What is new about hyperparathyroidism ?

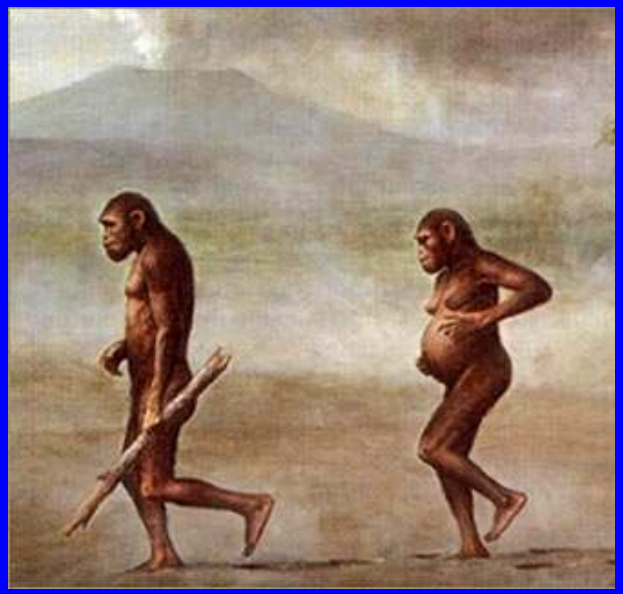
Eberhard Ritz
Heidelberg (Germany)

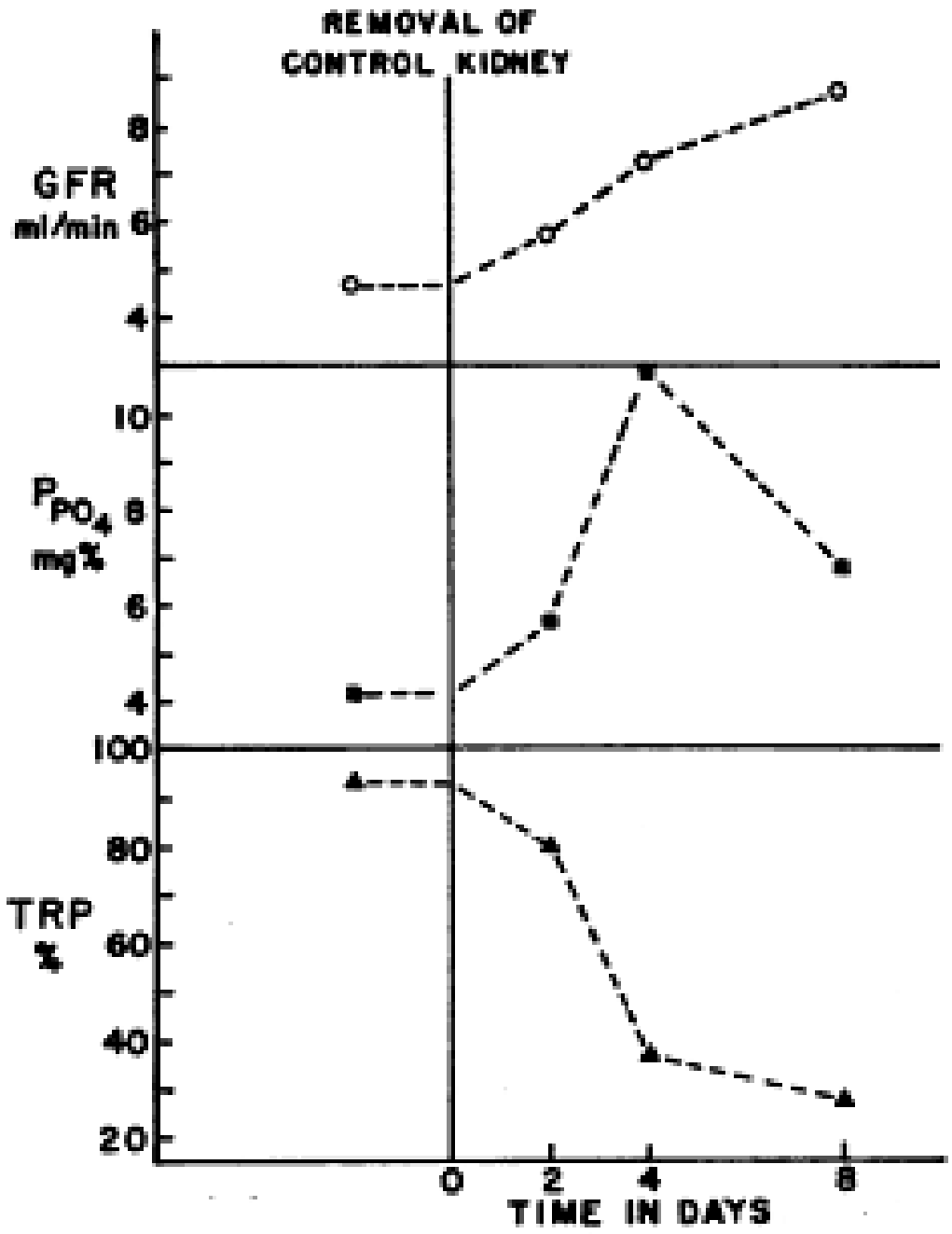
Incomplete insight into pathomechanisms triggering hyperparathyroidism ►

