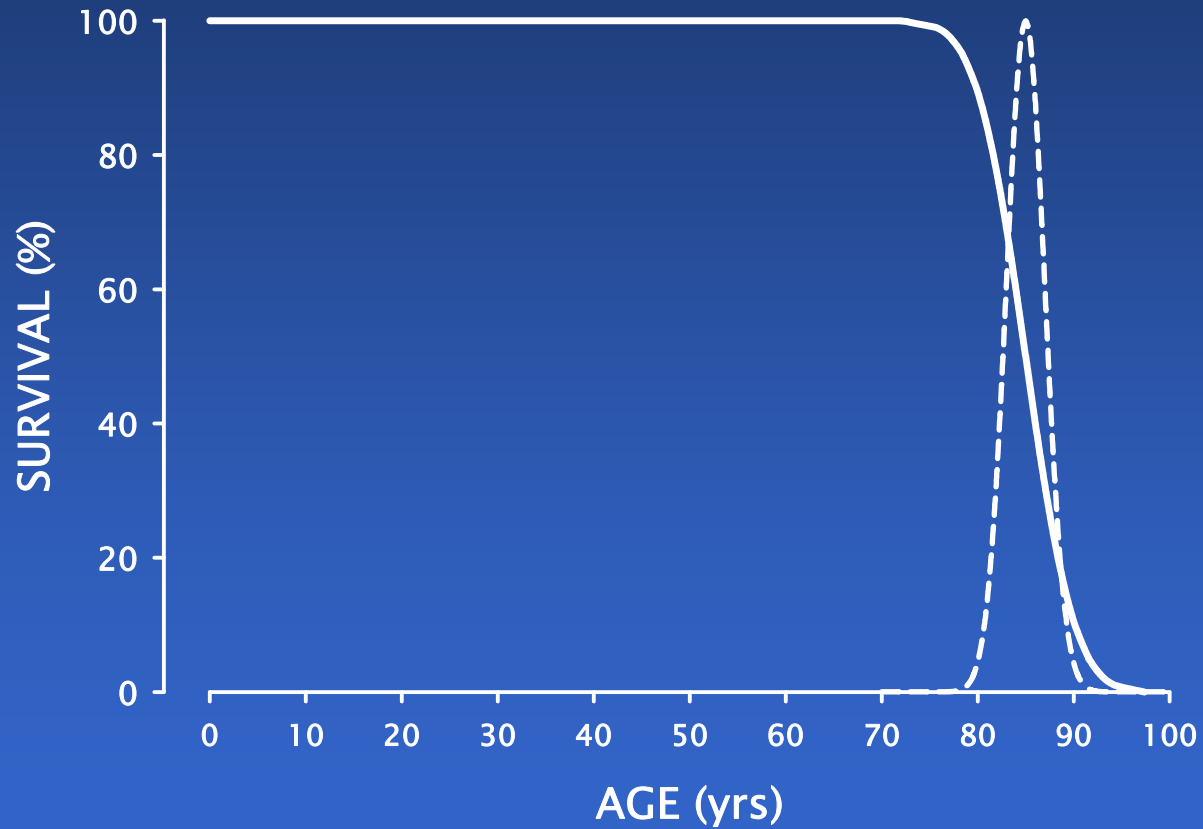
THE PREVENTIVE MAINTENANCE MODEL

- *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

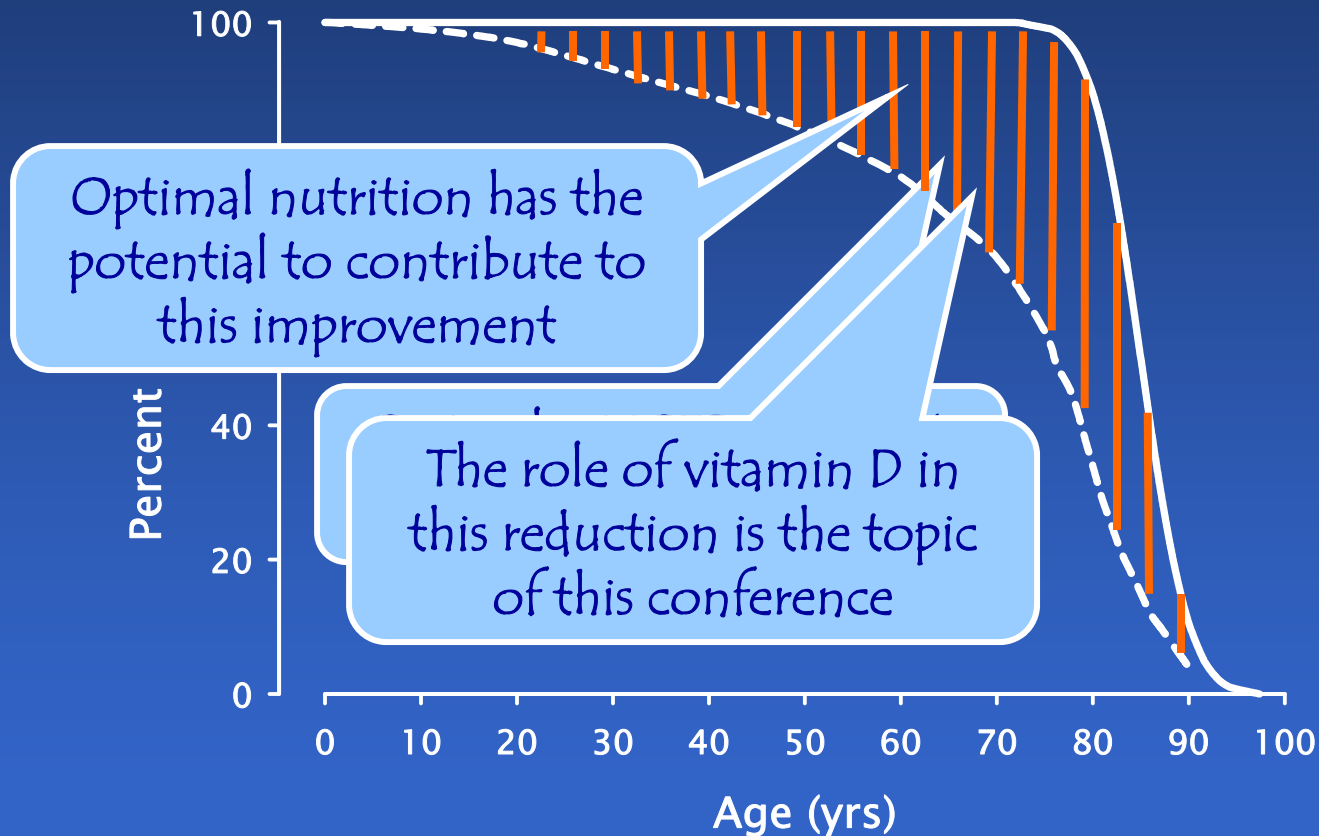
THEORETICAL MORTALITY CURVE



THEORETICAL MORTALITY CURVE

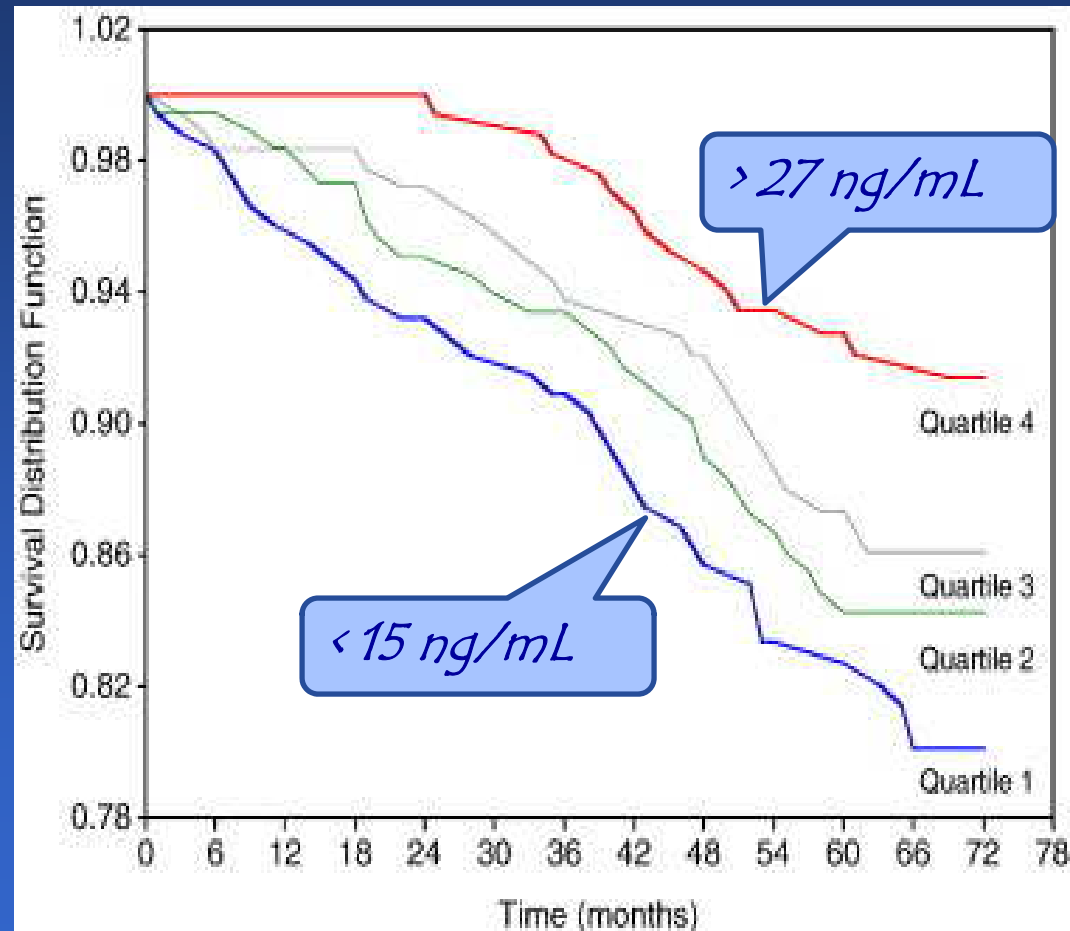


SQUARING THE MORTALITY CURVE



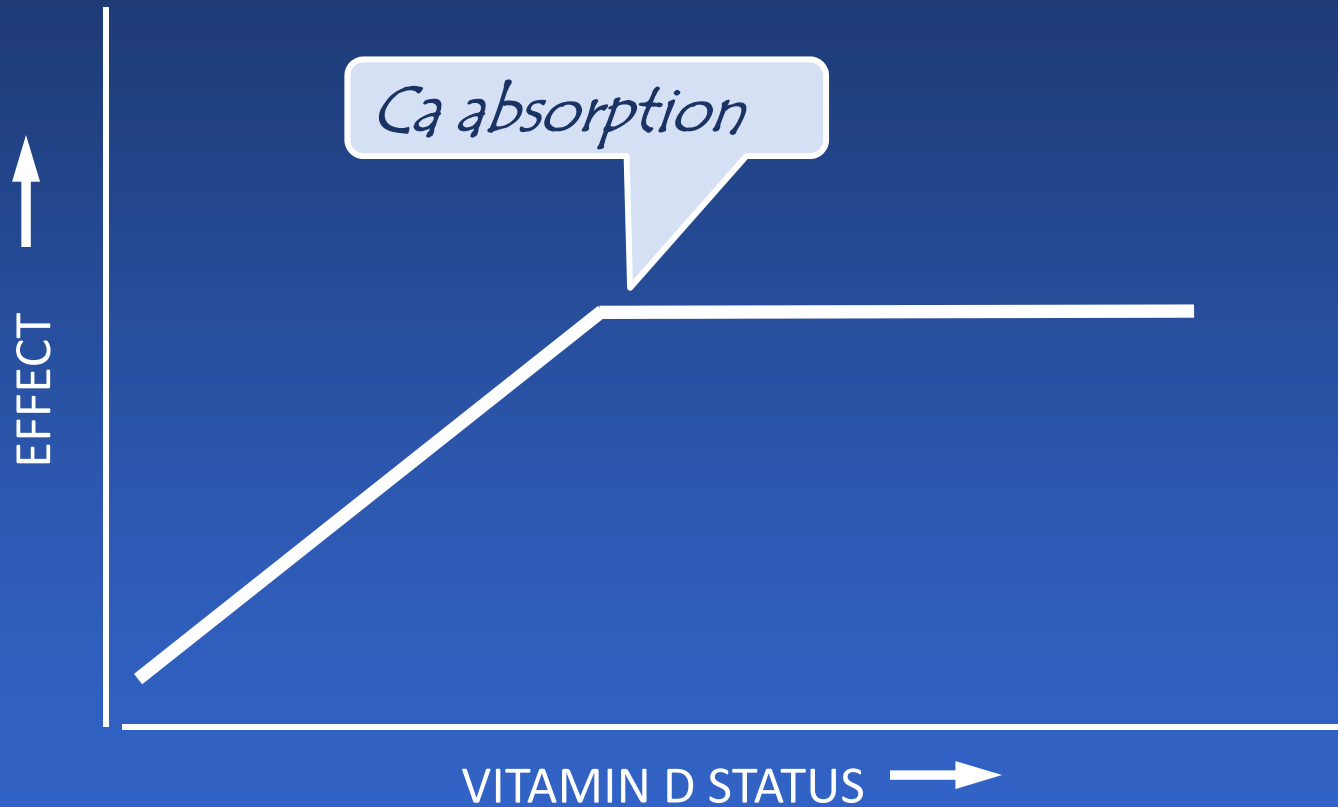
ALL-CAUSE MORTALITY*

- 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

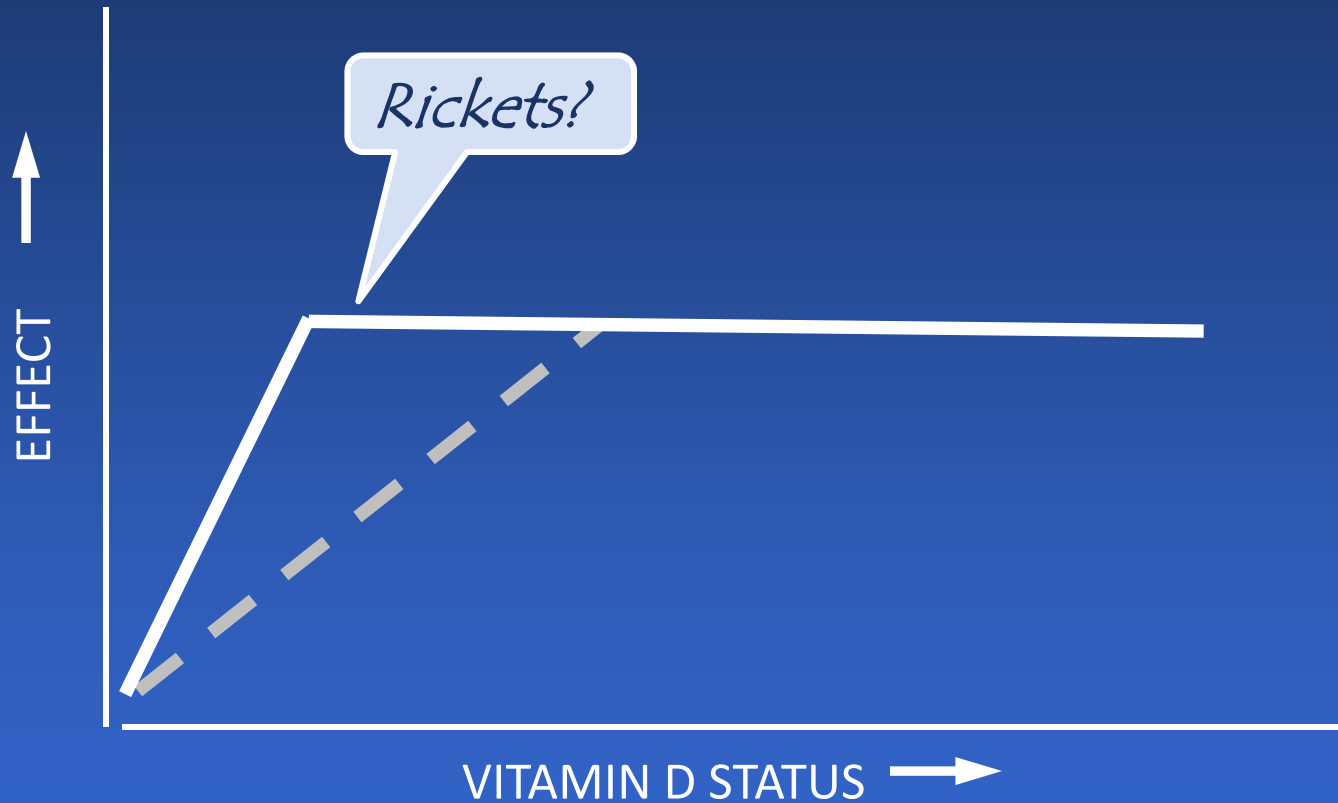


* Semba et al. (2009) Nutr Res 29:525–530

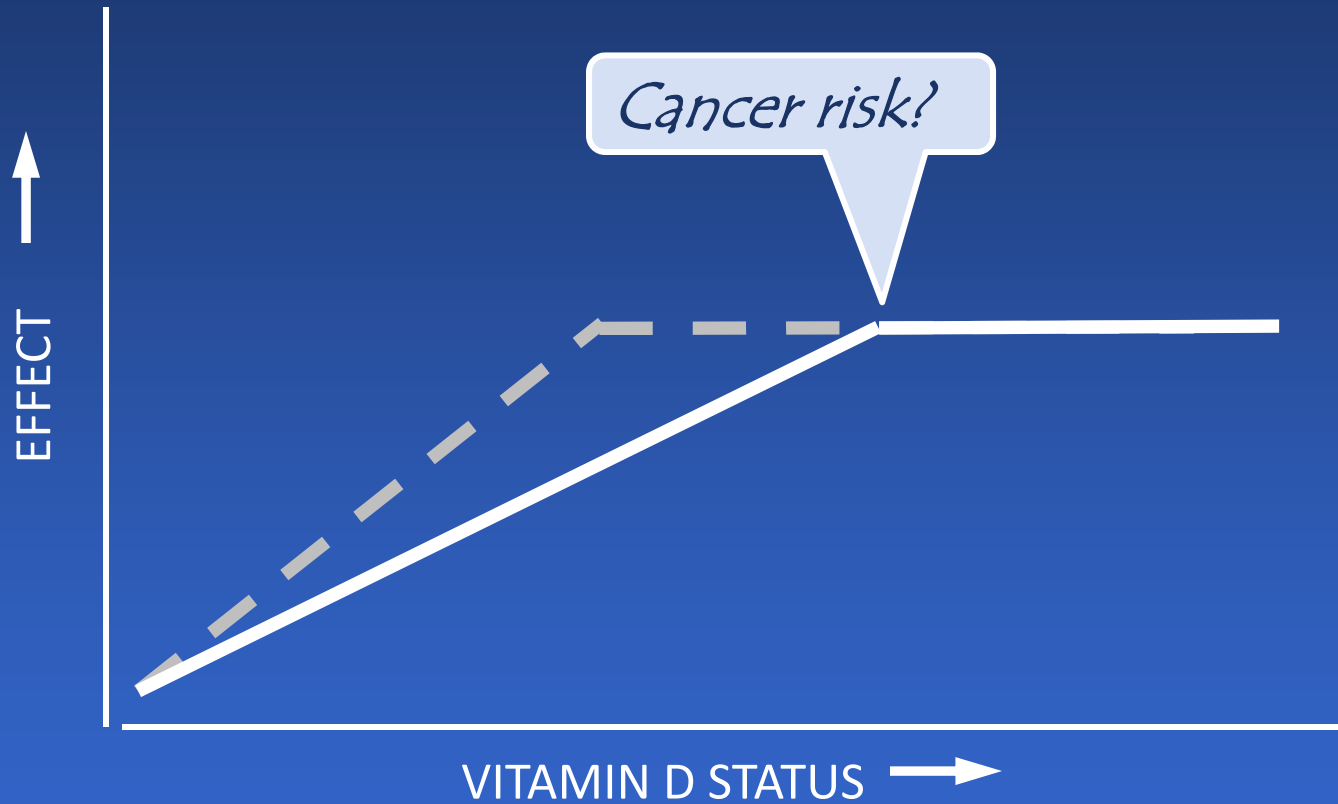
THE RESPONSE THRESHOLD



THE RESPONSE THRESHOLD



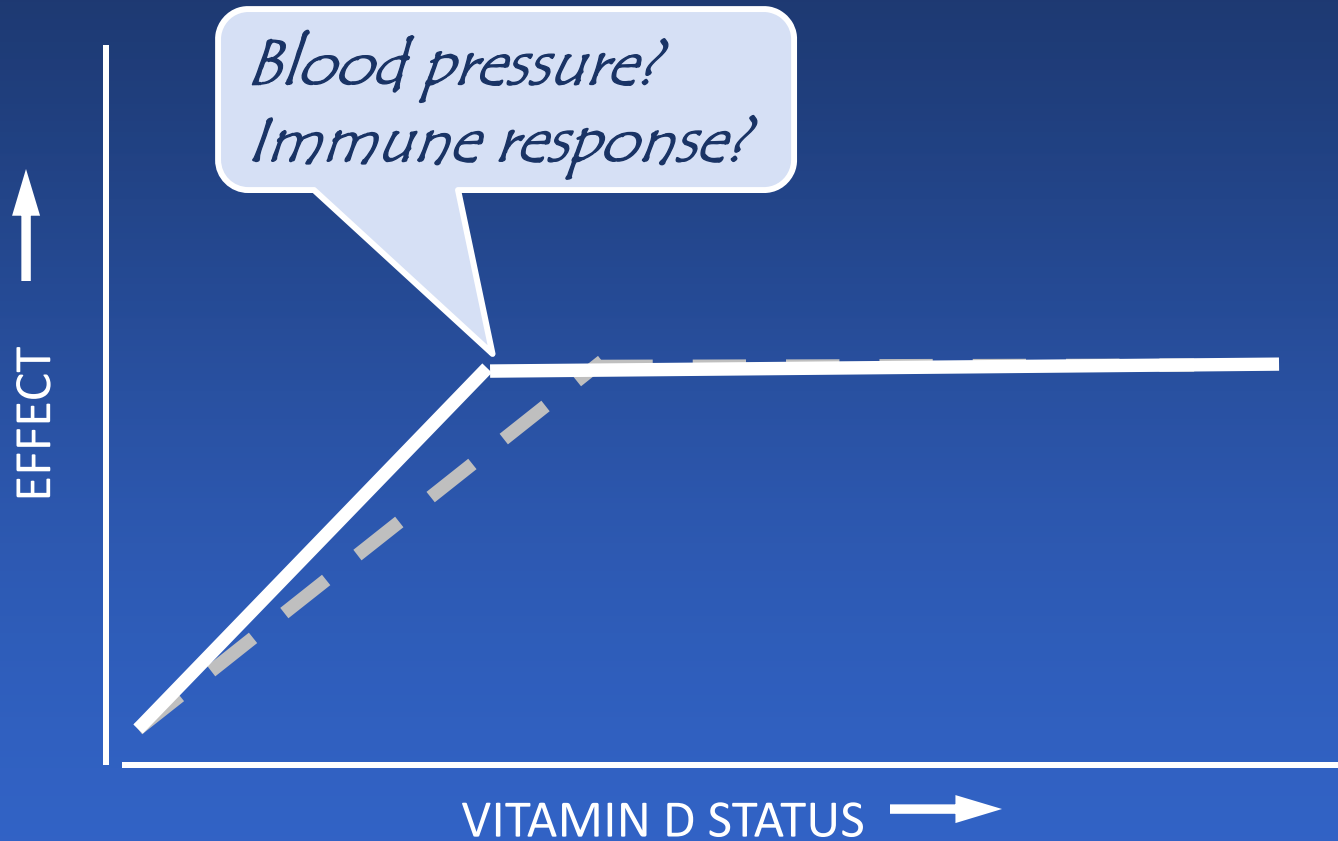
THE RESPONSE THRESHOLD