- *Unfounded guidelines and*
- *unsatifactory results of treatment*

What triggers (secondary) hyperparathyroidsim

- hyperphosphatemia → low ionised Ca^{++}

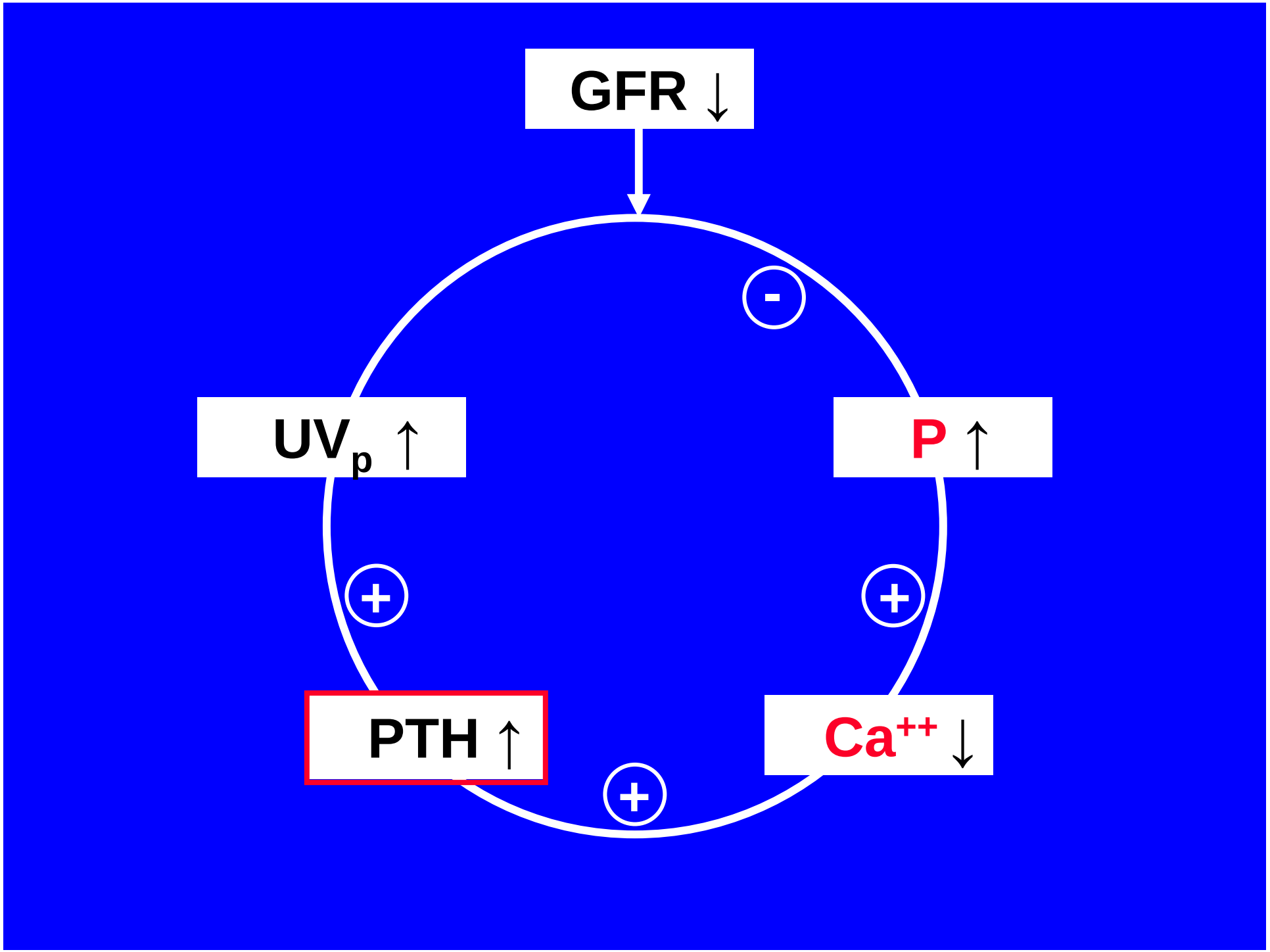


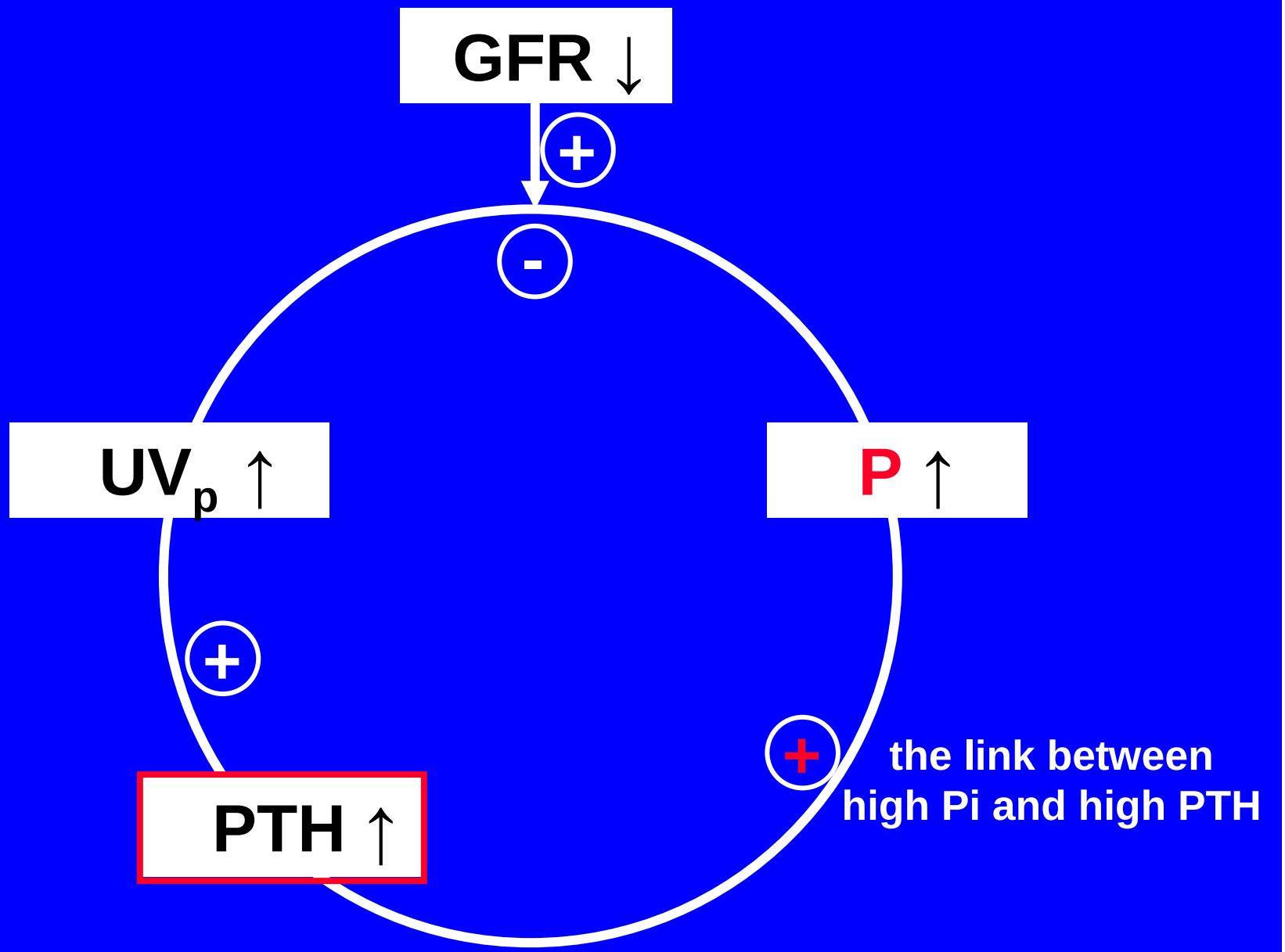


Trigger of hyperparathyroidism

Removal of one kidney → reduced fractional excretion of Pi (TRP)

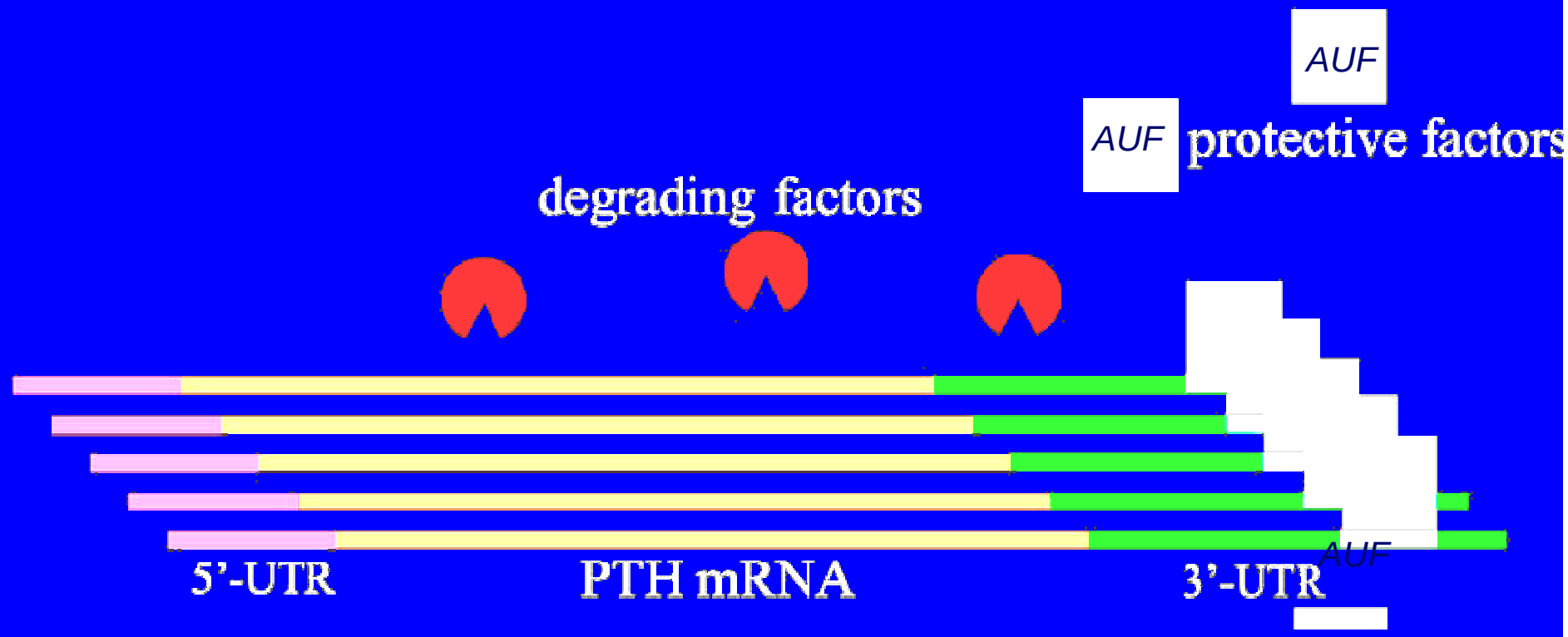
Slatopolsky, J.Clin.Invest (1966) 45:672


GFR ↓
-
UVp ↑
P ↑
+
+
PTH ↑
Ca++ ↓
+


GFR ↓
+
-
UVp ↑
P ↑
+
+
PTH ↑
the link between
high Pi and high PTH

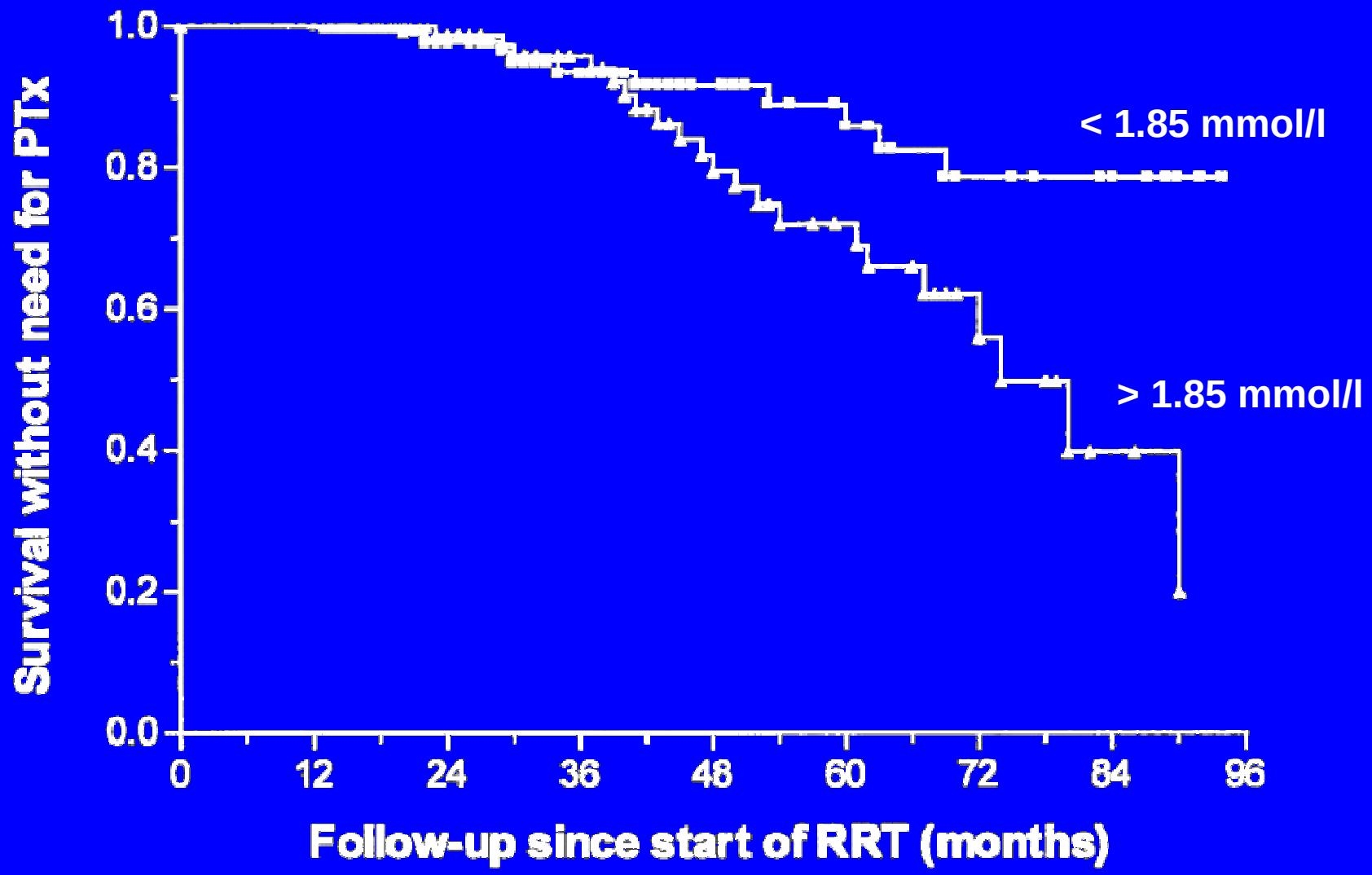
PTH mRNA –

stabilised by binding of the cytoplasmic protein AUF to the nontranslated 3'region preventing degradation



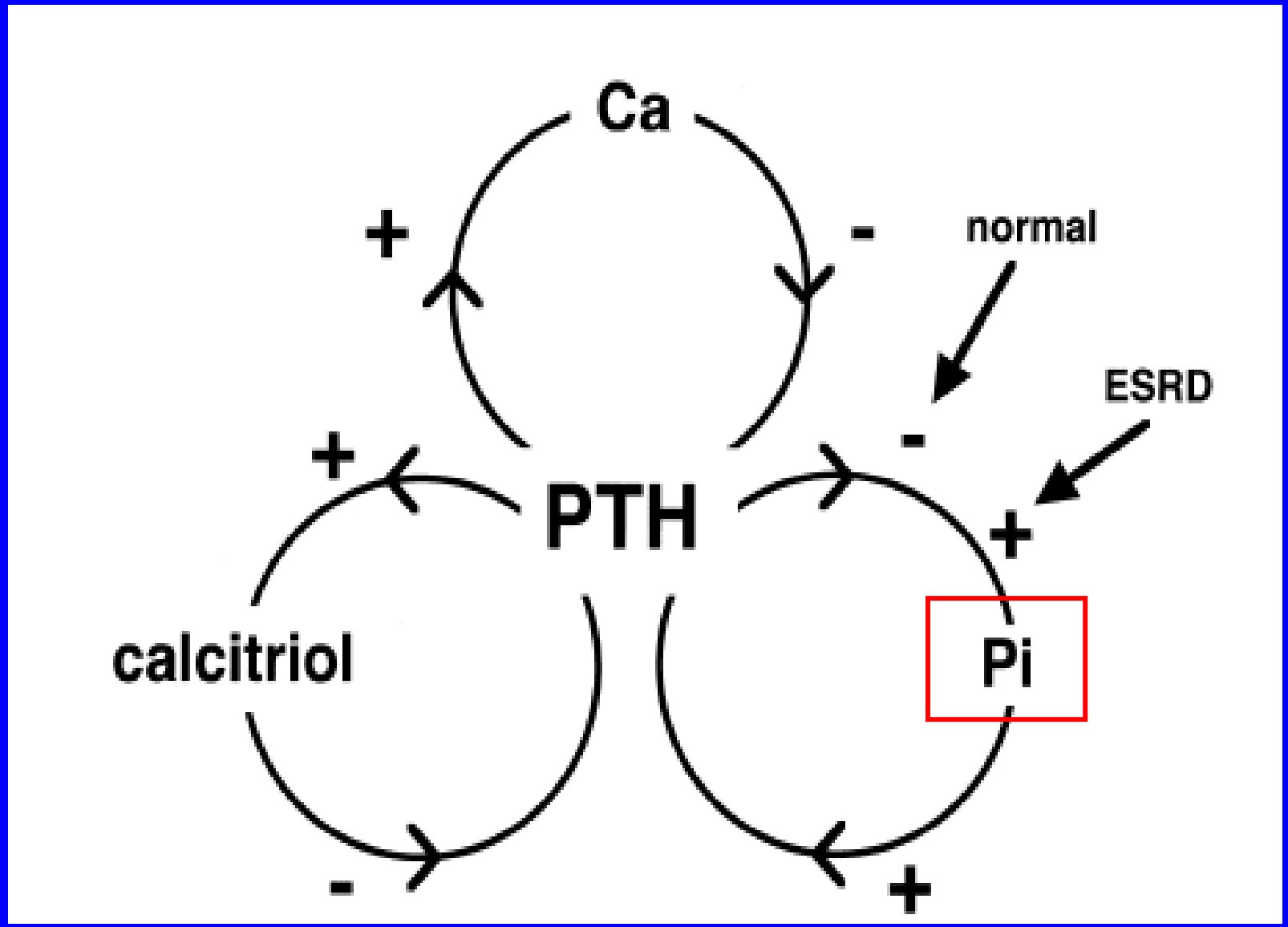
Yalcindag, J.Am.Soc.Nephrol. (1999) 10: 2562

Baseline serum phosphate predicts future need of parathyroidectomy



Jorna, Nephrol Dial Transplant (2004) 19: 1168

Pathogenesis of secondary hyperparathyroidism



Cunningham J., Kidn.Internat.(1999) 73, S59

What triggers (secondary) hyperparathyroidsim

- hyperphosphatemia → low ionised Ca^{++}
- lack of $1,25(OH)_2D_3$

Fraser D.R., Kodicek E.

Unique biosynthesis of a biological active vitamin D metabolite

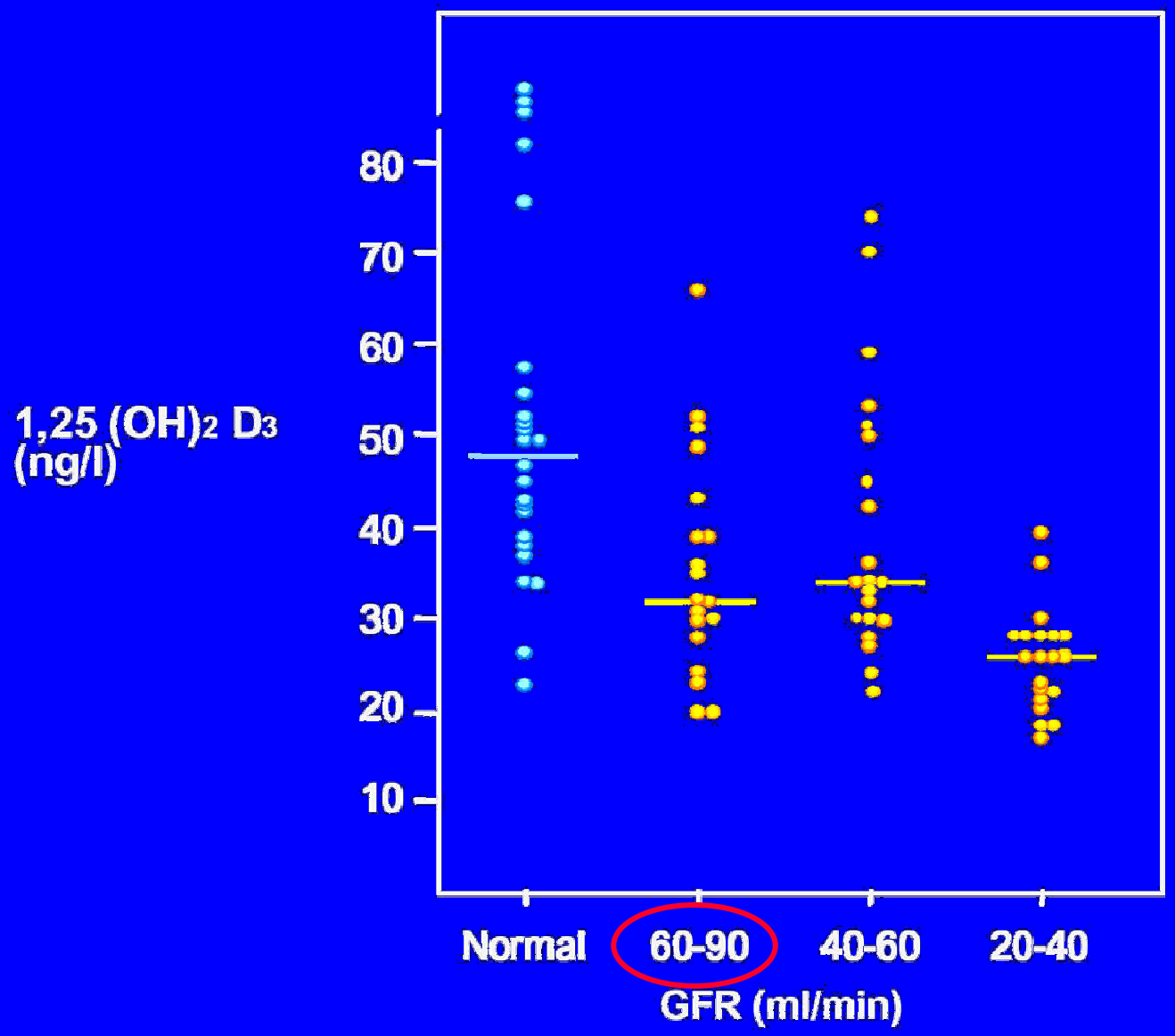
Nature (1970) 228:764

Brickman A.S., Coburn J.W., Massry S.G.,Norman A.W.