THE RESPONSE THRESHOLD



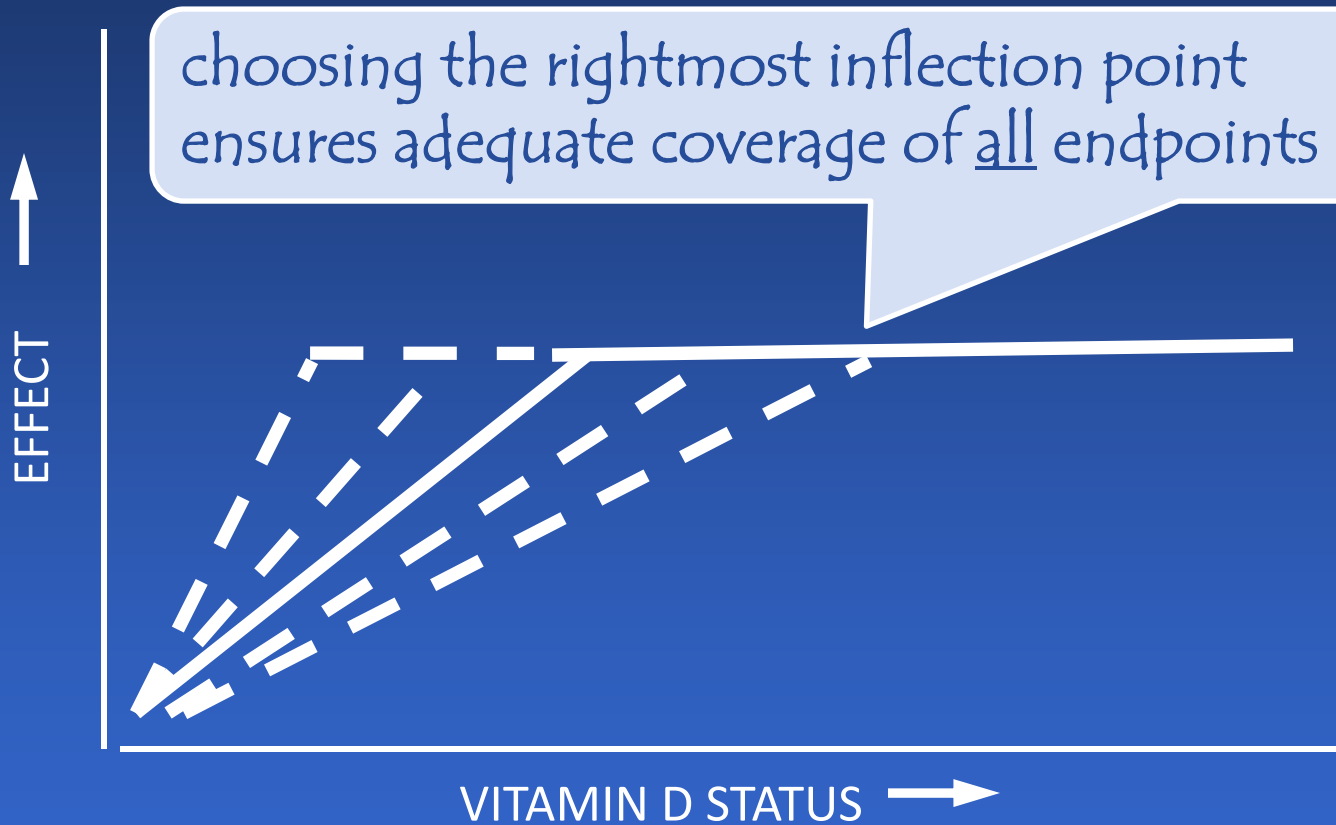
THE RESPONSE THRESHOLD



RESPONSE HETEROGENEITY

- different tissues within an individual
- and different individuals within a population
- will have varying threshold 25(OH)D response levels
- *hence*, inadequate vitamin D status will manifest itself differently from patient to patient and from population to population

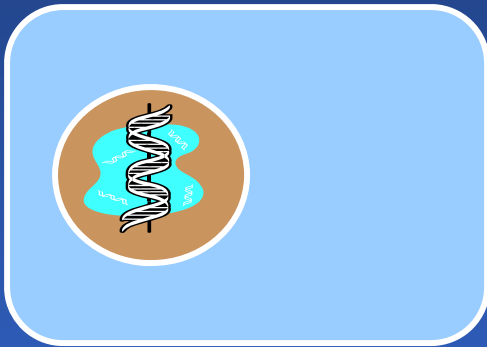
THE RESPONSE THRESHOLD



CELL MODELS

old:

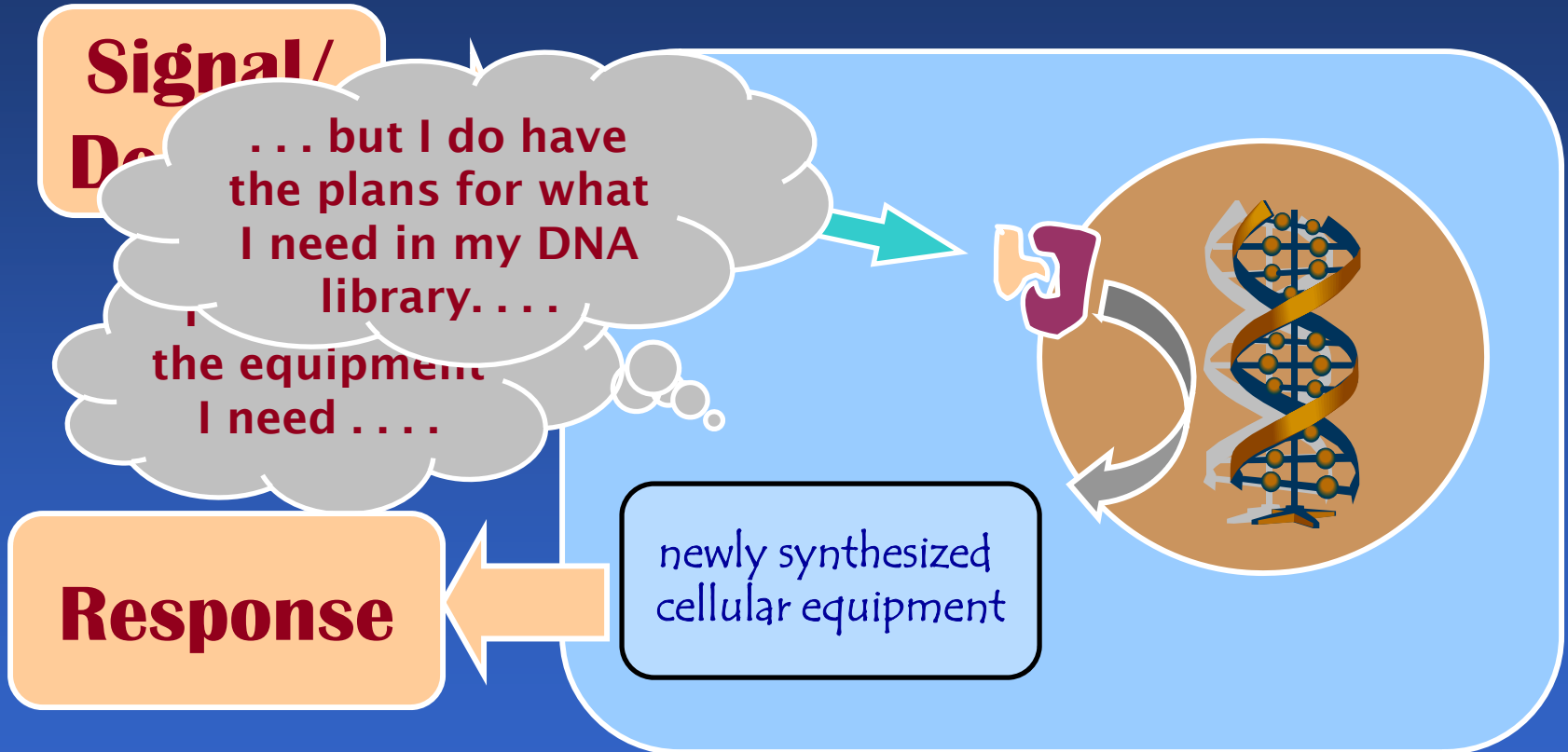
DNA in somatic cells functions mainly to make faithful copies for tissue repair or replacement



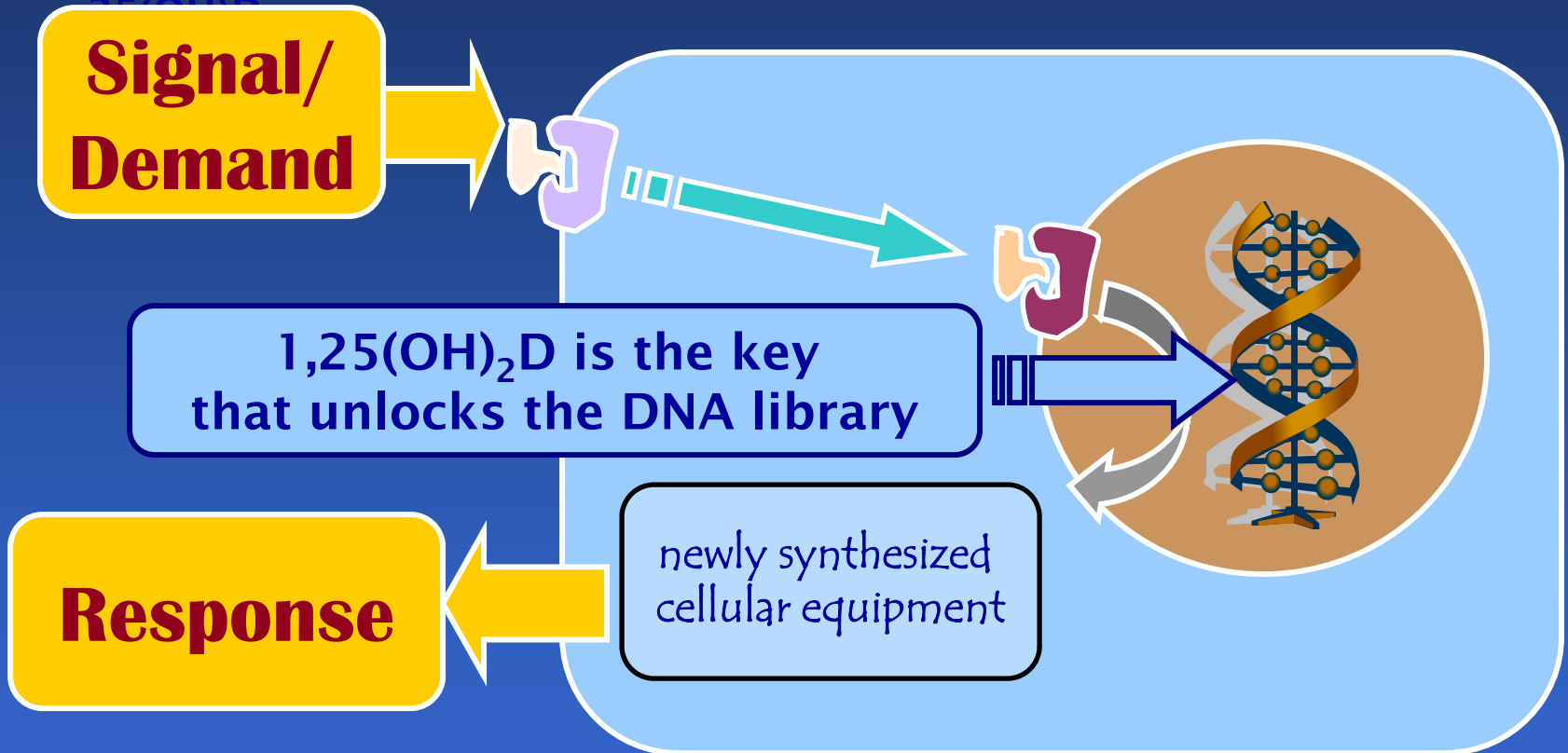
new:

DNA functions constantly in synthesis of needed cellular apparatus

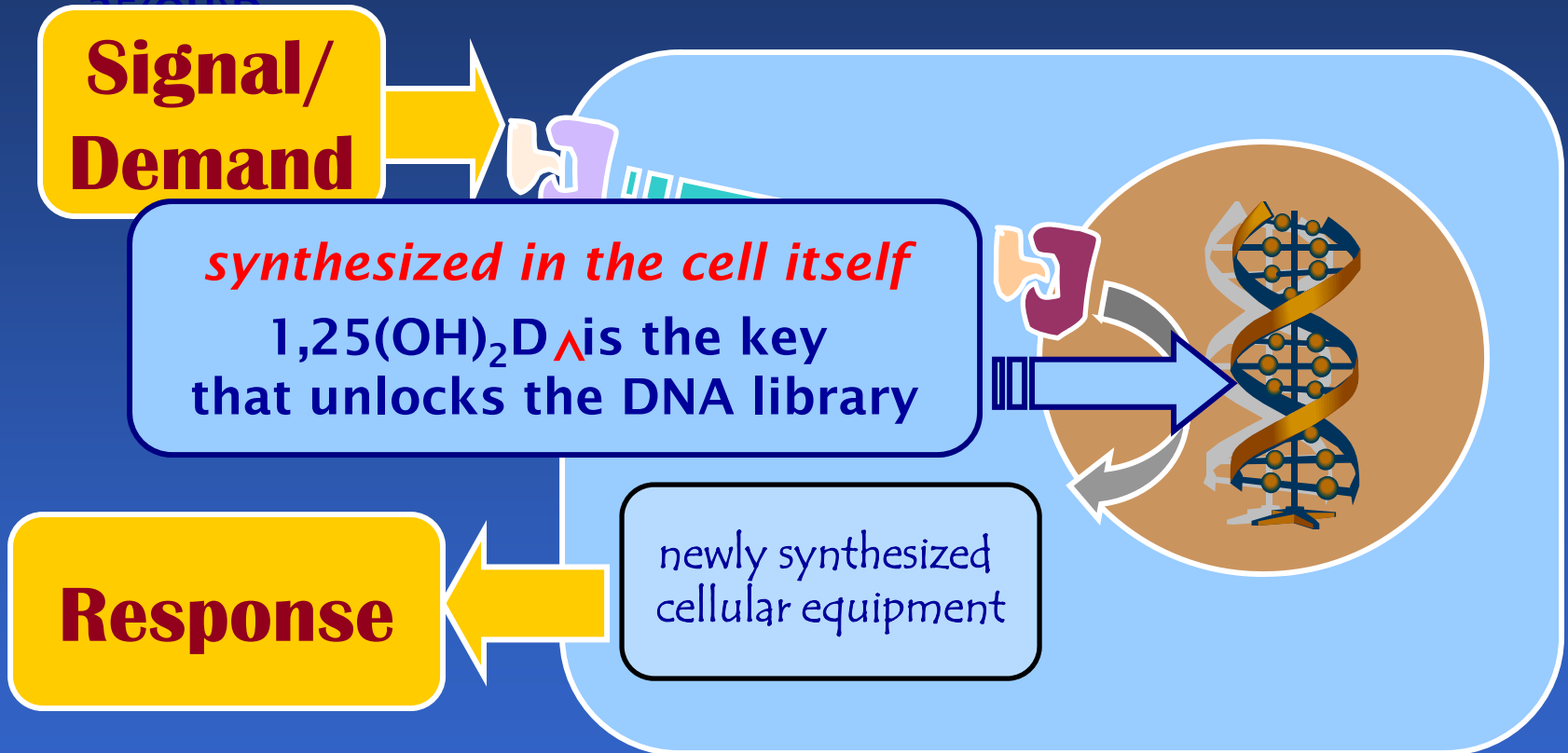
HOW A CELL RESPONDS



HOW A CELL RESPONDS



HOW A CELL RESPONDS



OLD VIT D - CANONICAL SCHEME

skin

liver

kidney

gut

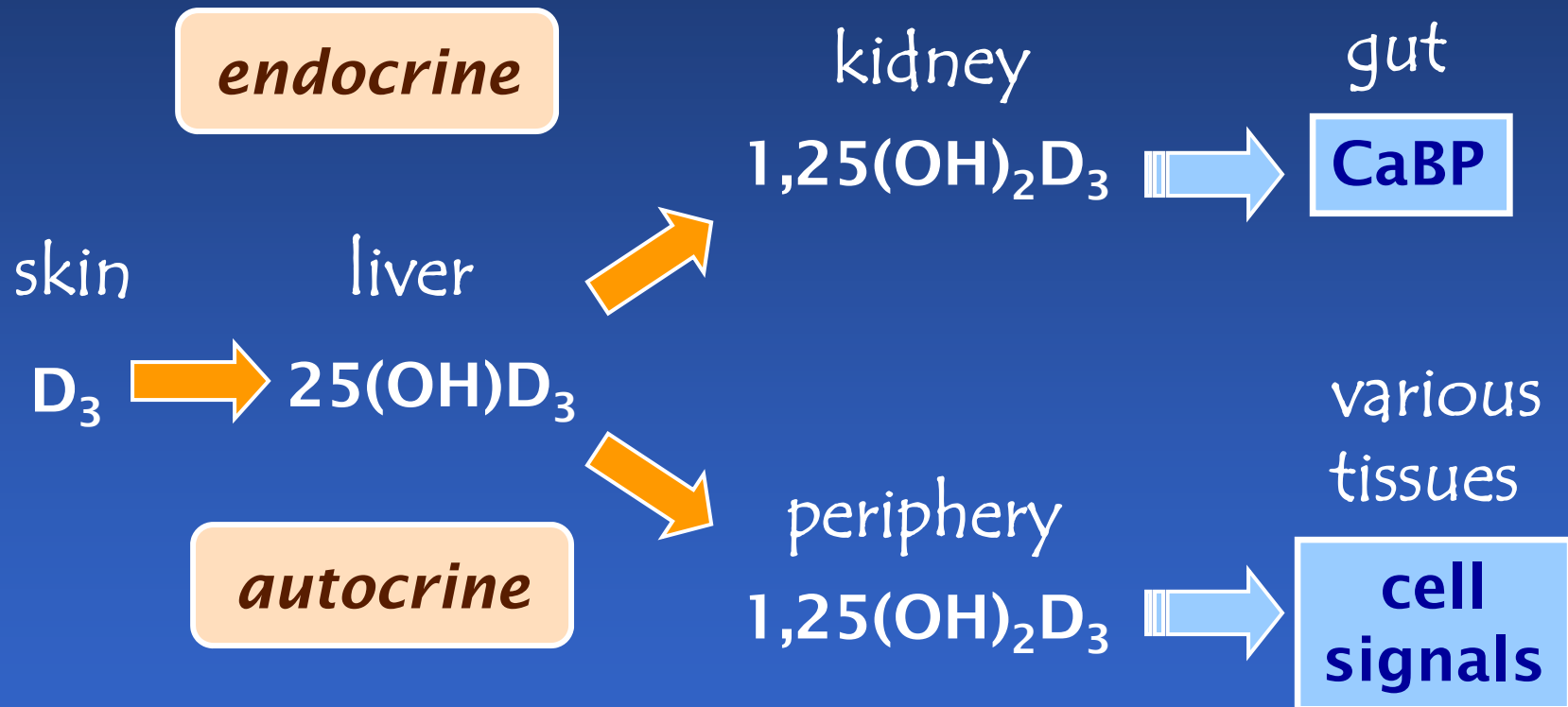


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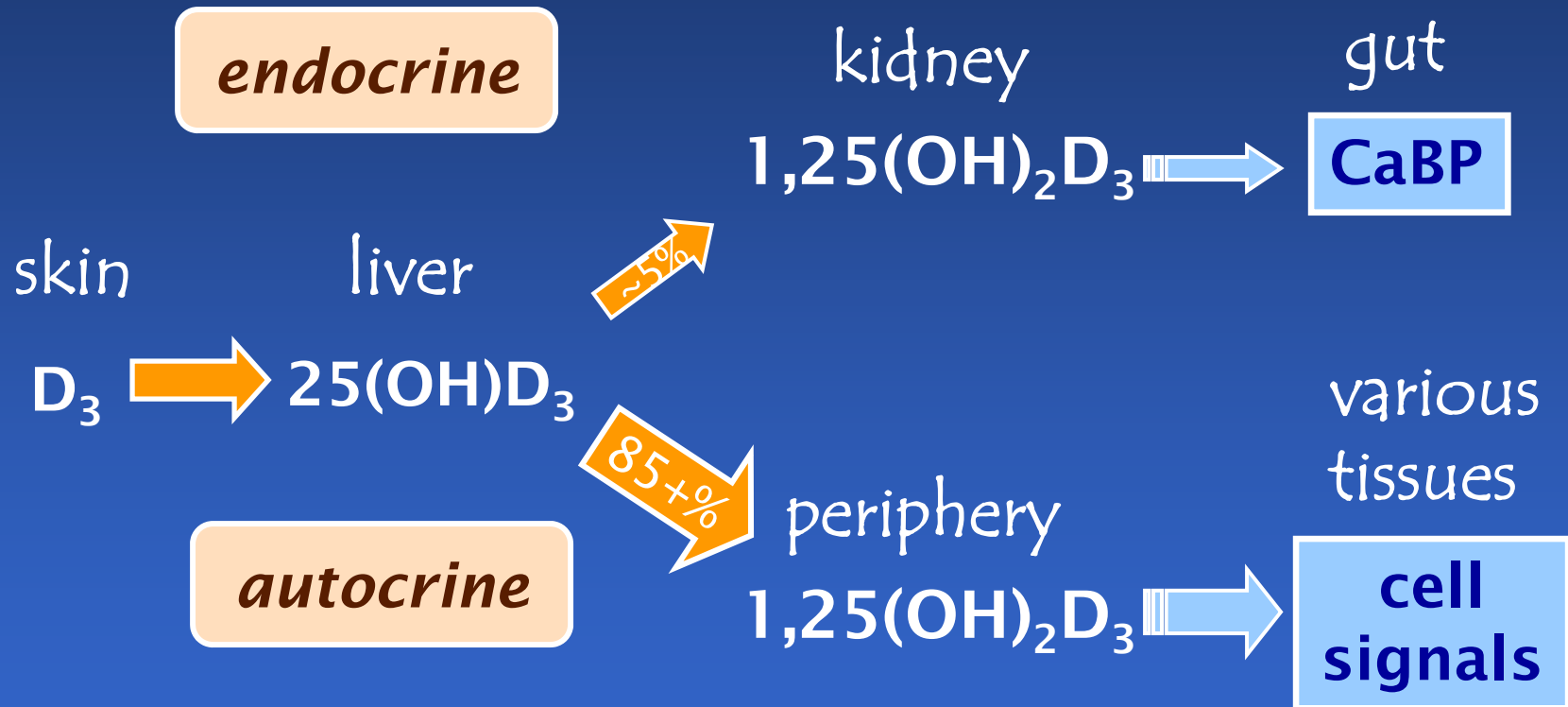


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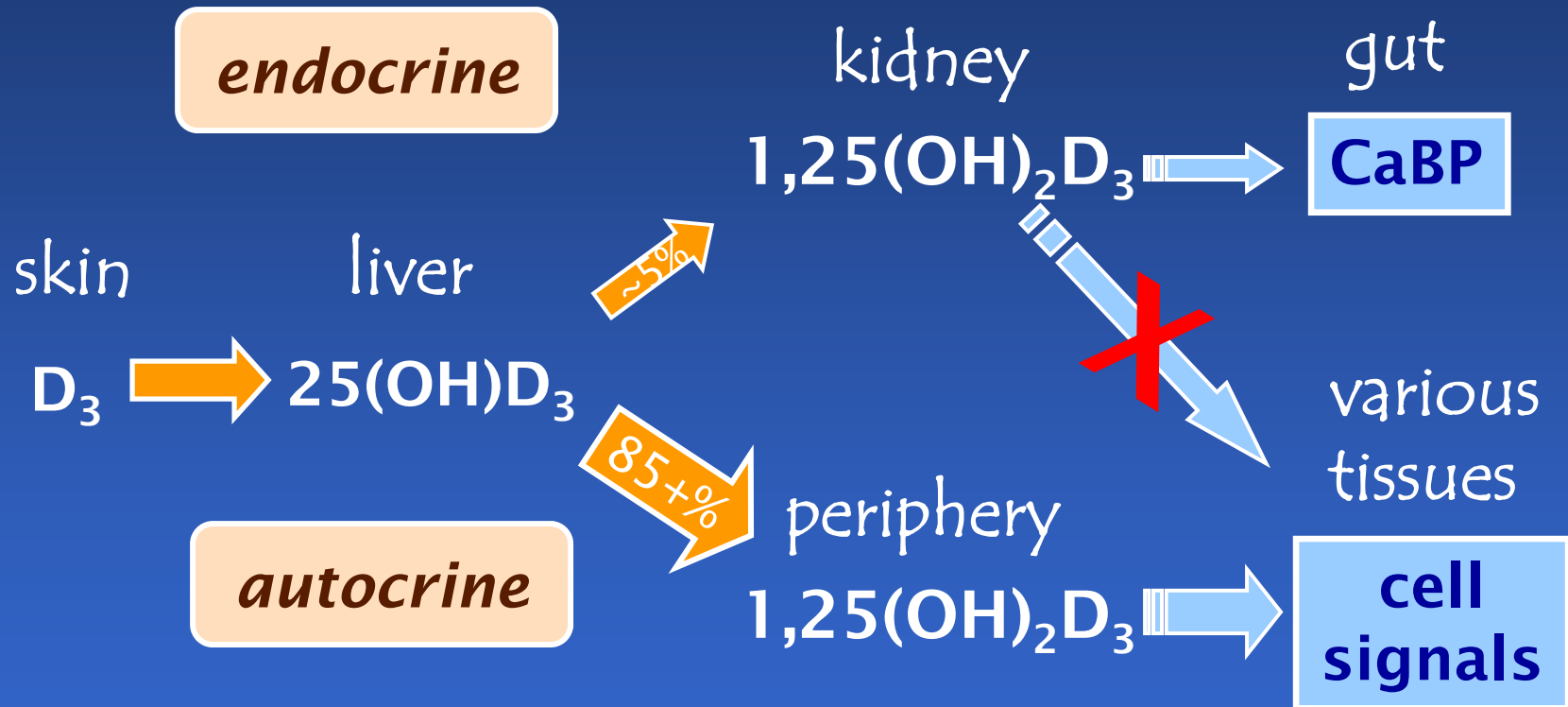
VIT D – EXPANDED SCHEME