1,25 Dihydroxy-vitamin D3 in normal man and patients with renal failure

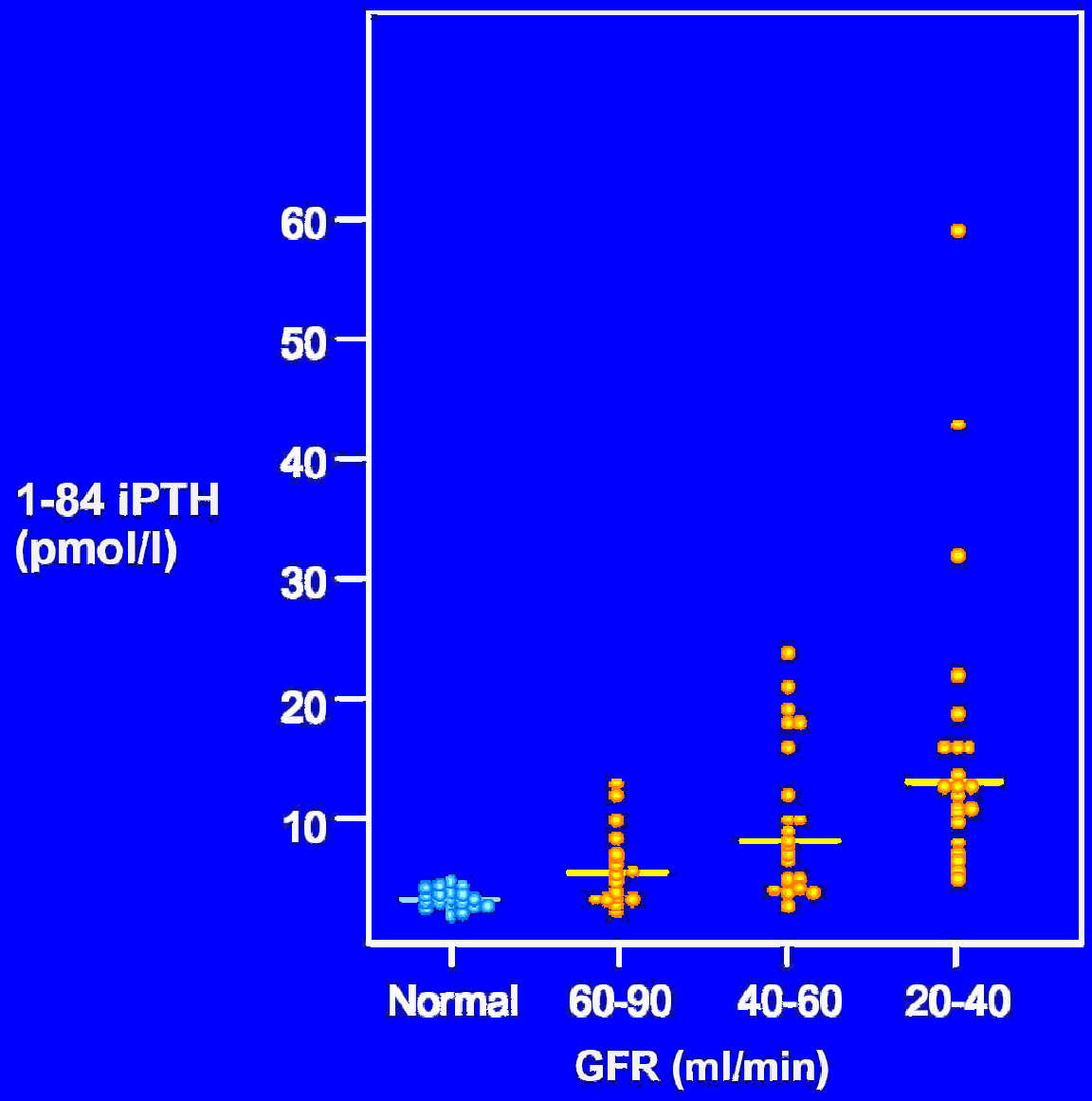
Ann Intern Med. (1974) 80:161

$1,25(OH)_2D_3$ concentrations at different stages of CKD



Reichel, Nephrol.Dial.Transplant (1991) 6: 162

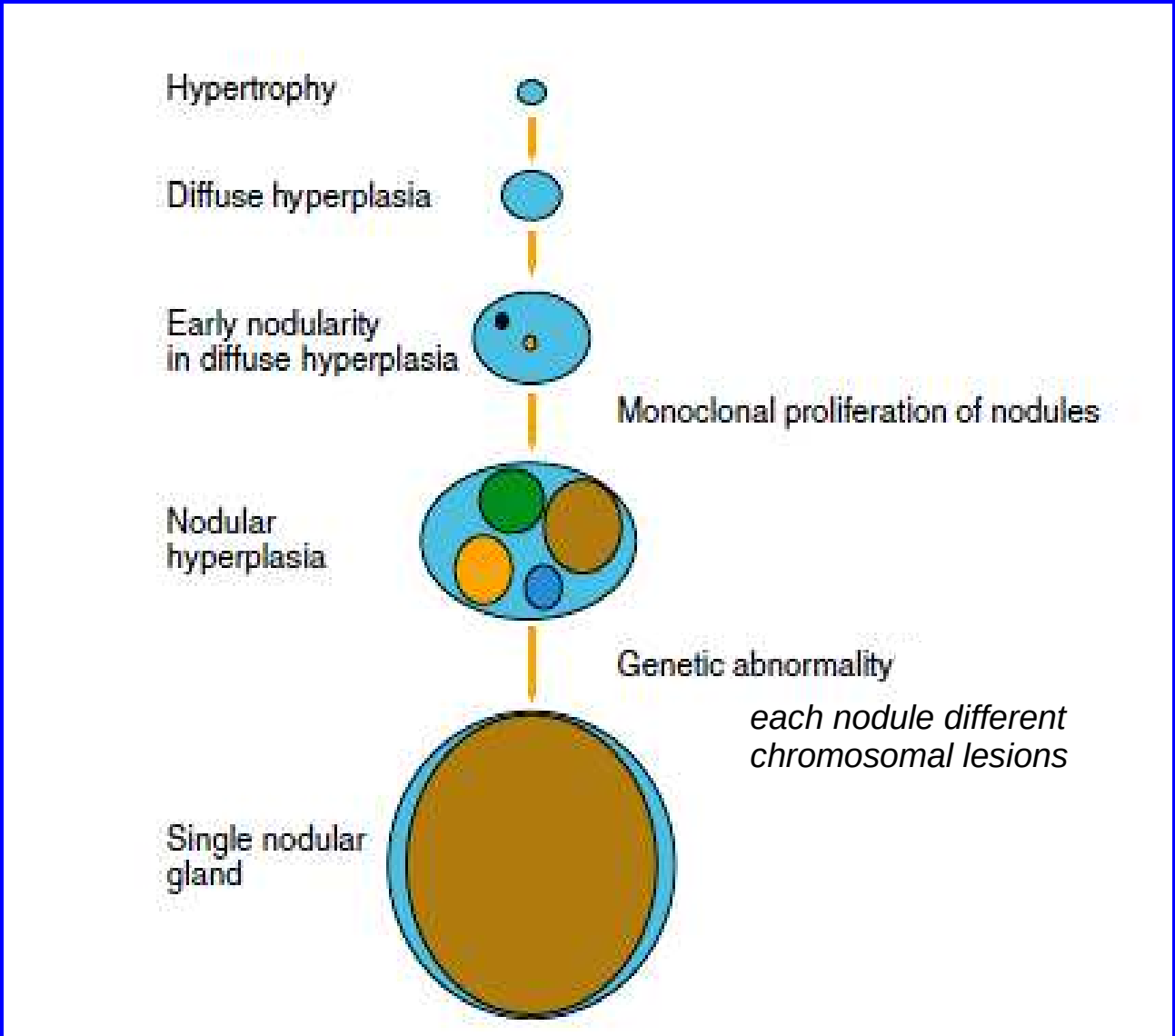
PTH at different stages of CKD



Reichel, Nephrol.Dial.Transplant (1991) 6: 162

Is excessive parathyroid hormone <u>secretion</u> the only abnormality of the parathyroids ?

The main problem in secondary hyperparathyroidism –
parathyroid hyperplasia and nodular hyperplasia



Fukagawa, Kidn.Intern.(2006) 70:S3

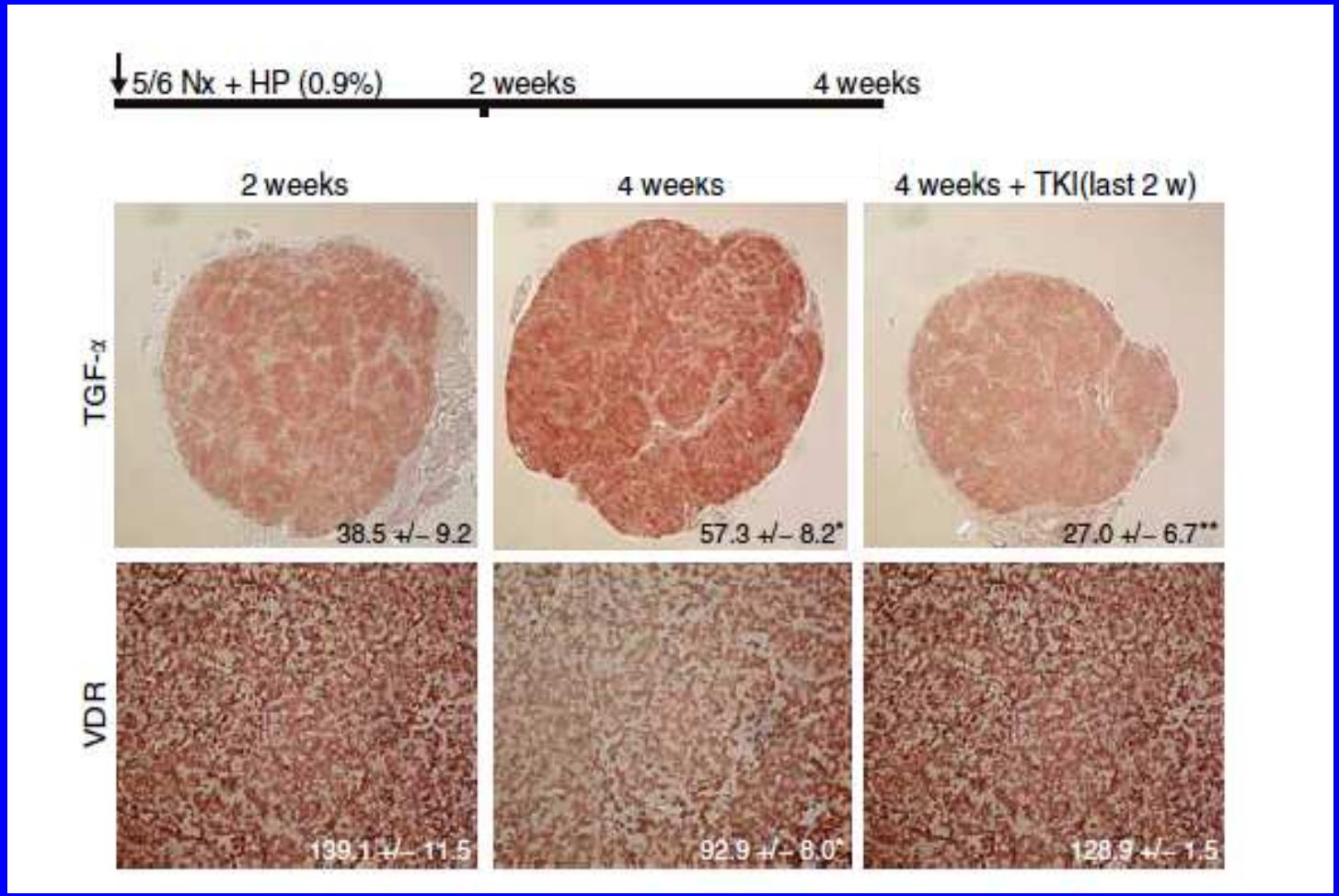
Parathyroid proliferation :
(analogies to tumour growth)

- **aggravated by high P_i , low Ca^{++}**
- **important signal :**
  TNF_{alpha} ➡
  epidermal growth factor receptor (EGFR)
- **EGFR downstream signalling :**

✓ **parathyroid hyperplasia**
✓ **downregulation of vitamin D receptor, Ca^{++} sensing receptor**