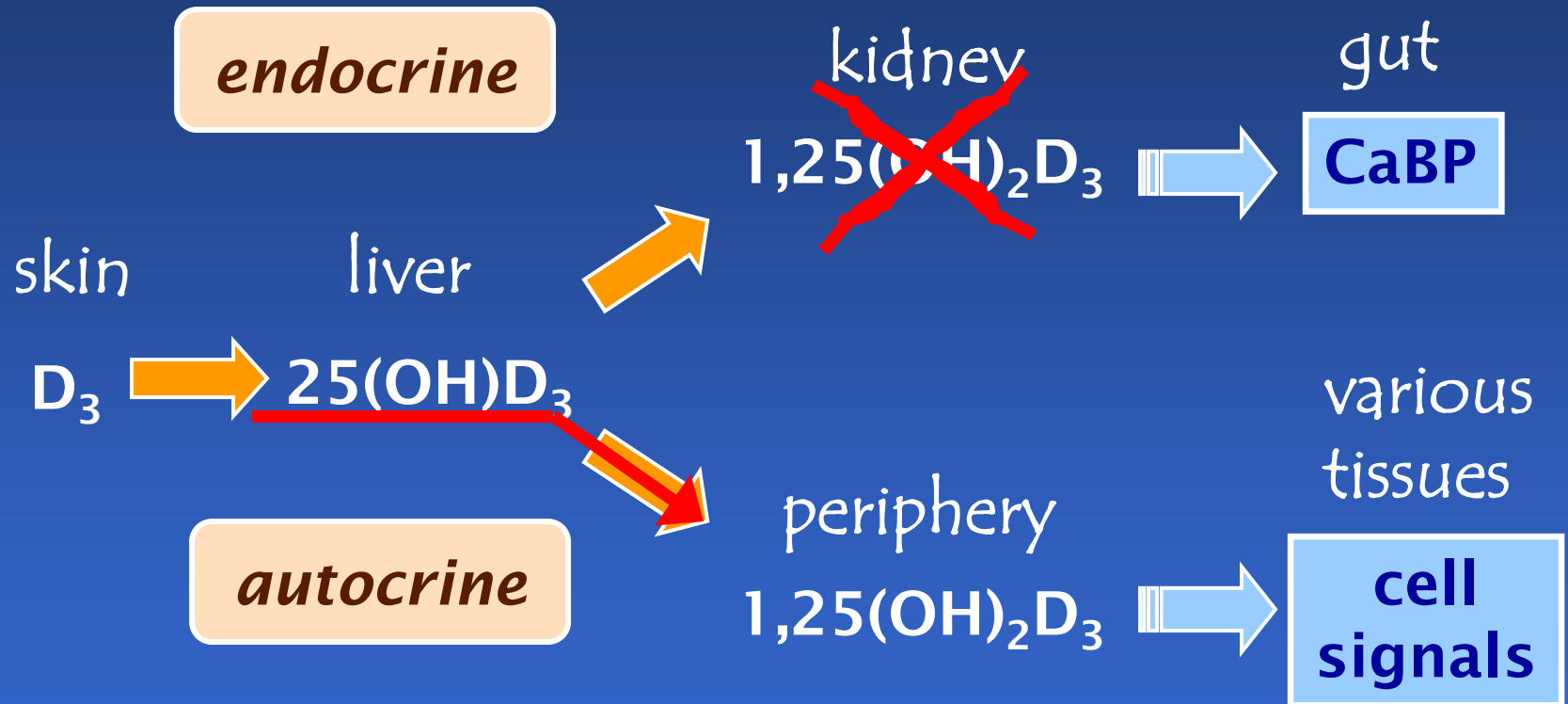
VIT D – EXPANDED SCHEME



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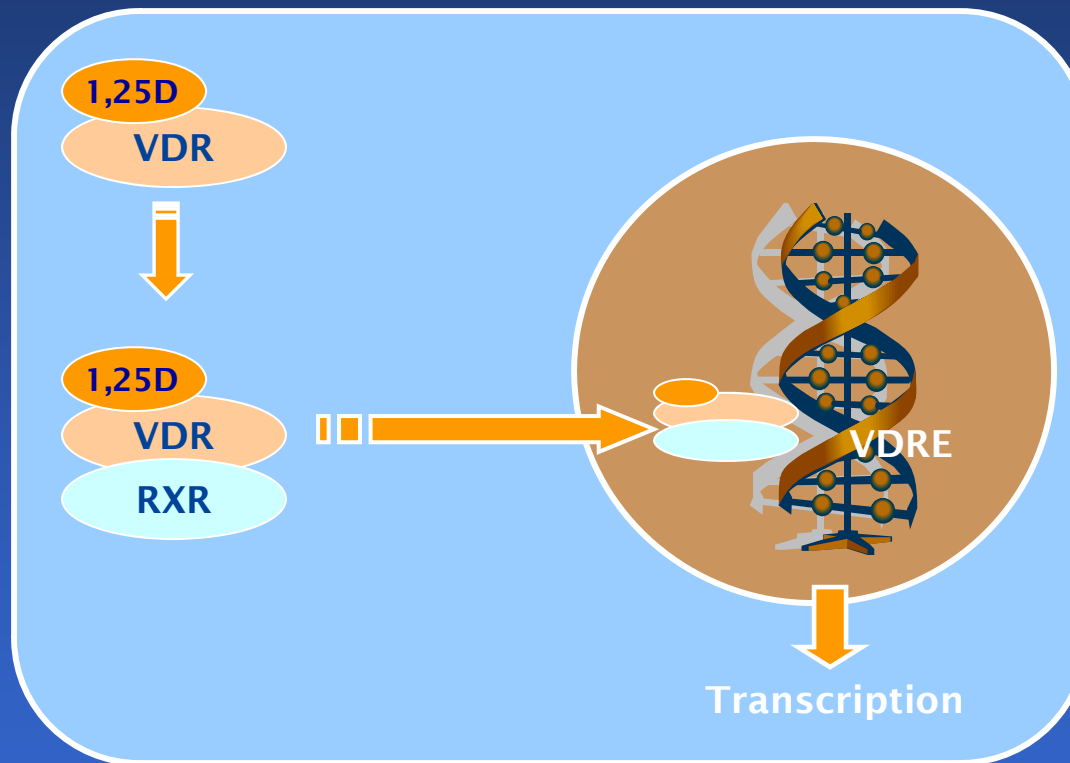


VIT D – EXPANDED SCHEME



AUTOCRINE ACTION

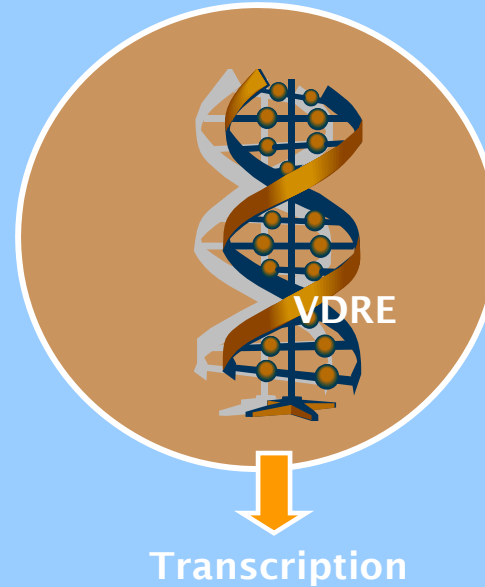
25(OH)D



AUTOCRINE ACTION

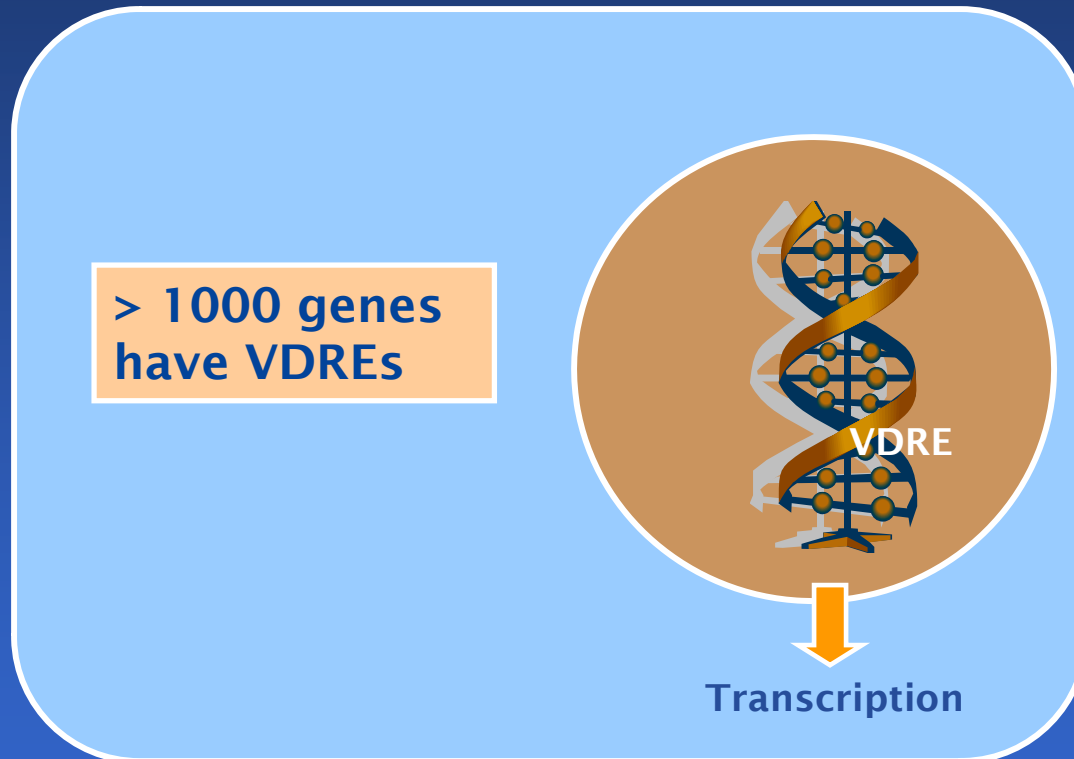
25(OH)D

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



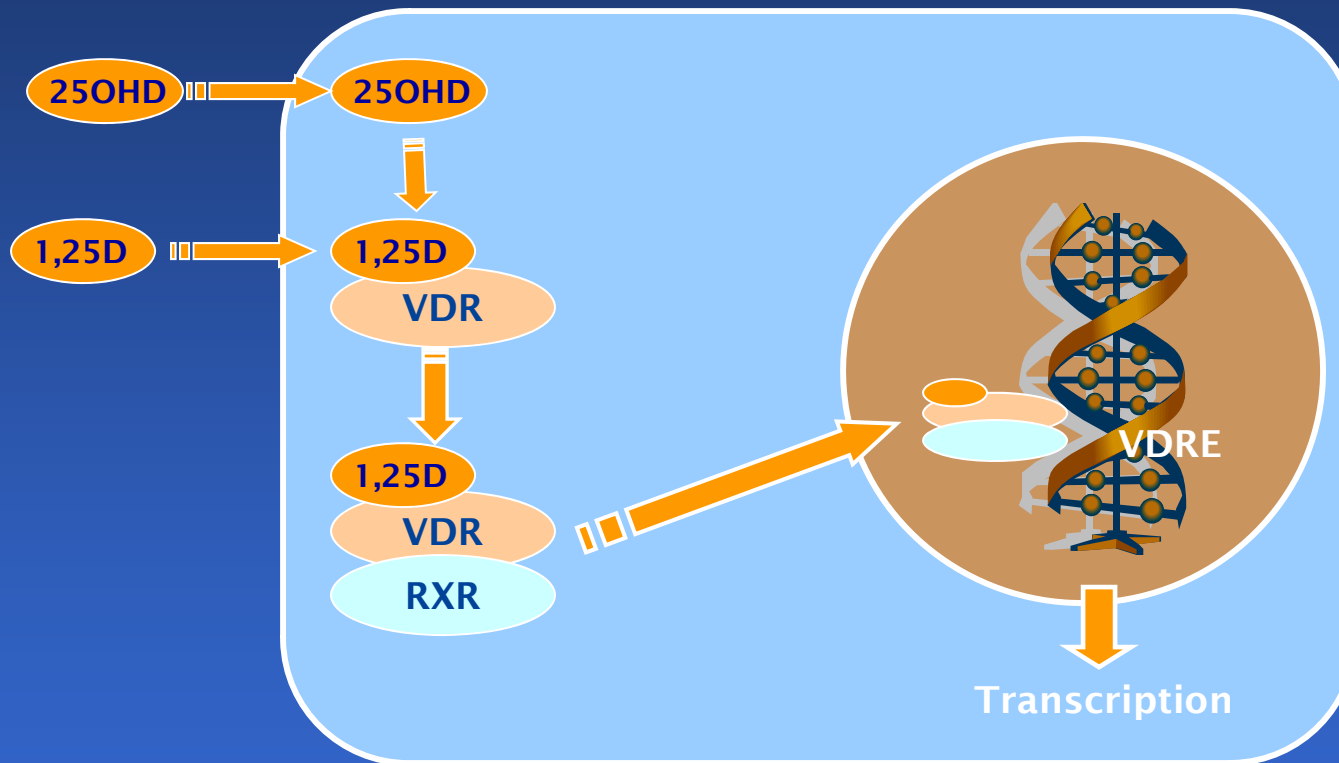
AUTOCRINE ACTION

25(OH)D



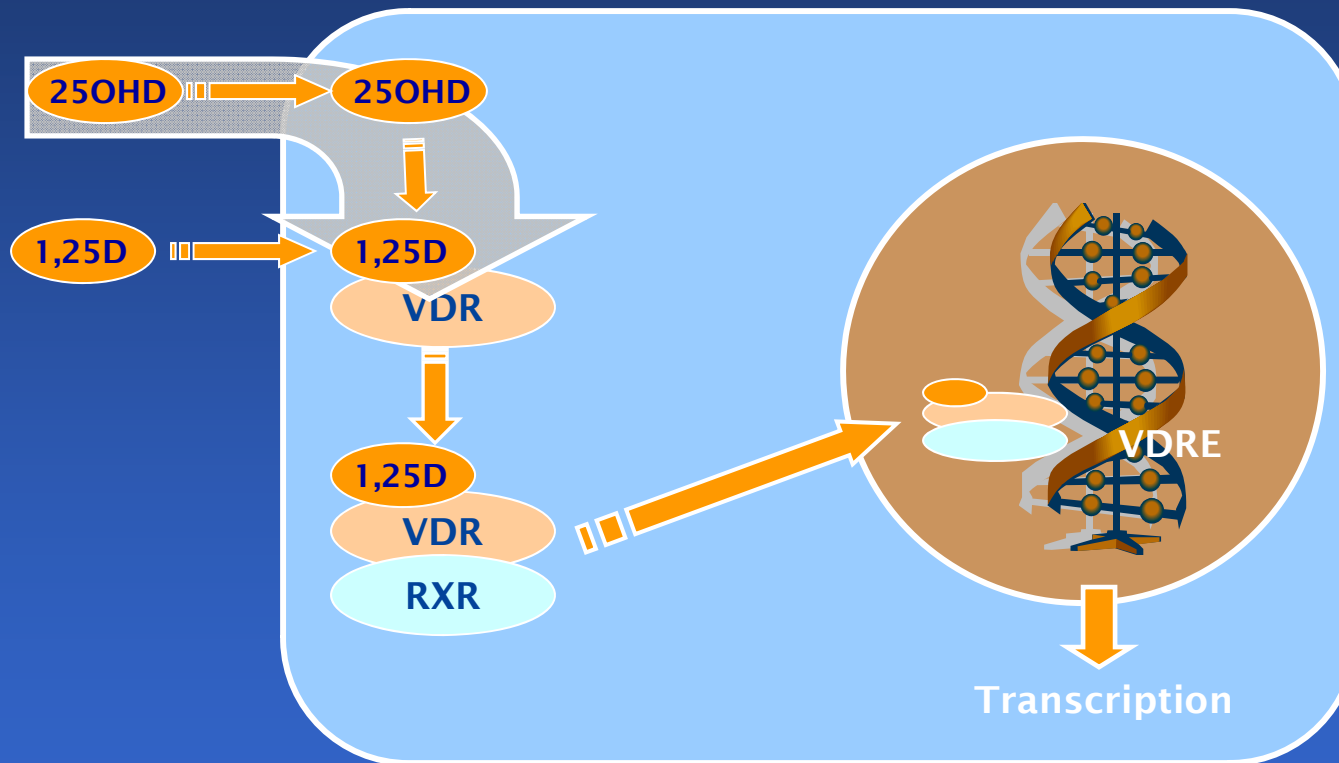
AUTOCRINE ACTION

25(OH)D



AUTOCRINE ACTION

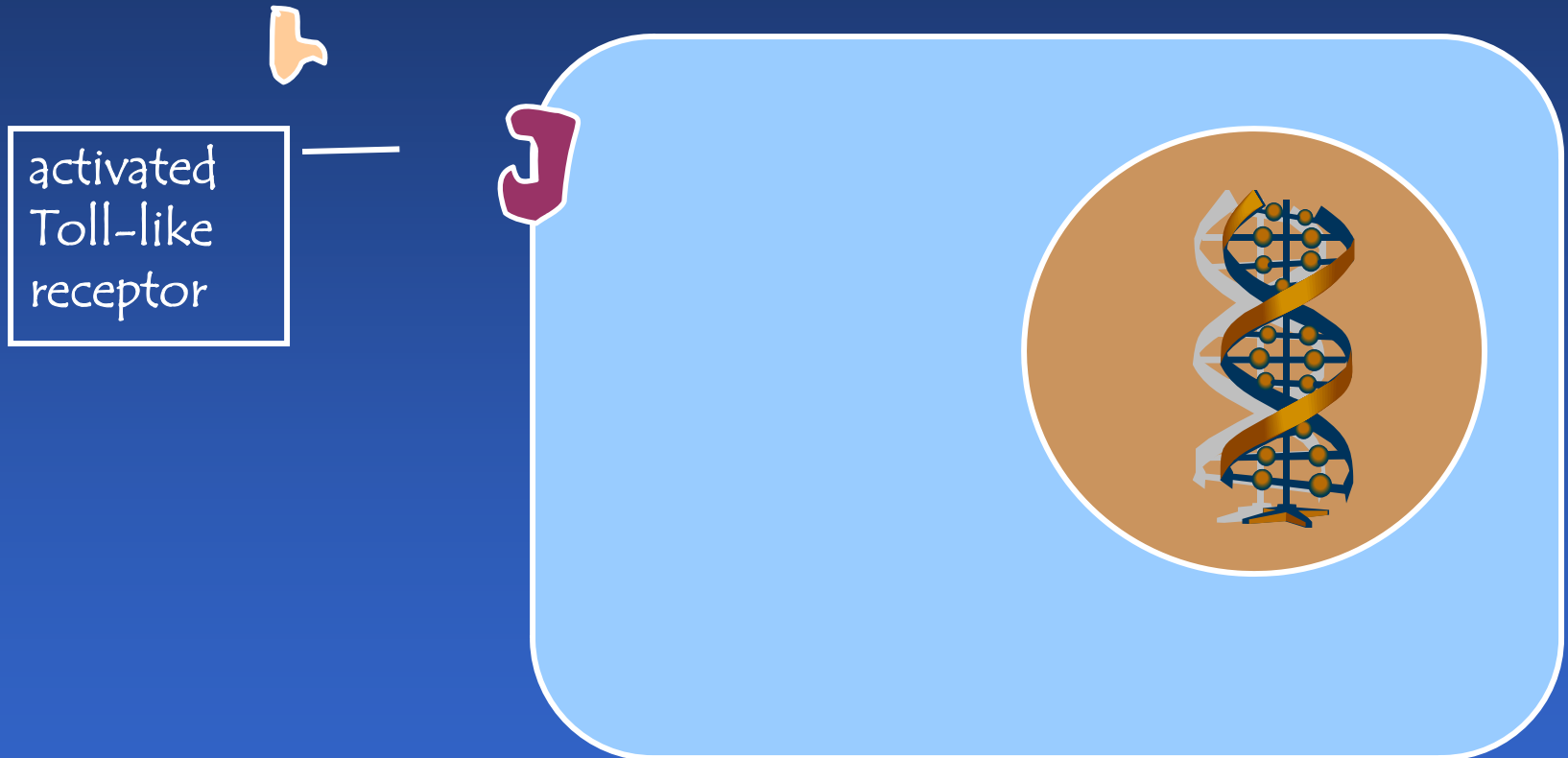
25(OH)D



This scheme means that each tissue

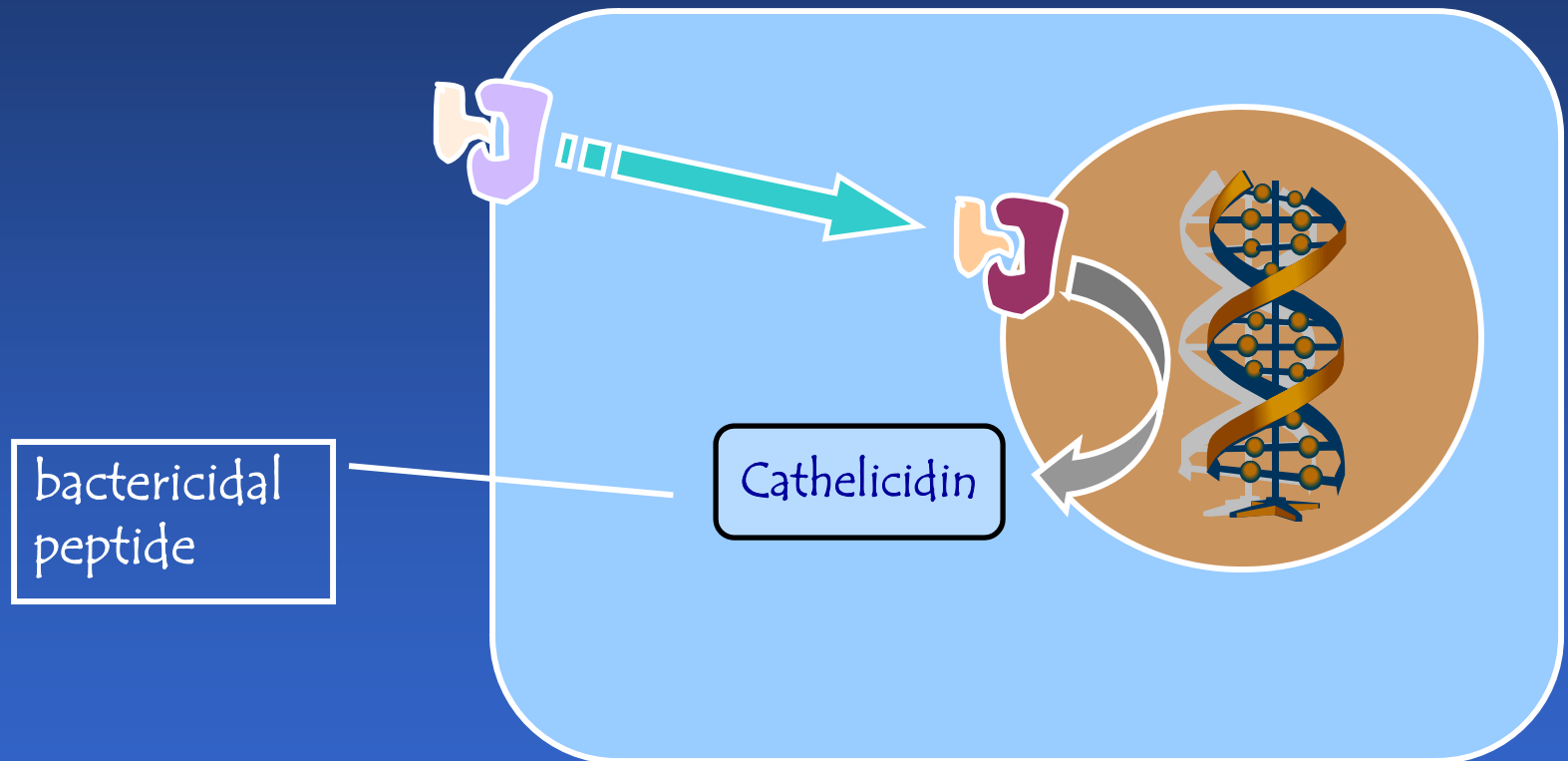
- has the amount of $1,25(\text{OH})_2\text{D}$ it needs
- when it needs it
- and is not dependent upon a "one-size-fits all" systemic level of circulating $1,25(\text{OH})_2\text{D}$

VITAMIN D & INNATE IMMUNITY*



VITAMIN D & INNATE IMMUNITY*

25(OH)D



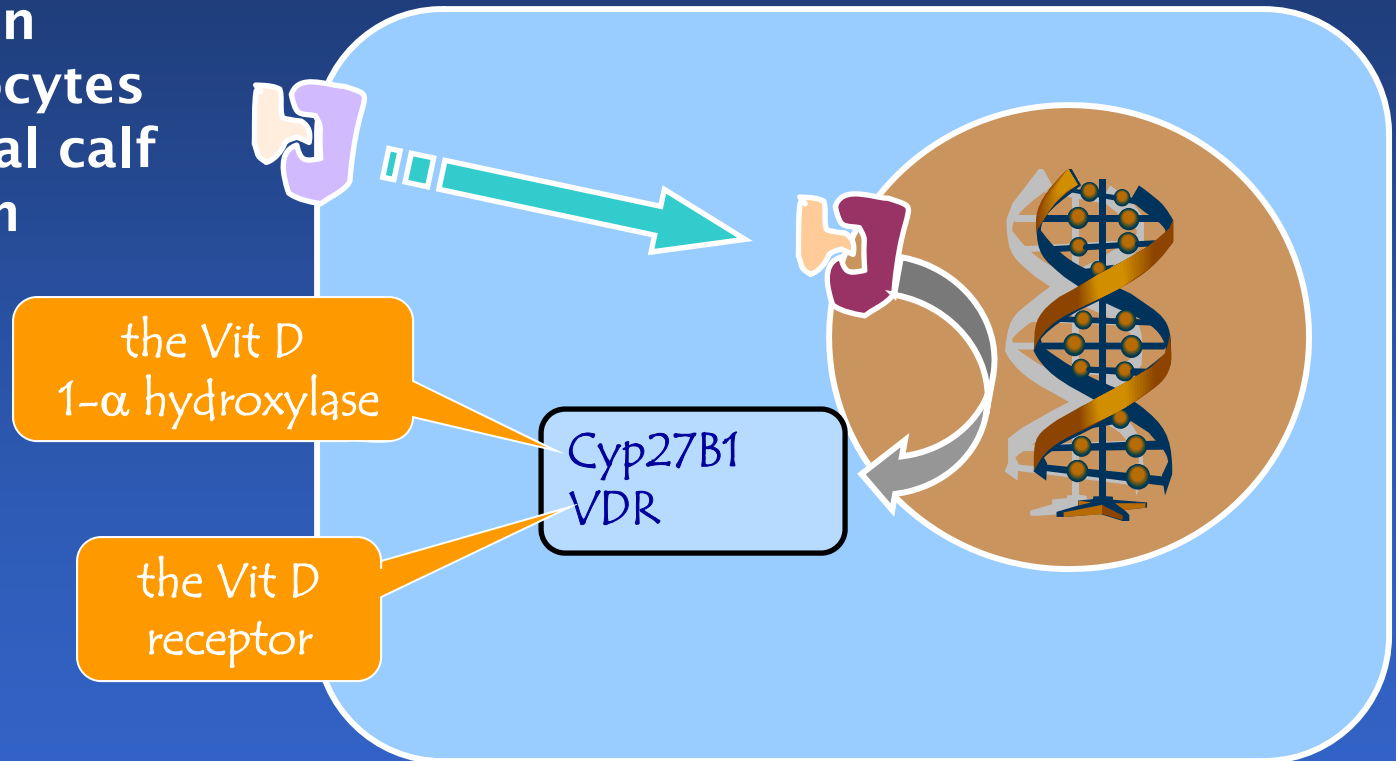
bactericidal peptide

Cathelicidin

VITAMIN D & INNATE IMMUNITY*

25(OH)D

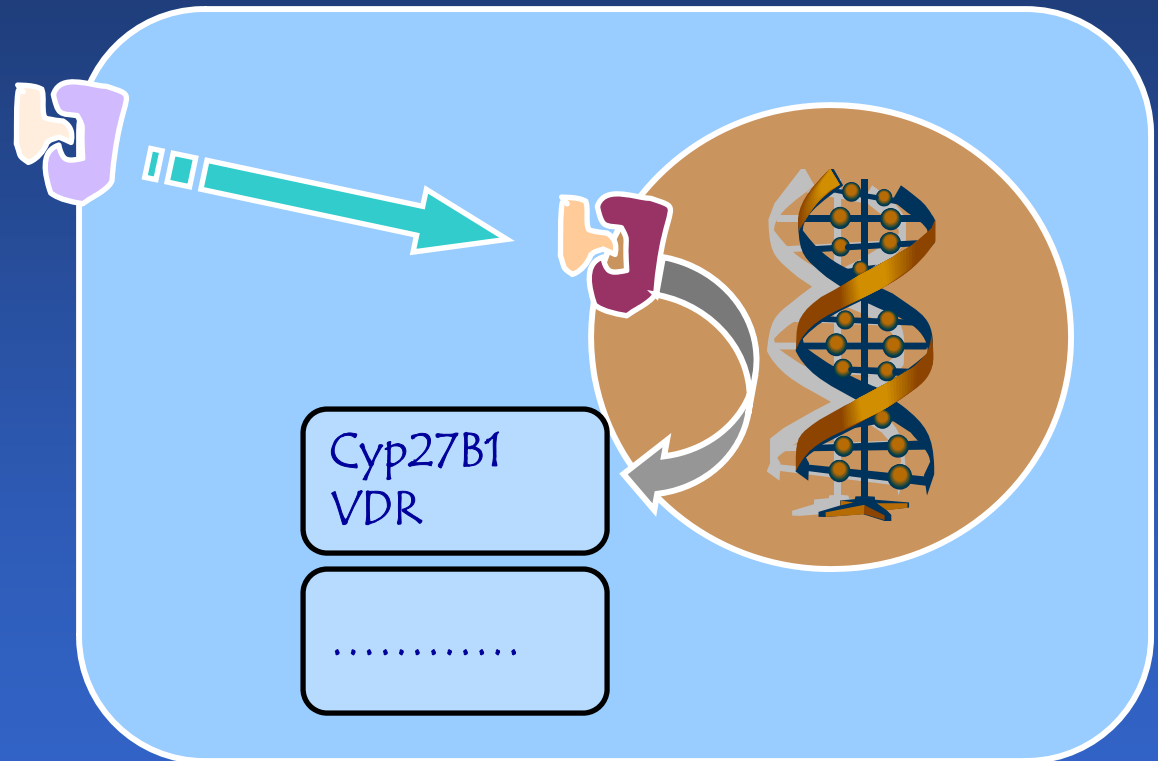
- human monocytes in fetal calf serum



VITAMIN D & INNATE IMMUNITY*

25(OH)D

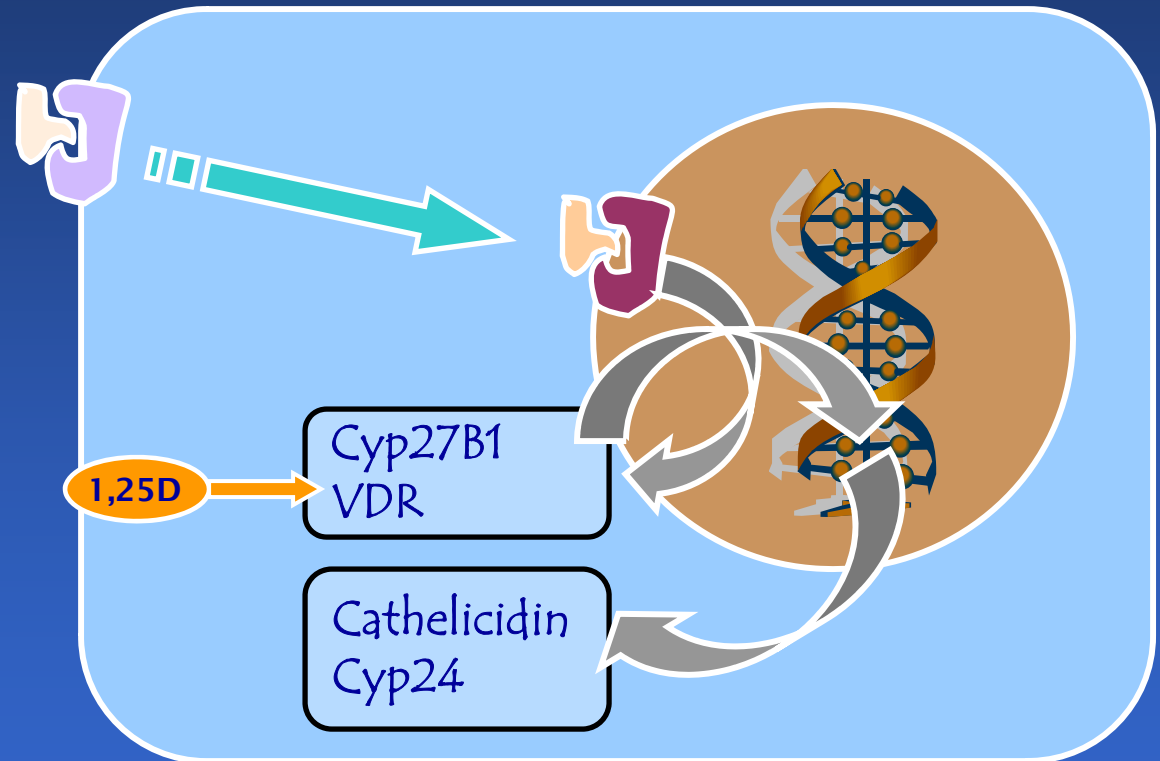
- human monocytes in fetal calf serum
- fetal calf serum is low in both 25(OH)D & 1,25(OH)₂D



VITAMIN D & INNATE IMMUNITY*

25(OH)D

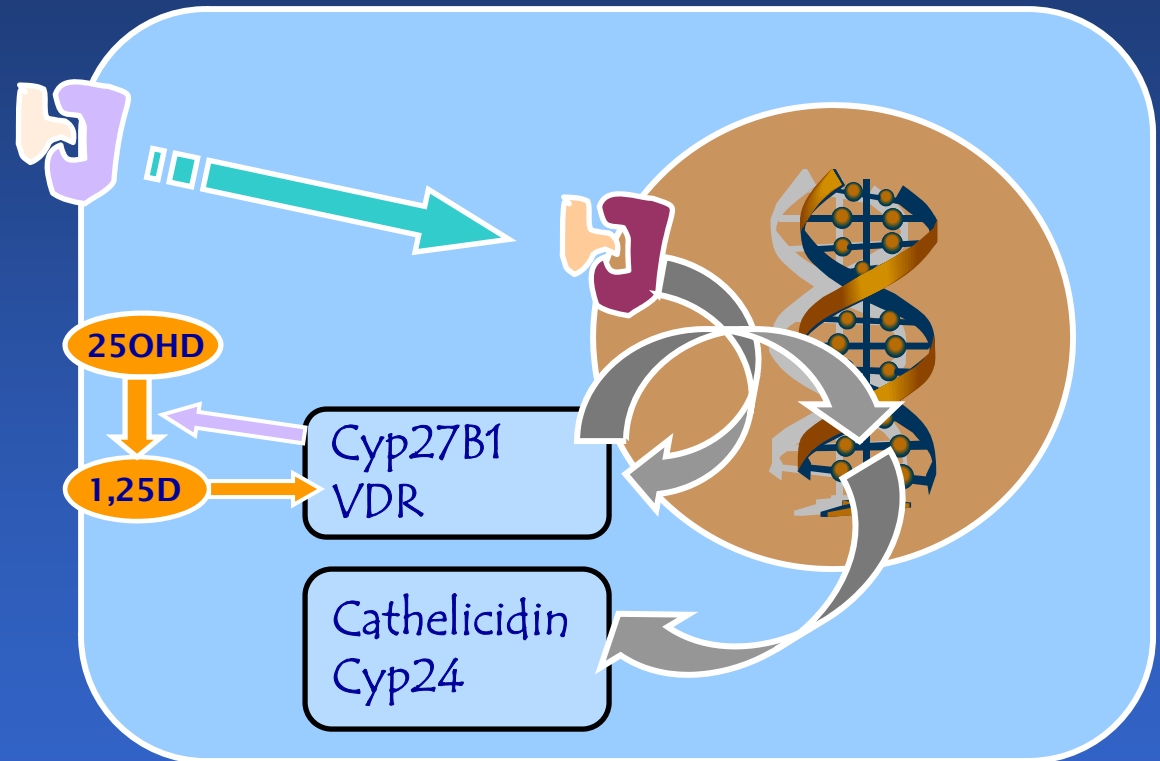
- human monocytes in fetal calf serum
- add $1,25(\text{OH})_2\text{D}$ to the system



VITAMIN D & INNATE IMMUNITY*

25(OH)D

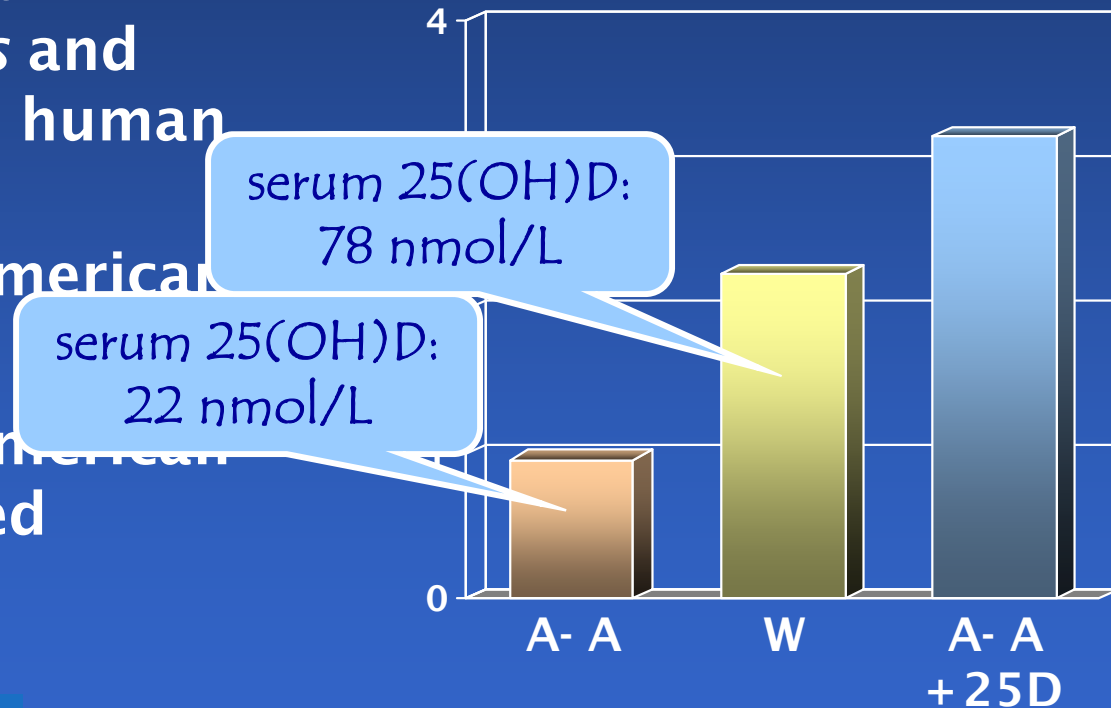
- human monocytes in fetal calf serum
- add 25(OH)D to the system