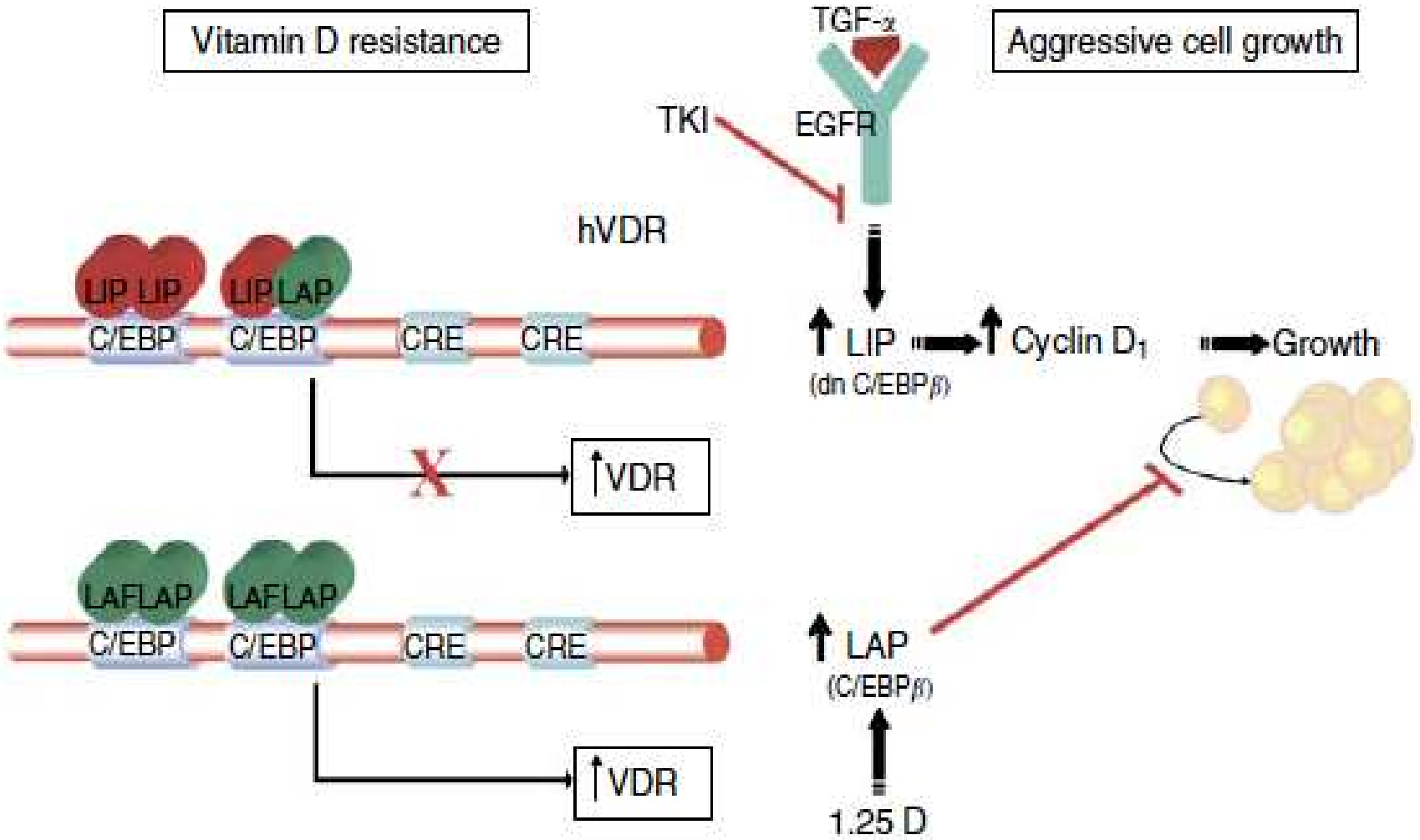
[blockade of downstream signalling prevents P_i and Ca^{++} mediated hyperplasia]

Blockade of the EGF receptor abrogates and reverses effects of high P_i on # *TGFα selfinduction (top)* and # *vitamin D receptor expression* (bottom)



Dusso, Kidn.Internat.(2006) 70:S8

Parathyroid hyperplasia – analogies to tumor growth



Dusso, Kidn.Intern.(2006) 70:S8

In proliferating parathyroid :

downregulation of receptors for agents inhibiting parathyroid cell proliferation:

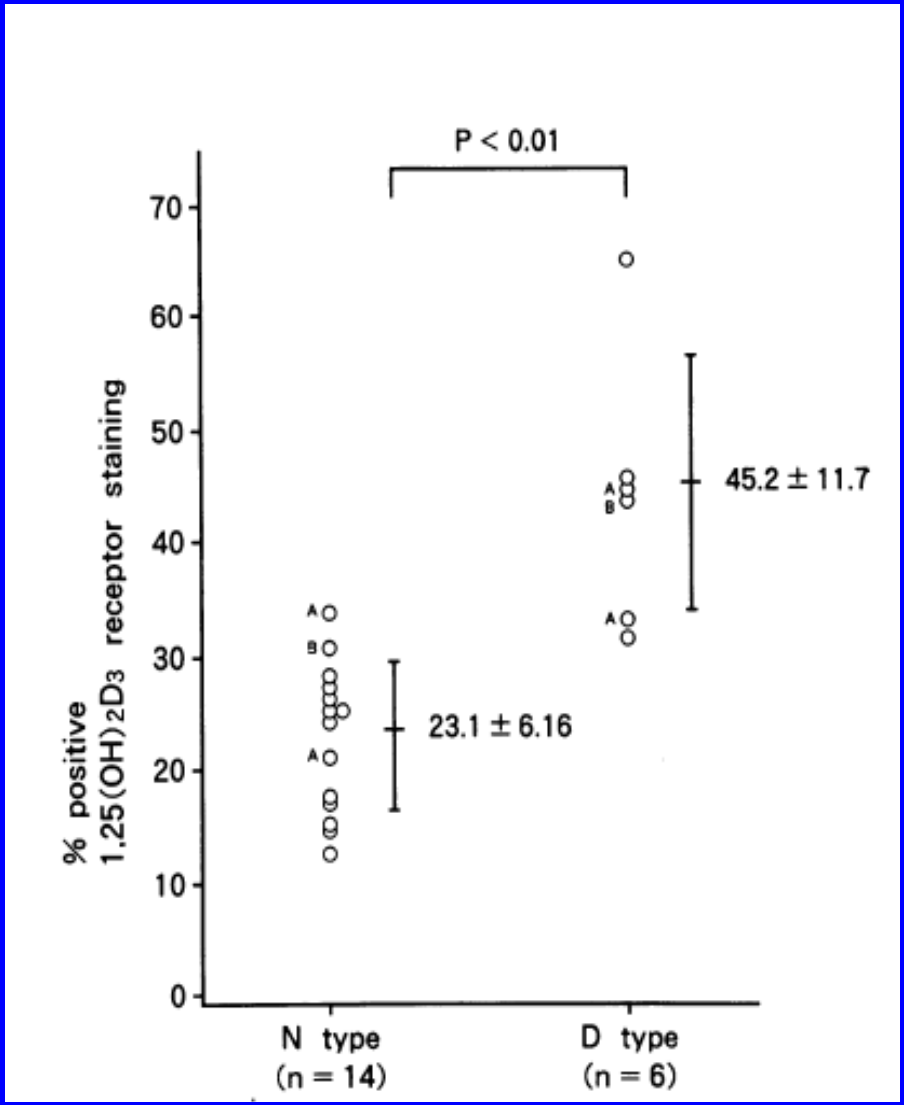
-VDR (vitamin D receptor)

Fukuda, J.Clin.Invest.(1993) 92: 1436

- Ca sensing receptor

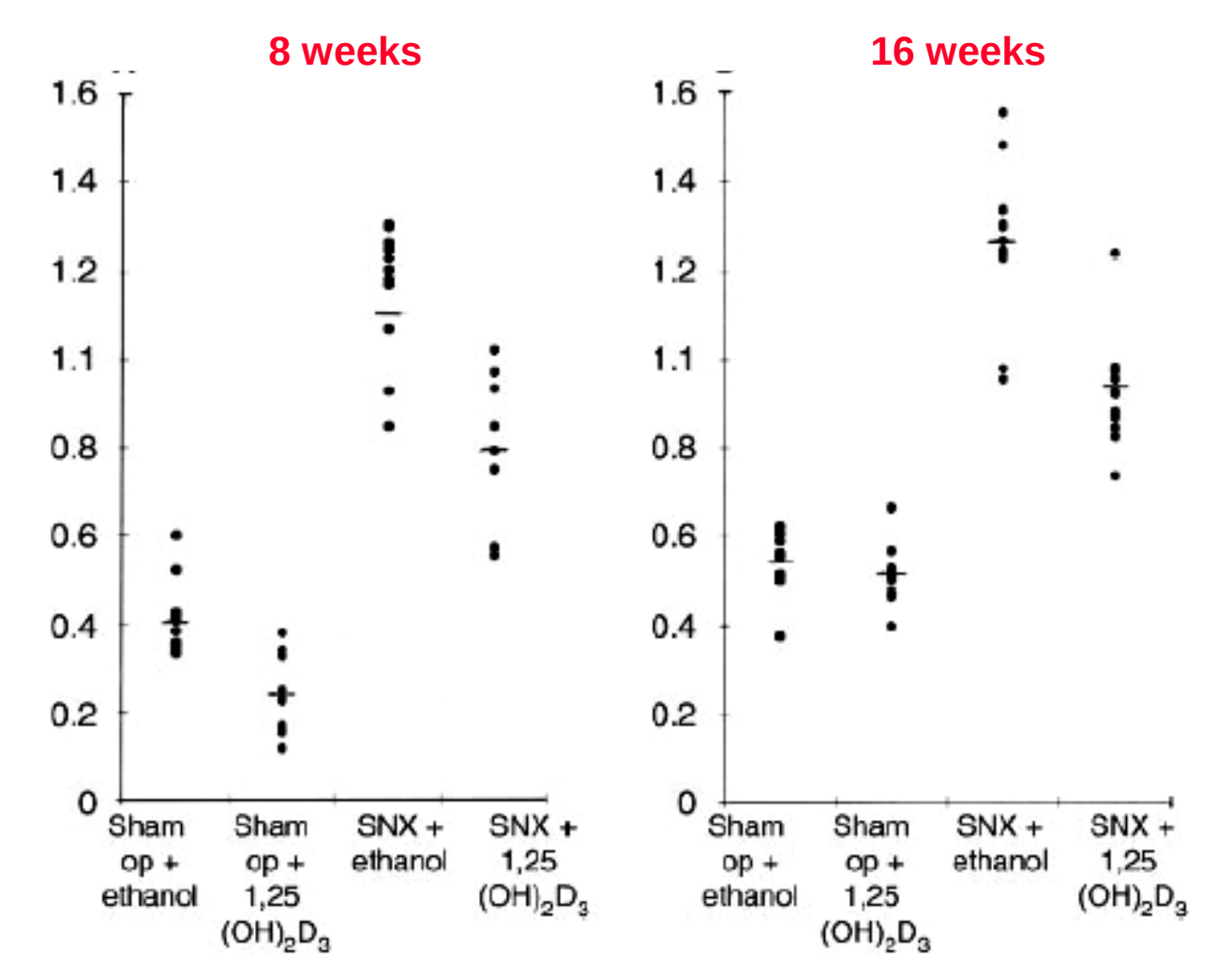
Kifor, J.Clin.Endocr.Metab.(1996) 81: 1598

Reduced VDR expression in nodular parathyroid hyperplasia



Fukuda J.Clin.Invest (1993) 92:1436

Treatment with $1,25(OH)_2D_3$ –
lower glomerulosclerosis -index in subtotally nephrectomised rats