VITAMIN D & TUBERCULOSIS

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

Cathelicidin mRNA



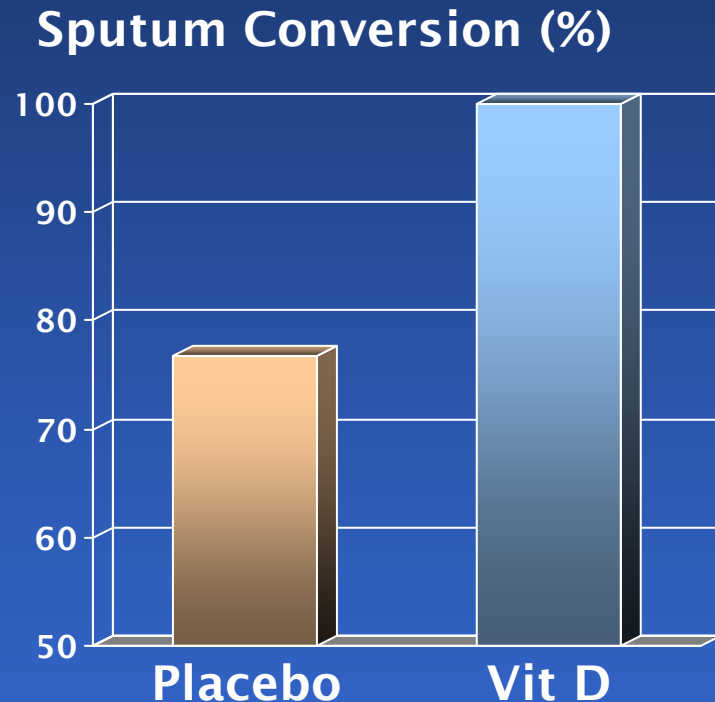
VITAMIN D & TUBERCULOSIS

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

VITAMIN D & TUBERCULOSIS*

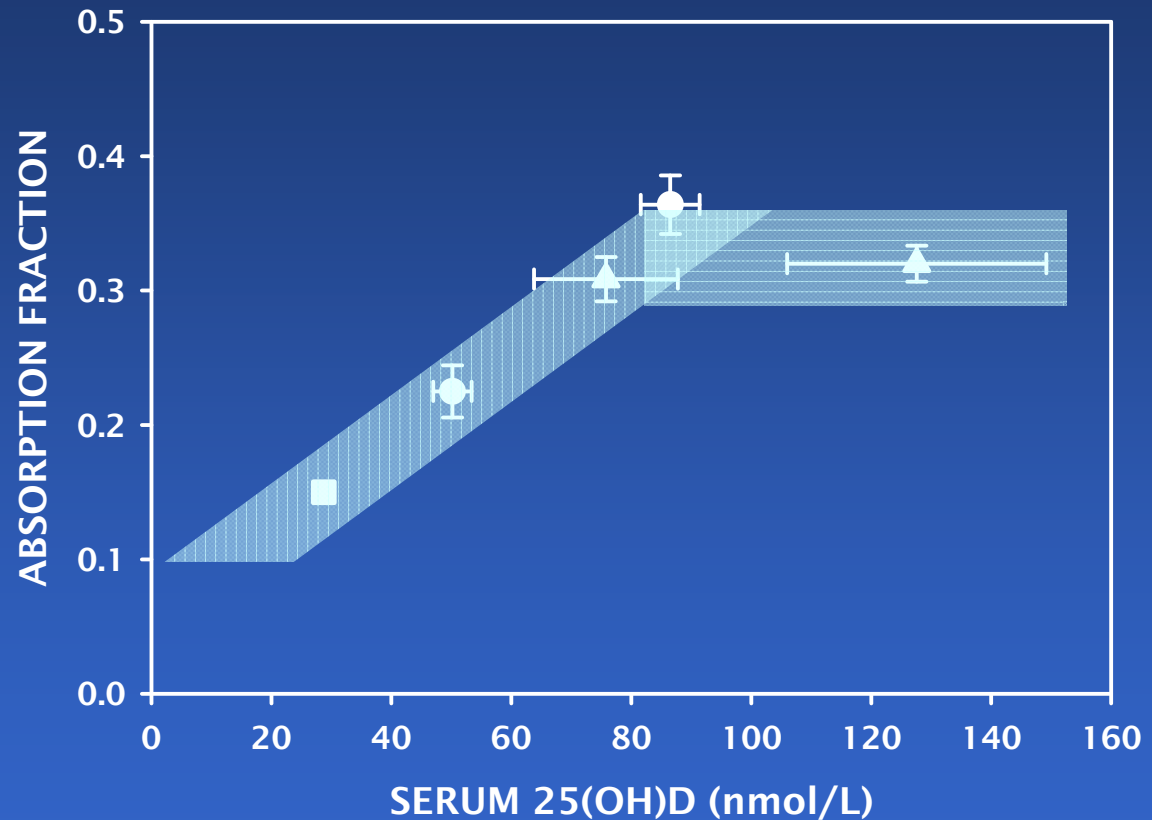
- 67 pts with pulmonary TB
- standard treatment for all
- in addition, randomized to either vit D 10,000 IU/d or placebo
- $P = 0.002$



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)D₂ is of no value unless the MD is following treatment with vit D₂
- serum 1,25(OH)₂D does not measure vit D status (instead, it measures Ca need)

A VITAMIN D THRESHOLD

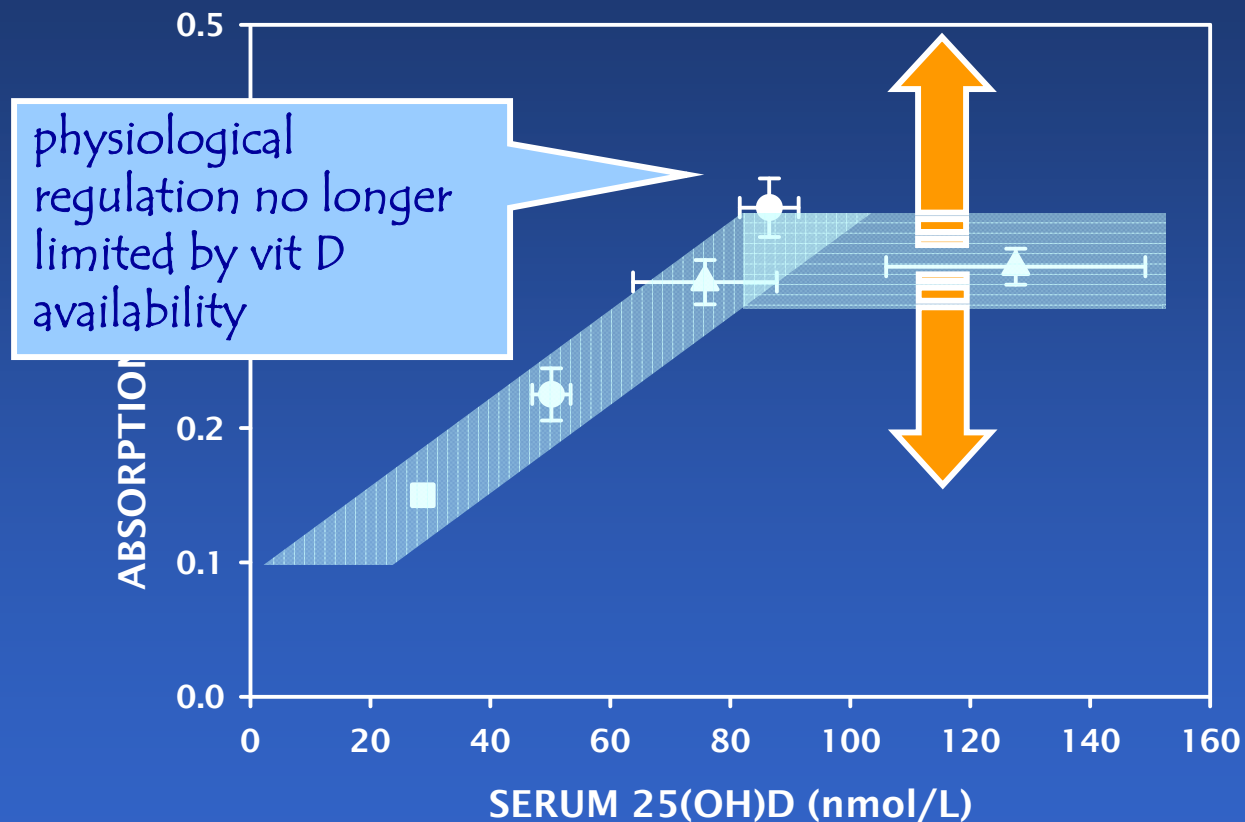


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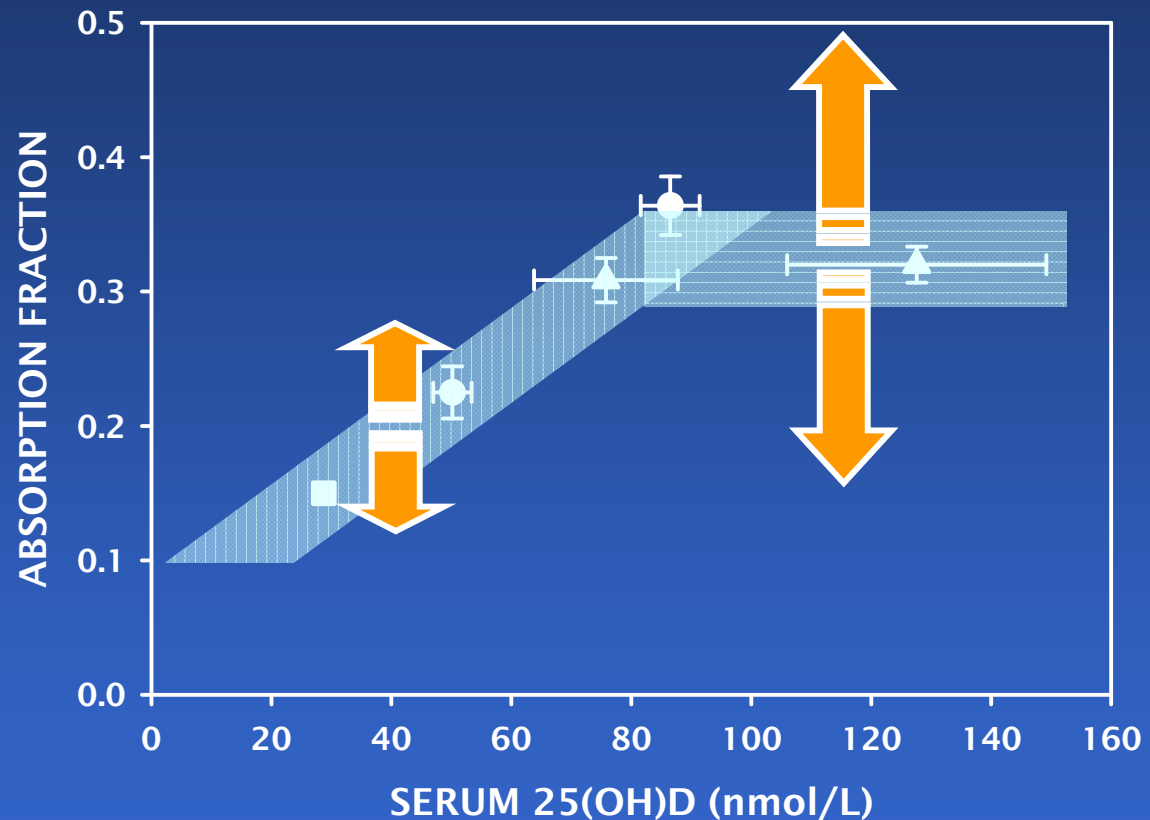


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A VITAMIN D THRESHOLD



A VITAMIN D THRESHOLD



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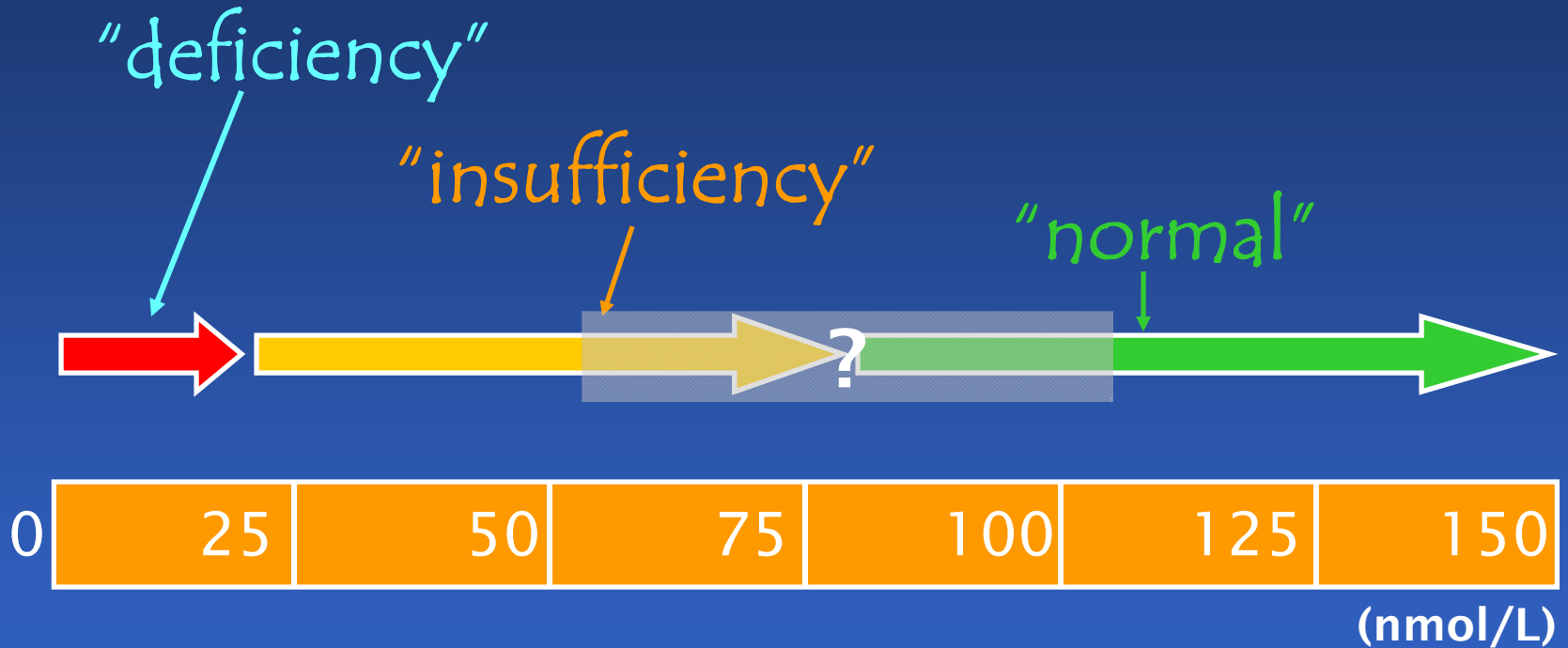
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The evidence to be presented in the papers of this meeting points to a requirement for serum 25(OH)D that is above 80 nmol/L* (and perhaps as much as 100–125 nmol/L**).