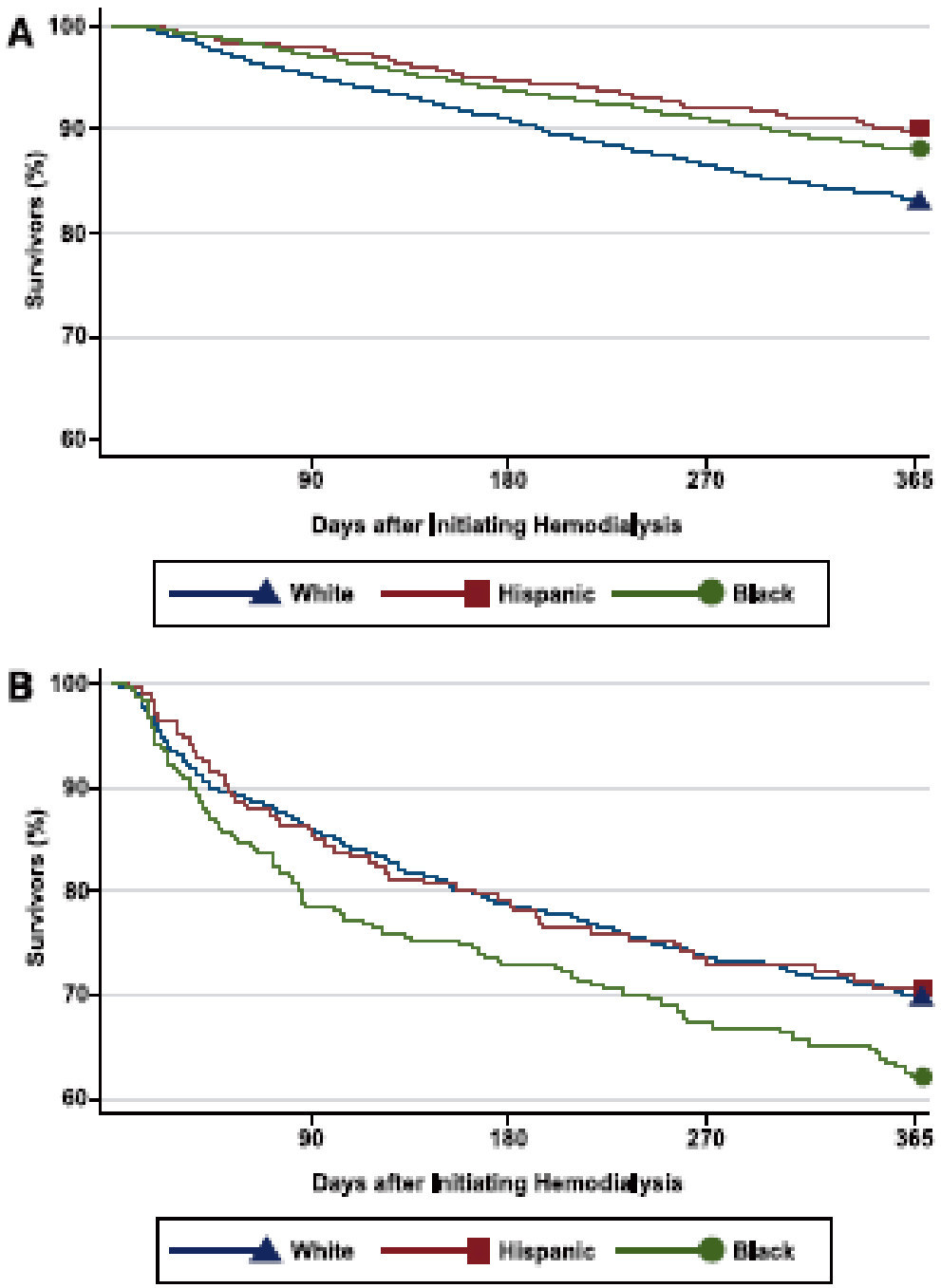


Schwarz,Kidn.Intern.(1998) 53:1696

Proliferation and calcification of aorta of uremic rats – calcimimetics vs calcitriol

subtotal nephrectomy :	PCNA 1/mm² *intima*	PCNA 1/mm² *media*	Cbfa-1 score
vehicle	0.14±0.29	11.9±18.1	1.52 ± *1.23*
calcimimetic	0.13±0.42	8.1±13.3	0.24 ± *0.19*
calcitriol	3.15±4.93	71.0±57.0	2.70 ± *1.57*

Koleganova, Kidn.Internat. (in press)



Survival of incident hemodialysis patients with and without active vitamin D treatment according to ethnicity

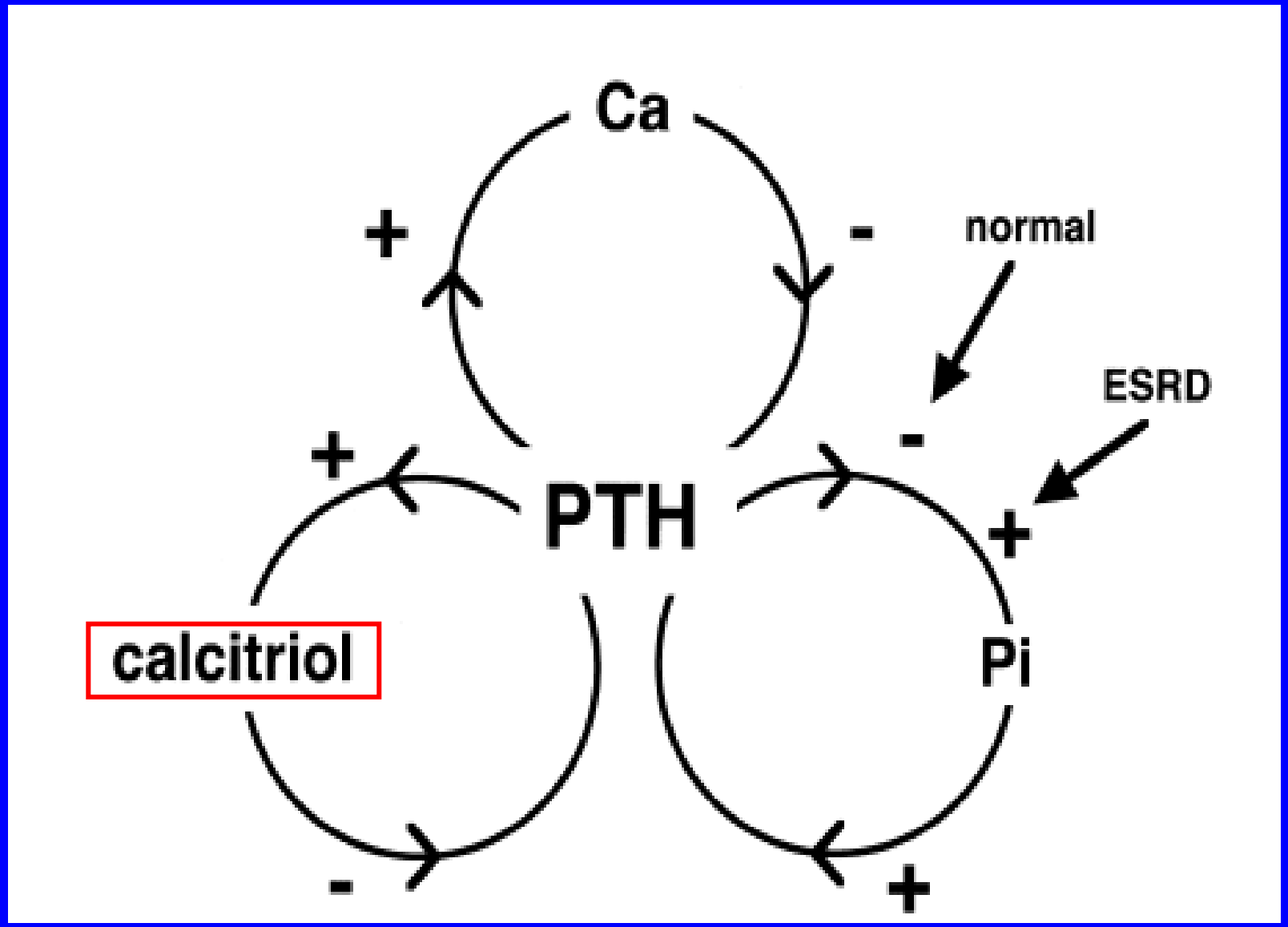
Vit.D vs no vit D

mortality - 16% in blacks and Hispanics

- 23% in whites (p<0.01)

Wolf, J.Am.Soc.Nephrol.(2008)19:1379

Pathogenesis of secondary hyperparathyroidism



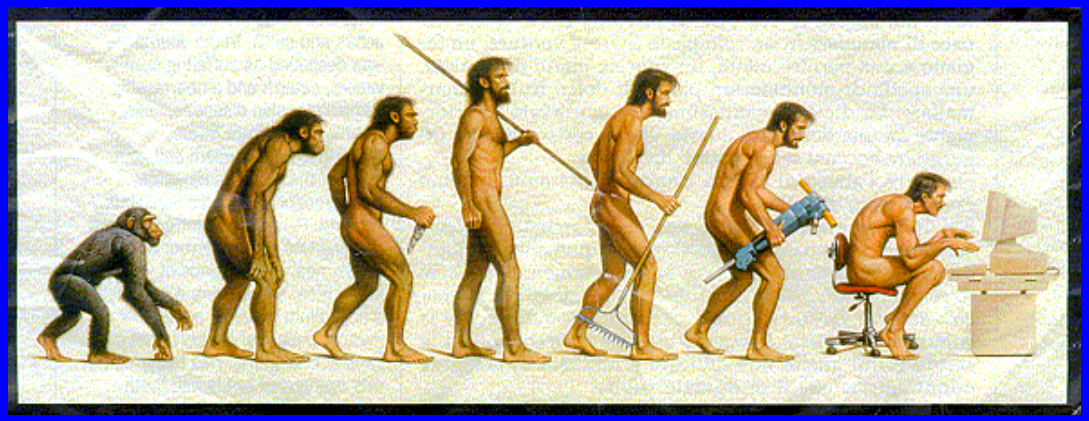
Cunningham J., Kidn.Internat.(1999) 73, S59

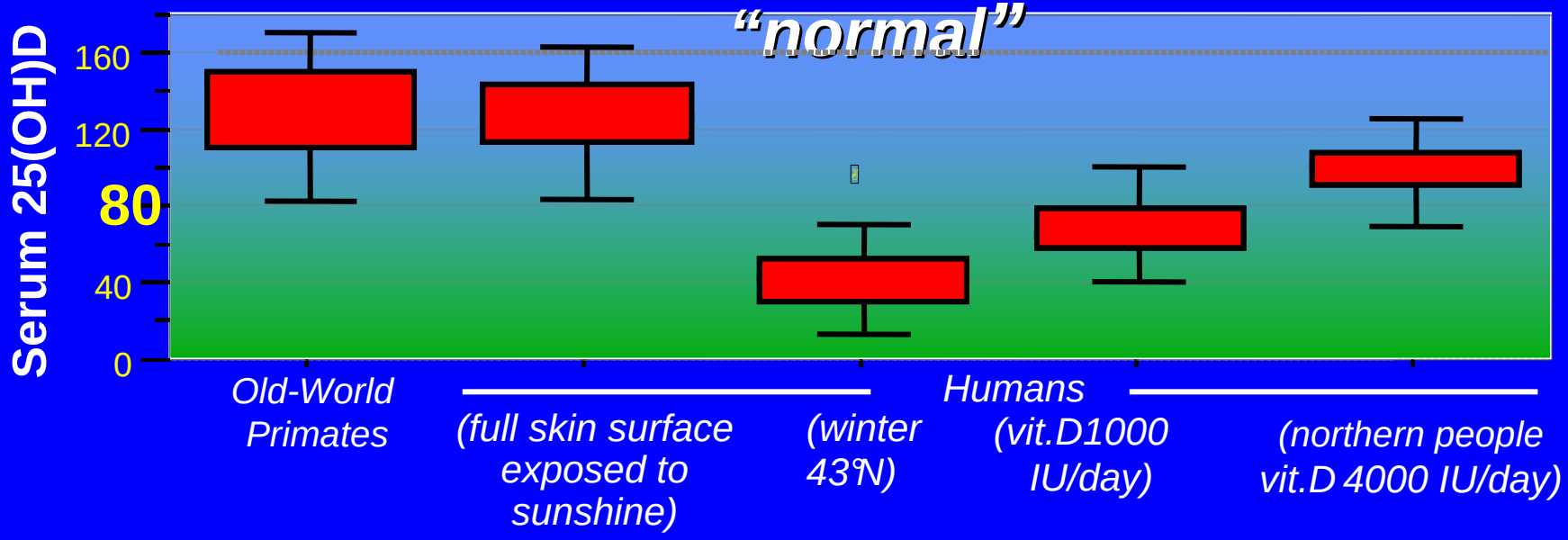
What triggers (secondary) hyperparathyroidsim

- hyperphosphatemia → low ionised Ca^{++}
- not only lack of $1,25(OH)_2D_3$
- but also lack of 25(OH)D →

because of local production of $1,25(OH)_2D_3$ by 1-alpha hydroxylase in the prathyroid ?

Vitamin D status of primates and humans

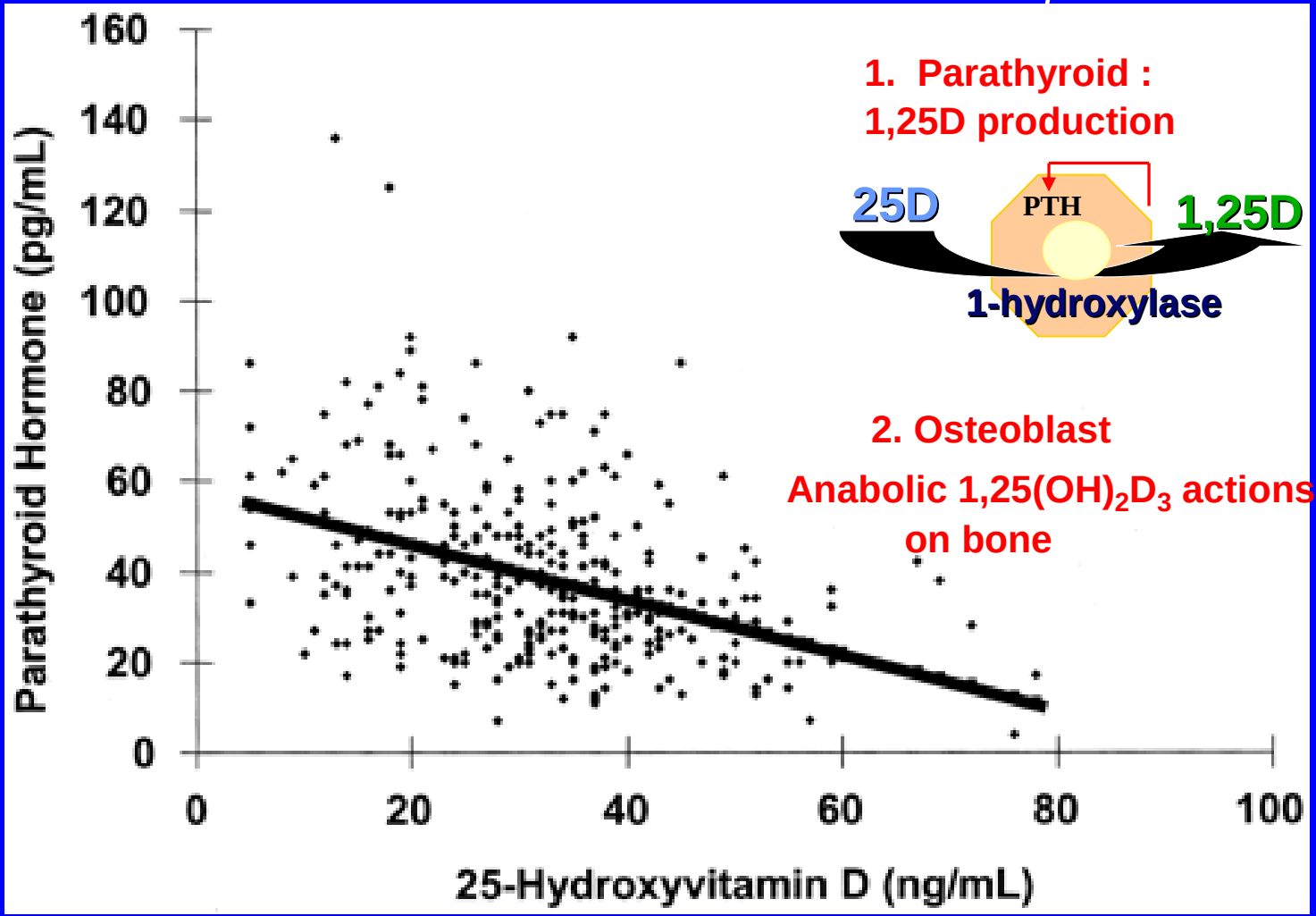




Fuleihan, New Engl J Med (1999) 340: 1840

Vitamin D deficiency –
high PTH concentration and risk of bone fractures

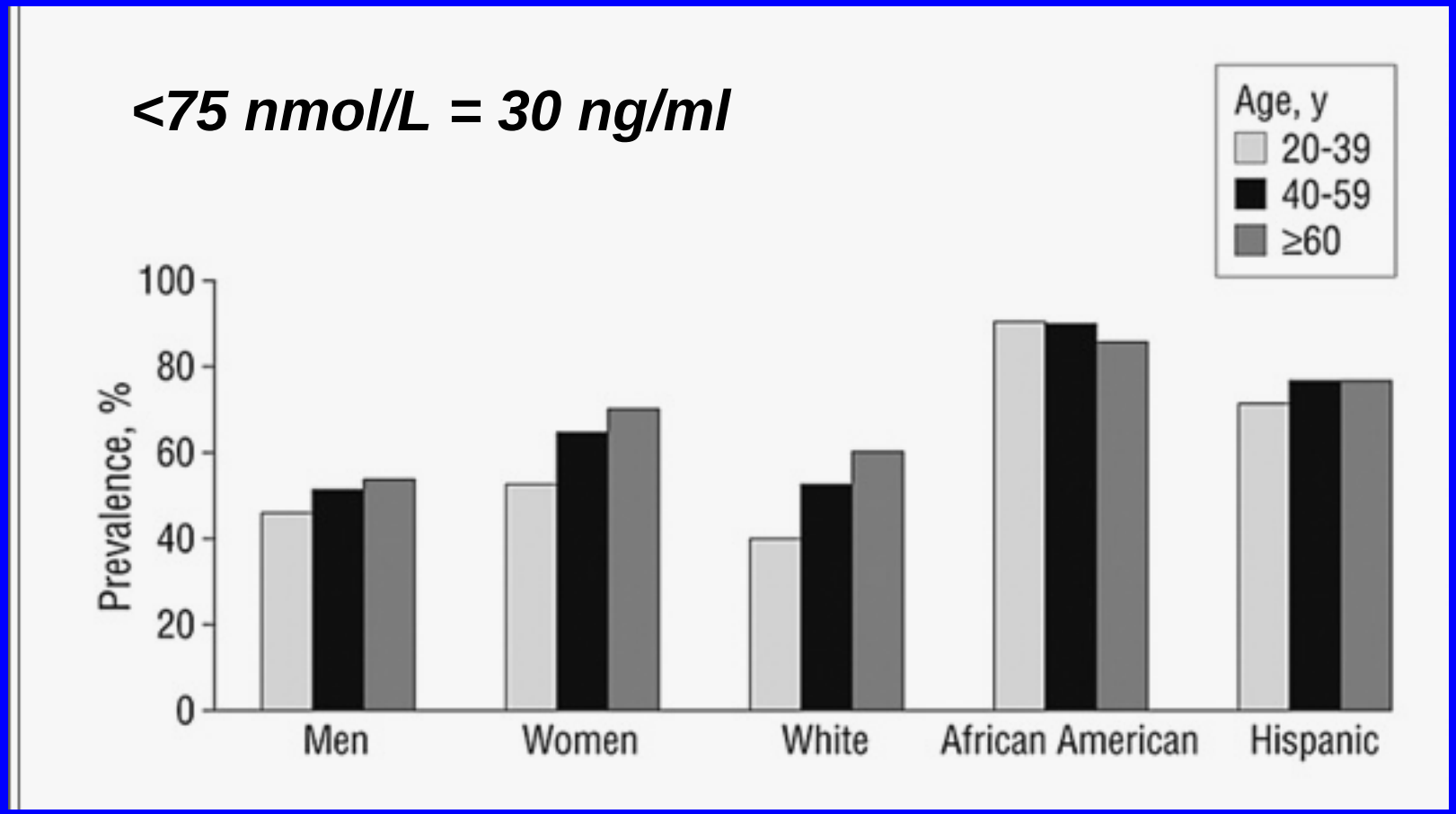
Potential explanations:



1. Parathyroid :
1,25D production

2. Osteoblast
Anabolic $1,25(OH)_2D_3$ actions on bone

Prevalence of insufficient 25(OH)vitamin D_3 concentrations in the general population (NHANES)