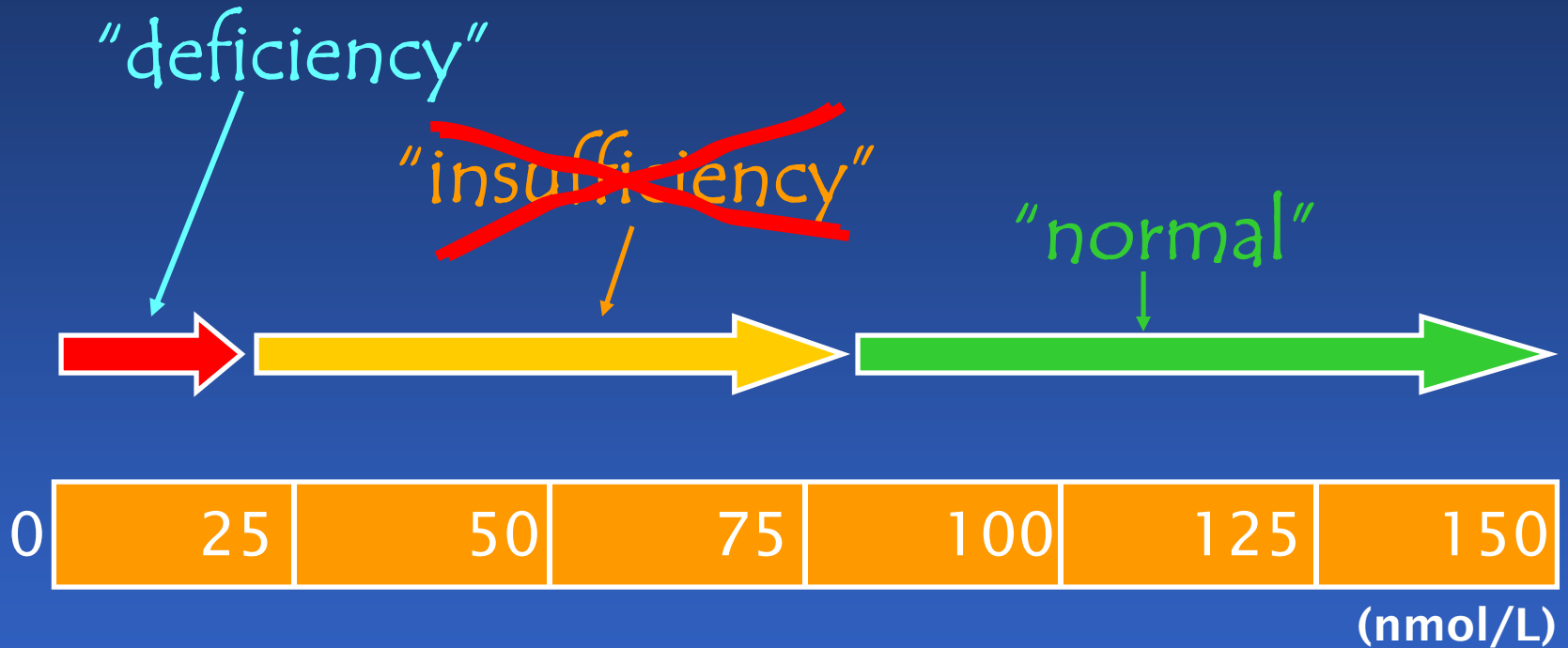
* 32 ng/mL

** 40–50 ng/mL

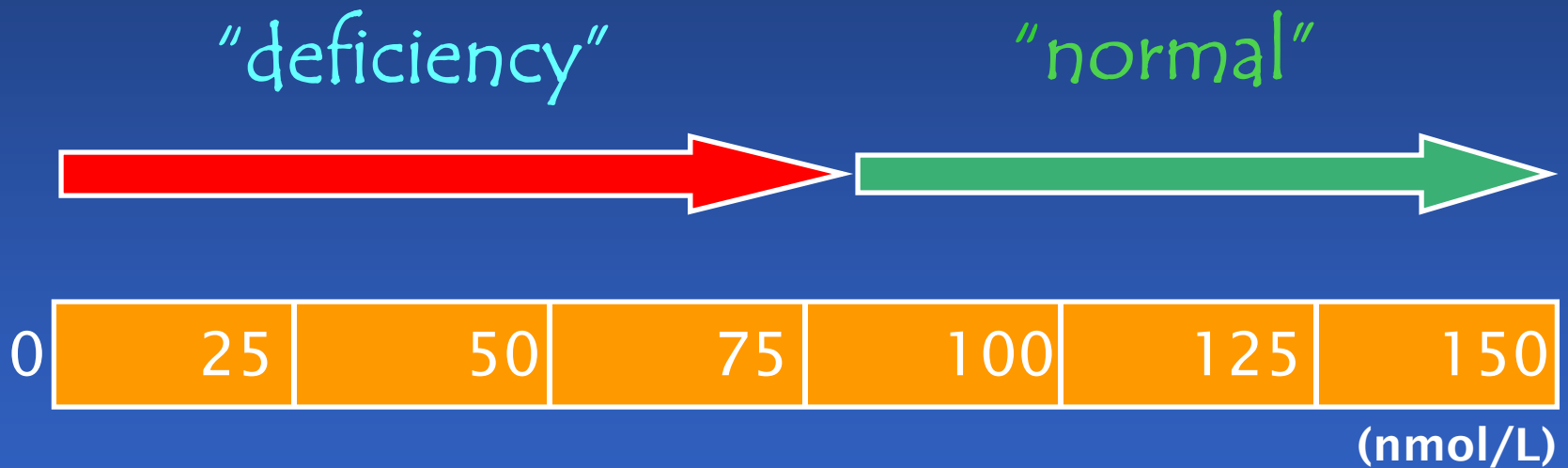
THE 25(OH)D CONTINUUM



THE 25(OH)D CONTINUUM

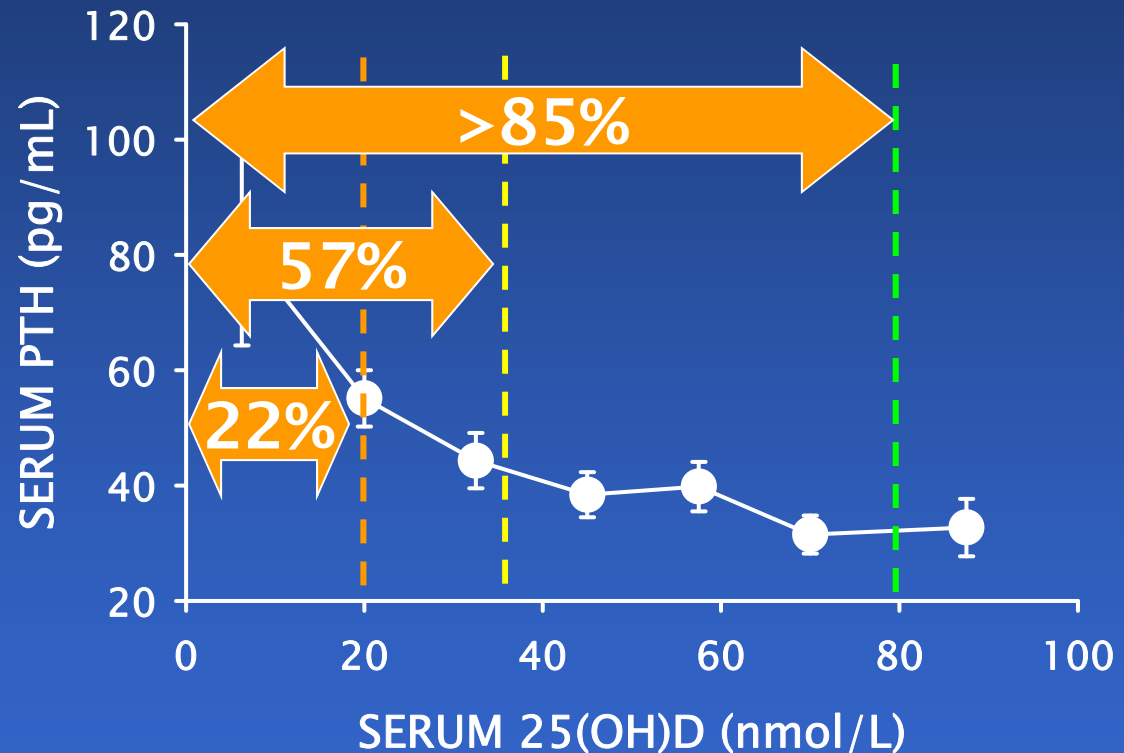


THE 25(OH)D CONTINUUM



25(OH)D & SERUM iPTH*

290
consecutive
pts. on a
general
medical
ward - MGH



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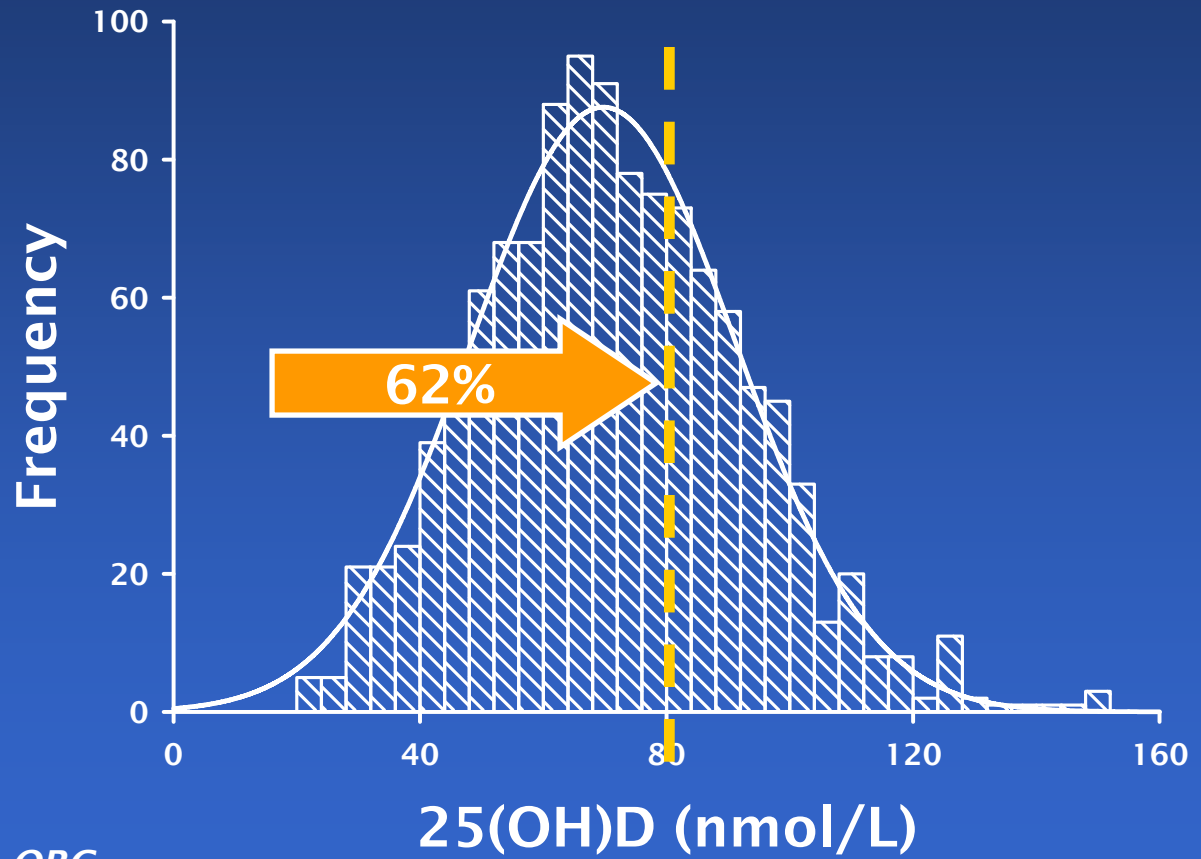
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*after Thomas et al., 1998 NEJM;338:777-783

25(OH)D IN OLDER WOMEN*

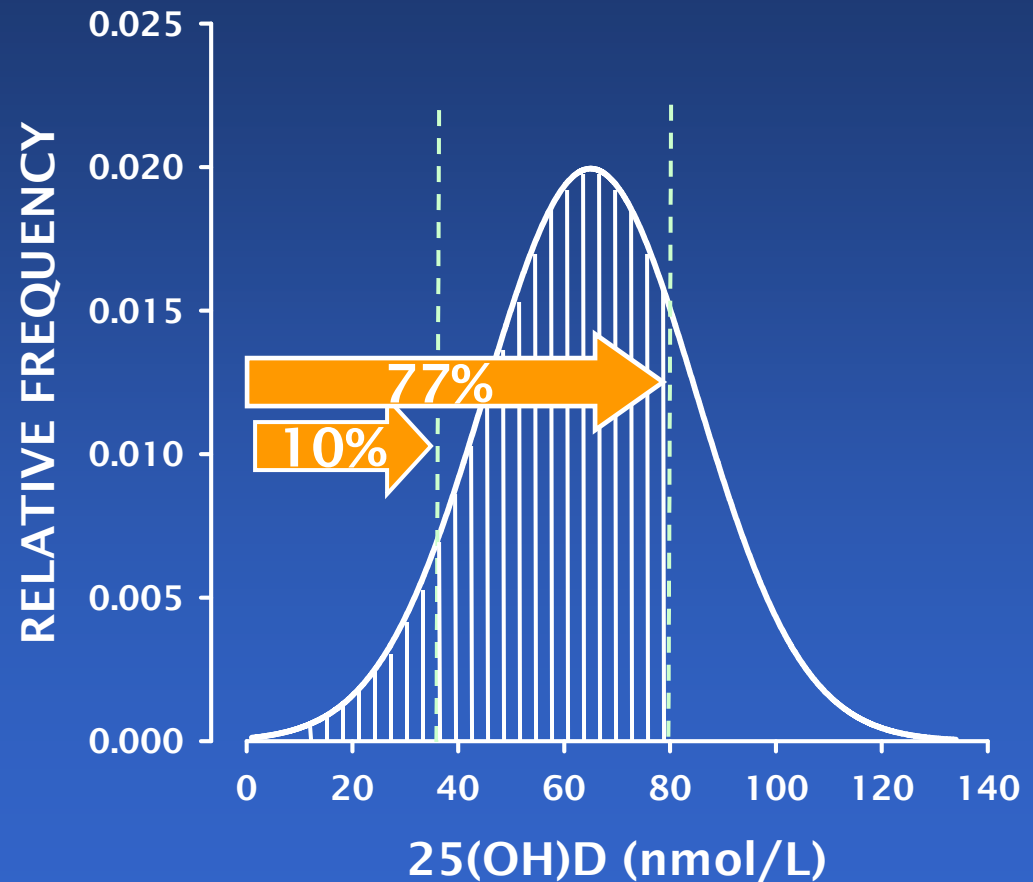
- 1168 women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU

*Lappe et al., JACN 2006



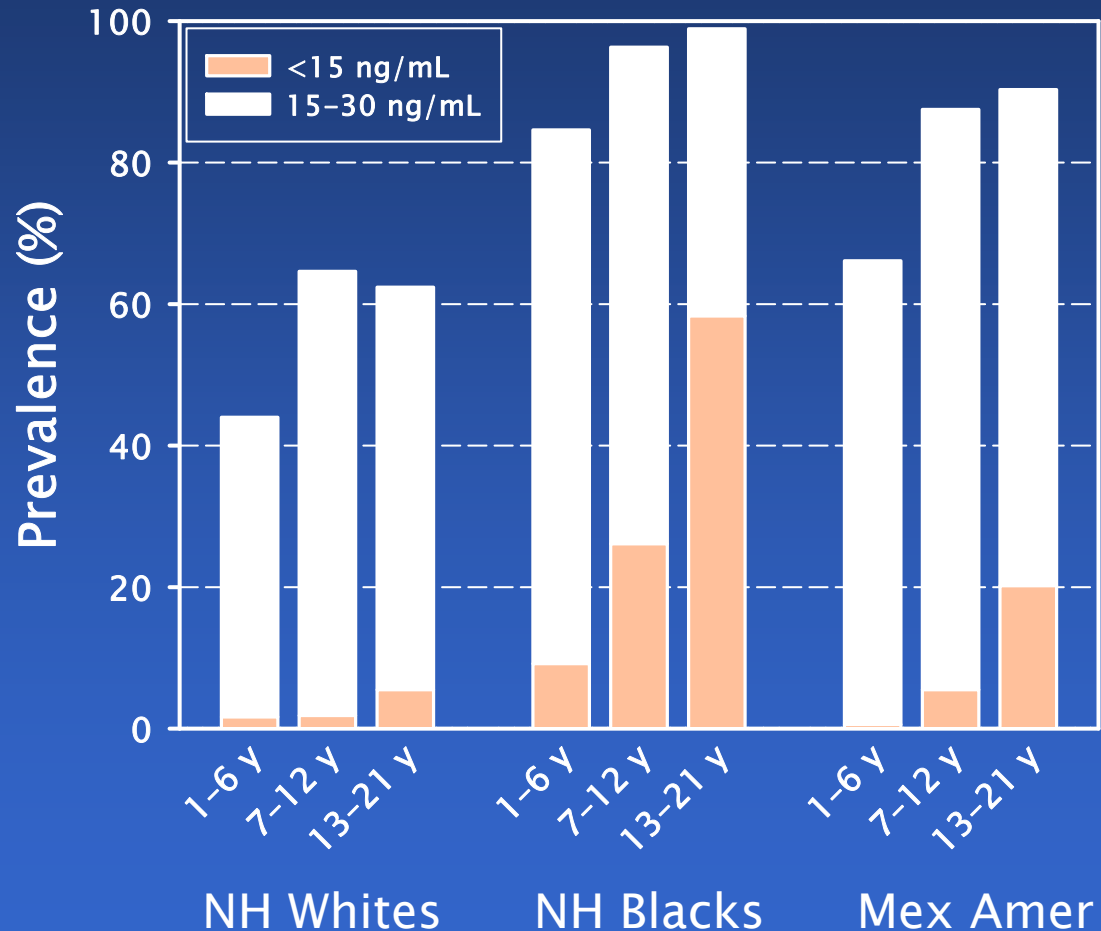
NHANES-III

- women aged 60–79
- summer, northern states
- Looker et al., (2002)
Bone 30:771–77



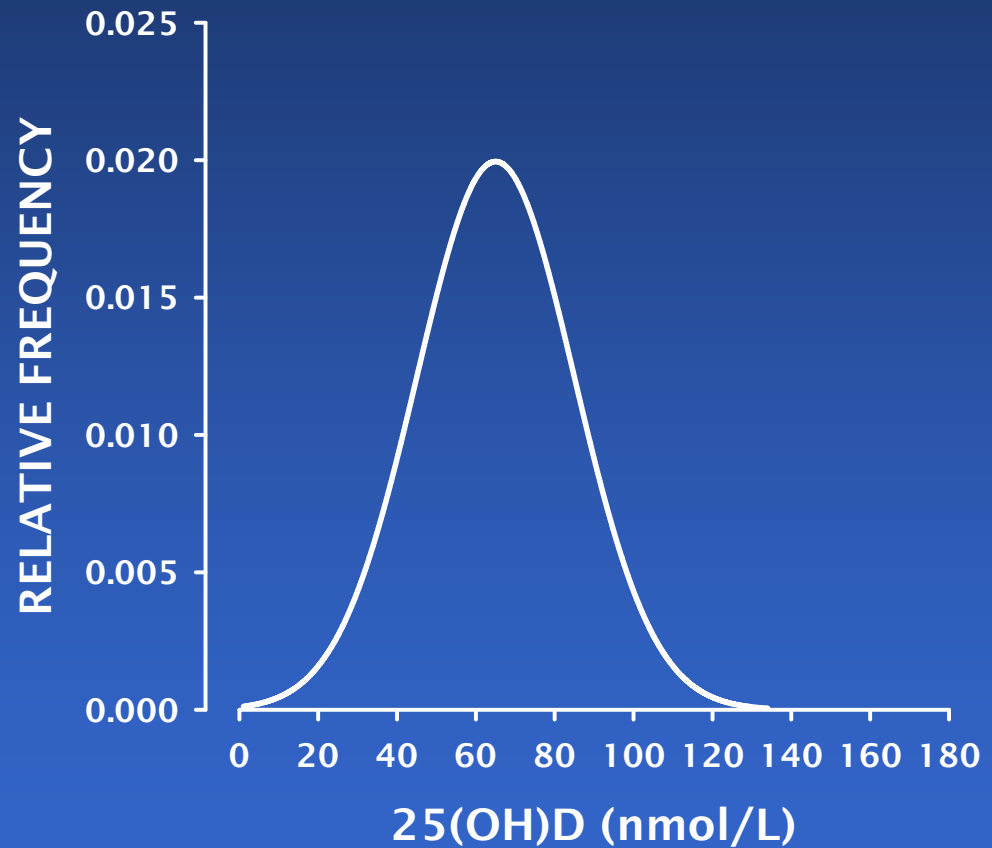
VIT D DEFICIENCY IN CHILDREN

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



What would this distribution look like if the entire population were to be supplemented with vitamin D?
– say, with 2600 IU/d?

NHANES-III* + THE TUIL



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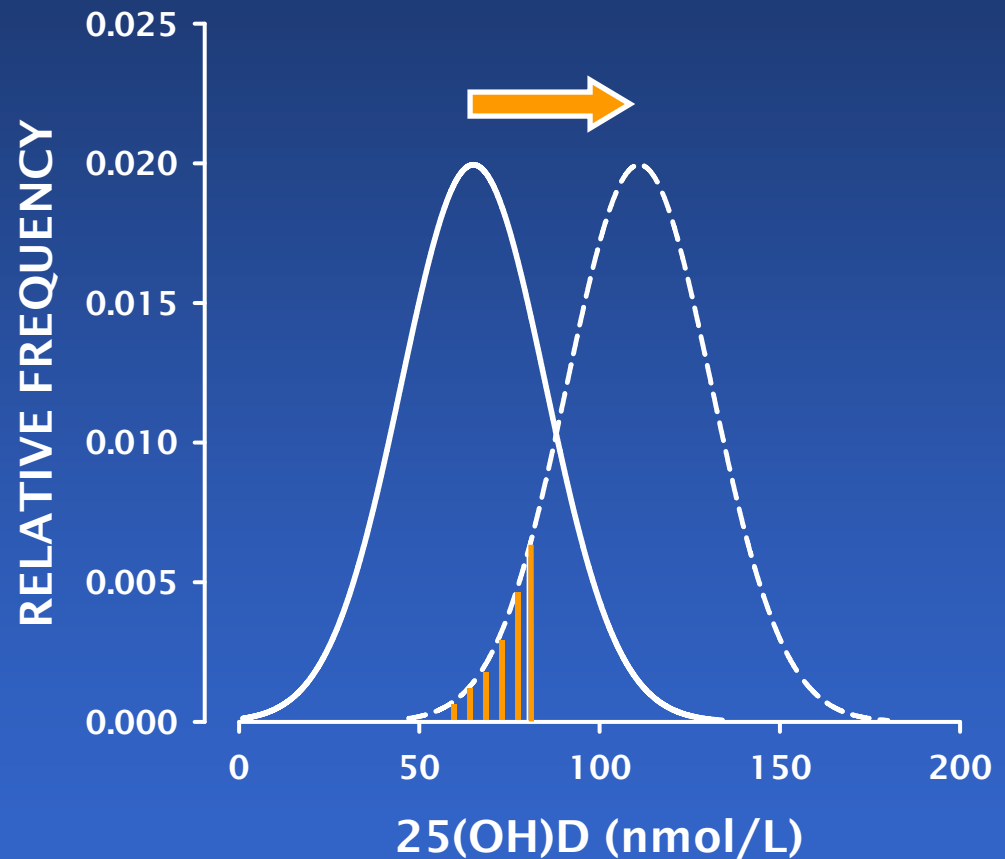


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*Looker et al., (2002) Bone 30:771-77

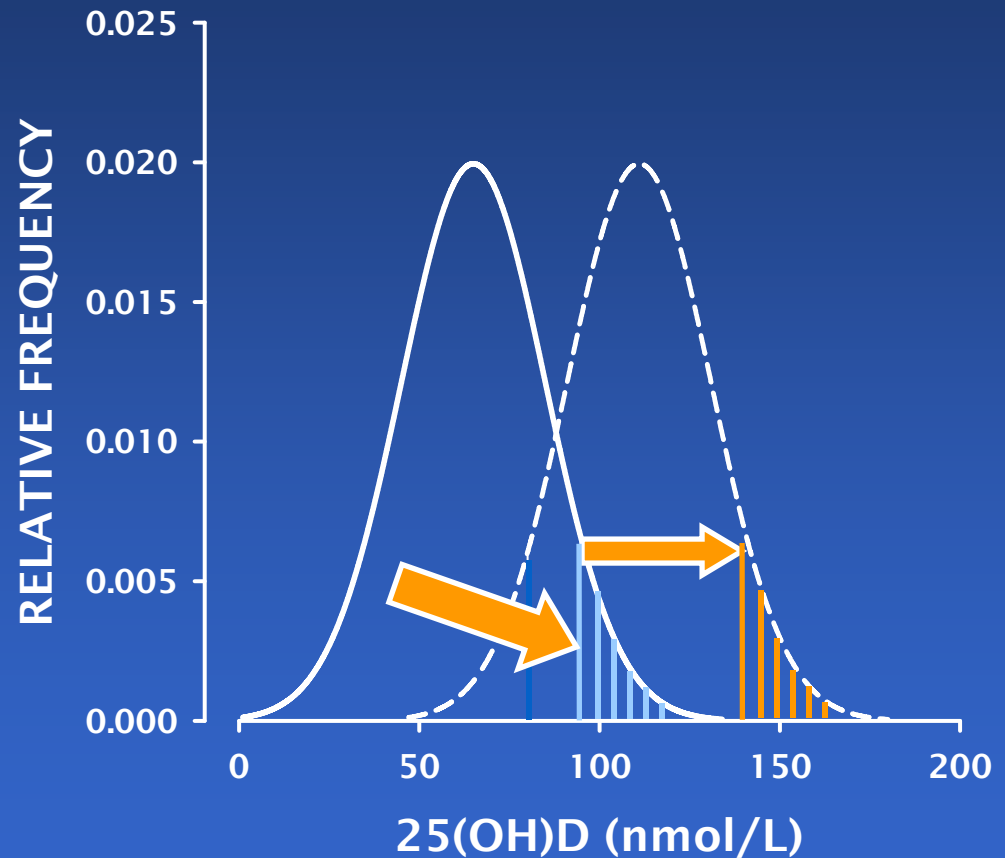
NHANES-III* + 2600 IU/D

- 2600 IU/d would raise 25OHD by ~ 46 nmol/L
- ~2.5 % of population still below 80 nmol/L
- thus 2600 IU/d \cong the RDA for women >60 yrs
- *but, that's over & above all current inputs*



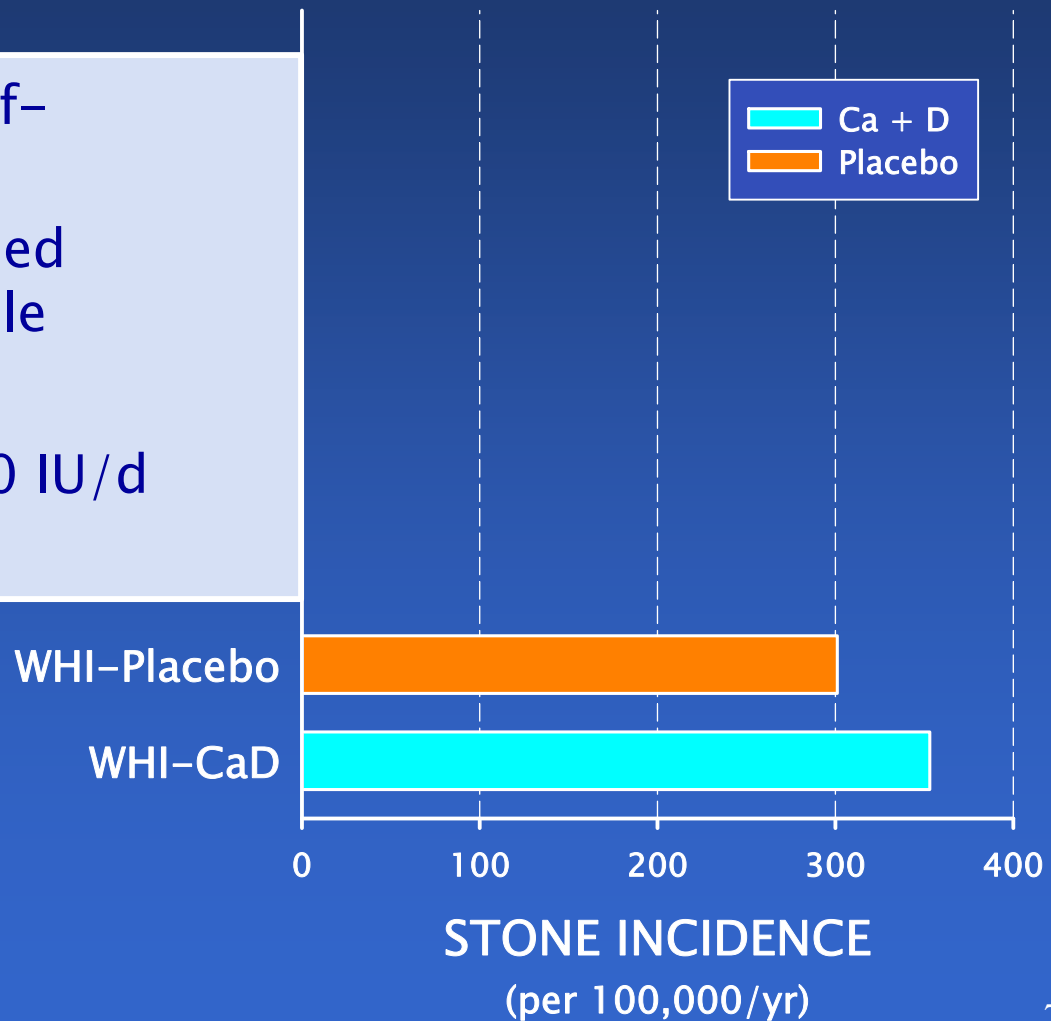
NHANES-III* + 2600 IU/D

- what about those already 2 SD above the mean?
- the rise with an extra ~2600 IU/d would be predicted to bring them to no more than 180 nmol/L – well below the toxic range

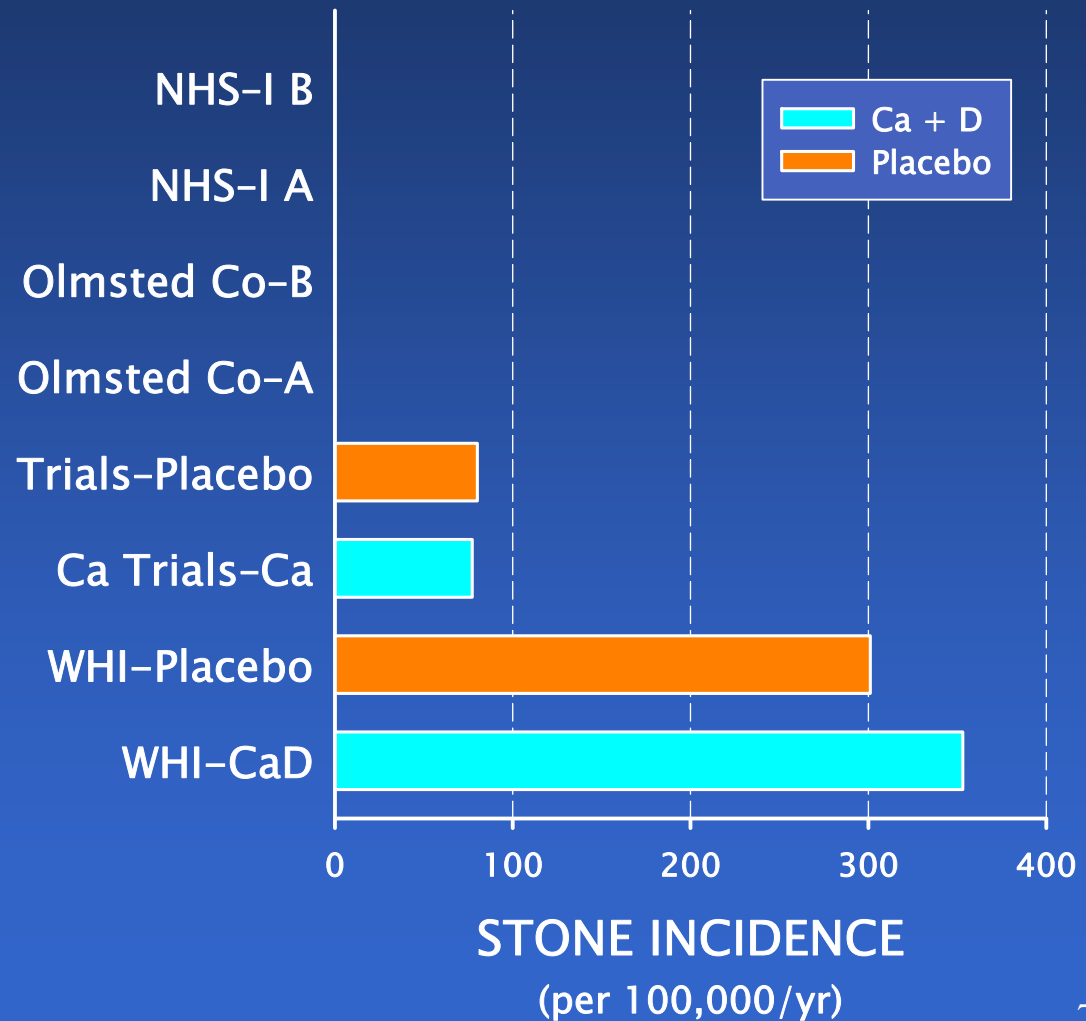


KIDNEY STONE RISK

- “stones” are self-reported AEs
- not a pre-planned outcome variable
- not adjudicated
- vit D dose \cong 200 IU/d

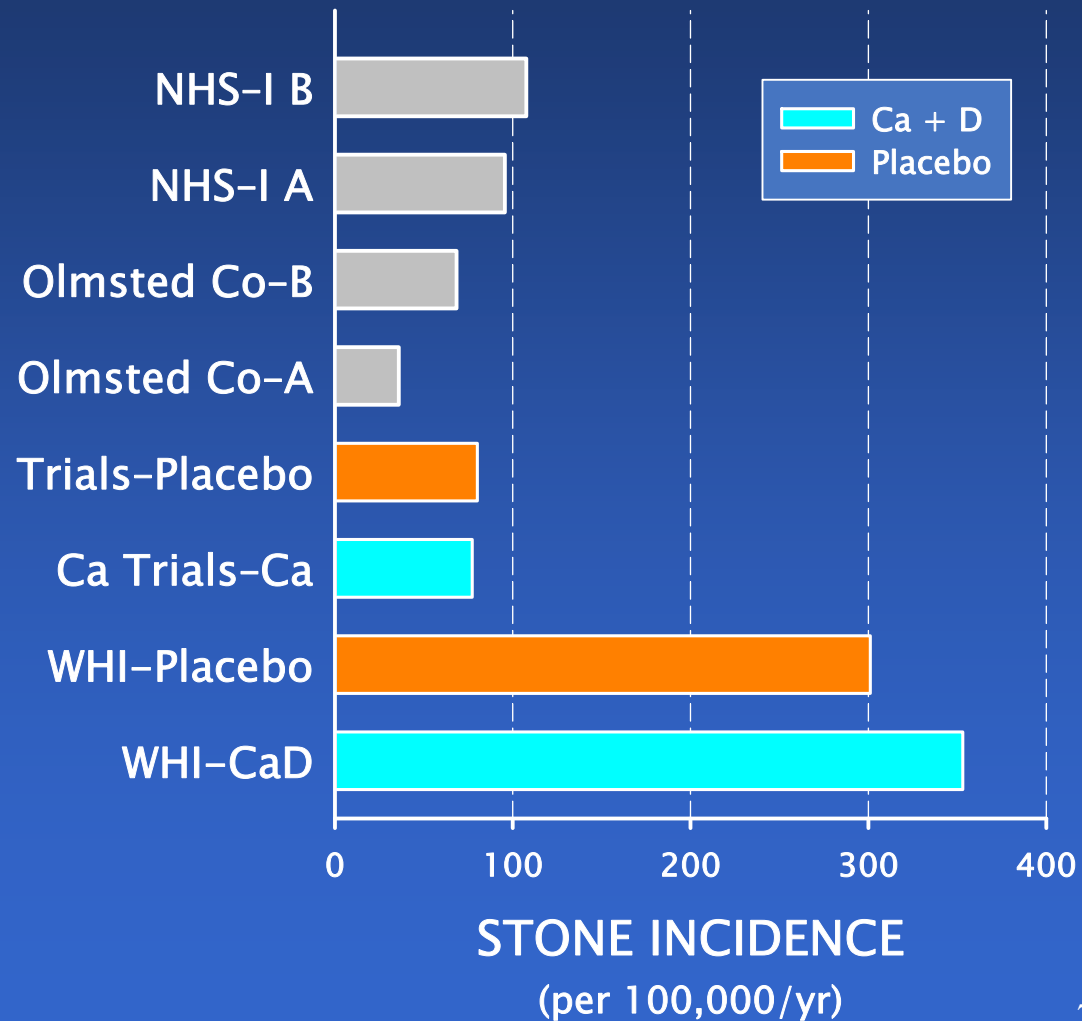


KIDNEY STONE RISK



KIDNEY STONE RISK

- in brief, the WHI stone numbers are so out of line with all other stone data they cannot be accepted as real
- nor could they plausibly be attributed to the small dose of vit D used in WHI



CONCLUSIONS

- 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
- in most healthy adults, 2000–2600 IU/d, in addition to all other inputs, will usually suffice

OBJECTIVES

- define nutrient deficiency
- define how vitamin D status is measured
- define the low end of the vitamin D sufficiency range
- describe how vitamin D can work in different tissues & organ systems

disease or dysfunction due to low intake

serum 25(OH)D concentration

≥ 80 nmol/L
(32 ng/mL)

the key that unlocks the DNA library in most tissues

Thank you