Martins, Arch.Int.Med.(2007) 167:1159

High prevalence of low 25(OH)D3 concentrations in CKD 3 and 4

- *"deficiency" < 10 ng/ml (< 25 nMol/L)*
- *"insufficiency" 10-30 ng/ml (25-75 nmol/L)*

 # sufficient concentrations (> 30 ng/ml) only in :

✓ **29% CKD 3** *(eGFR 30-60 ml/min)*

✓ **17% CKD 4** *(eGFR 15-30 ml/min)*

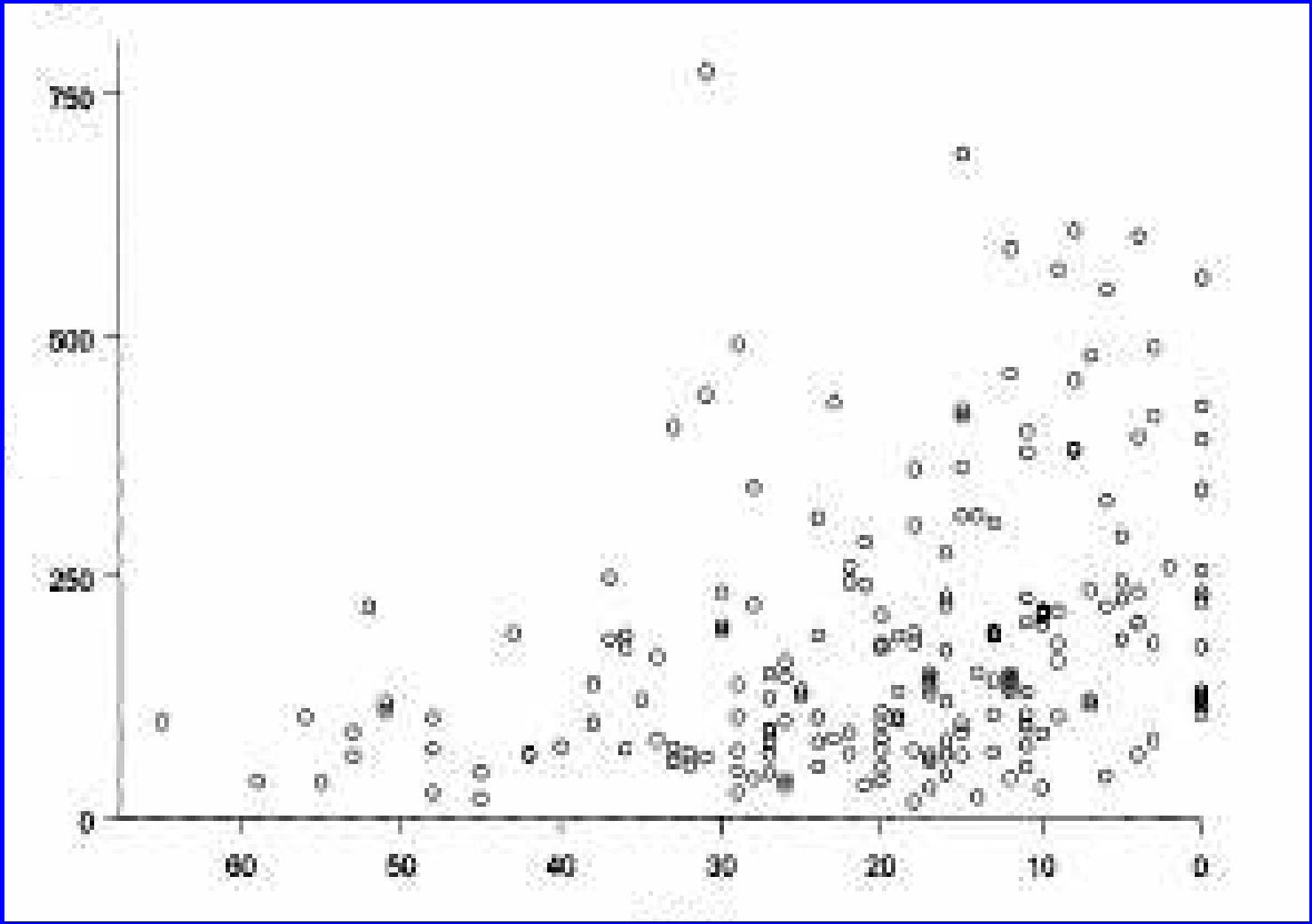
 # sun exposure only modest increase :

17.9→21.2 ng/ml

LaClaire, Am.J.Kidn.Dis.(2005) 45:1026

Correlation: low 25(OH)D_3 - high iPTH

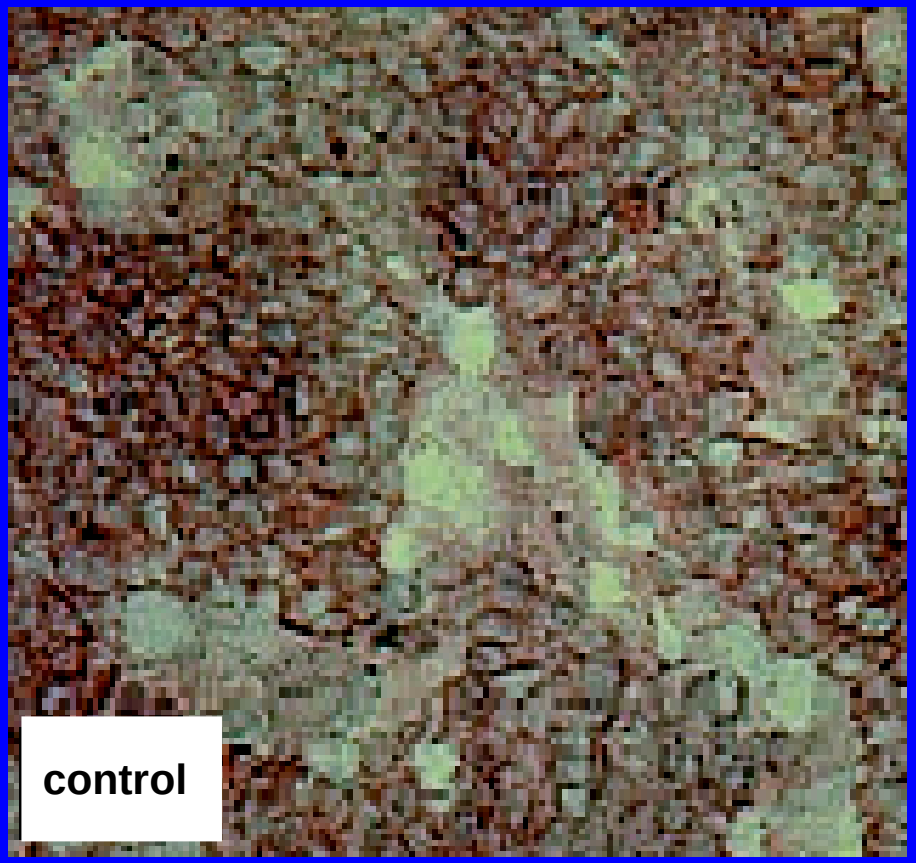
PTH (pg/ml)



Calcidiol *(ng/ml)*

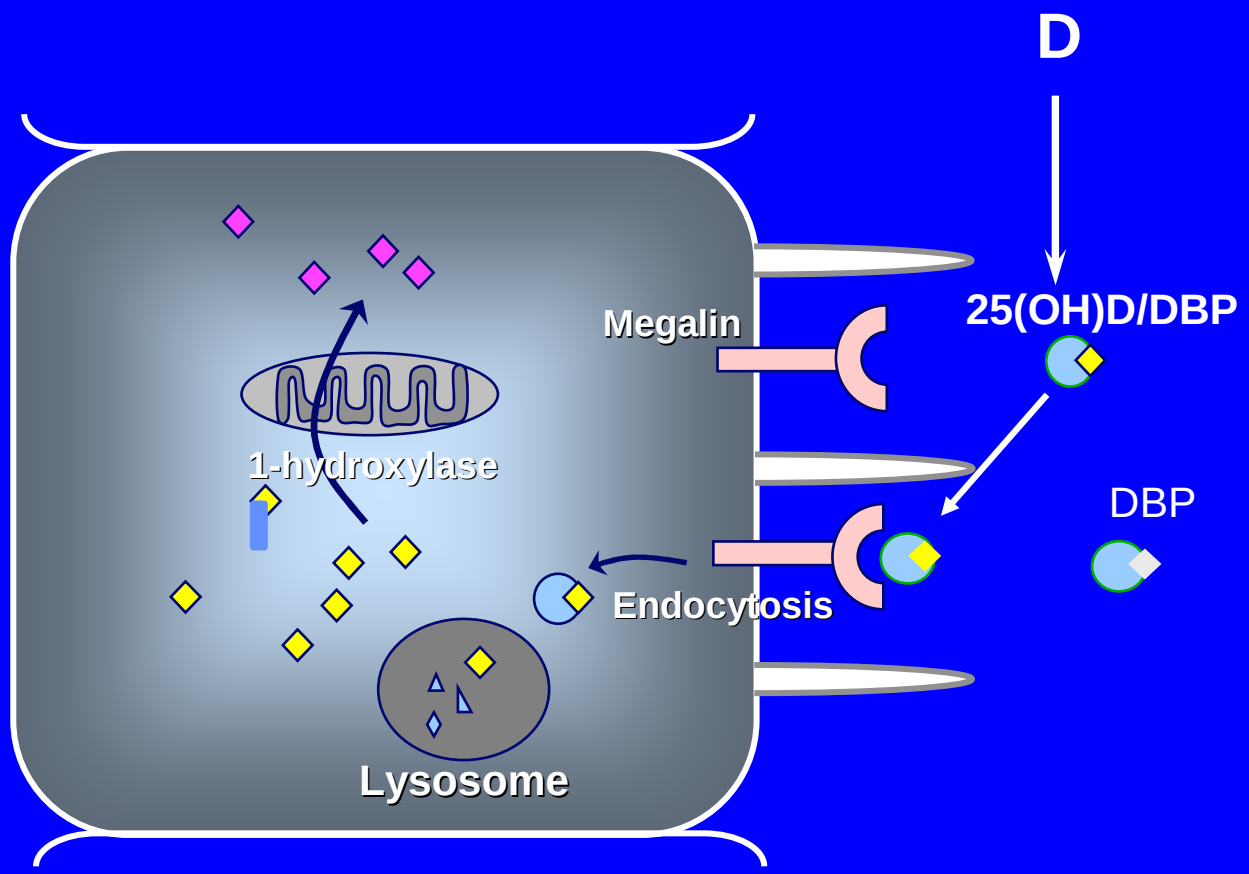
LaClaire, Am.J.Kidn.Dis.(2005) 45:1026

Expression of 1-α hydroxylase (and megalin) in parathyroids



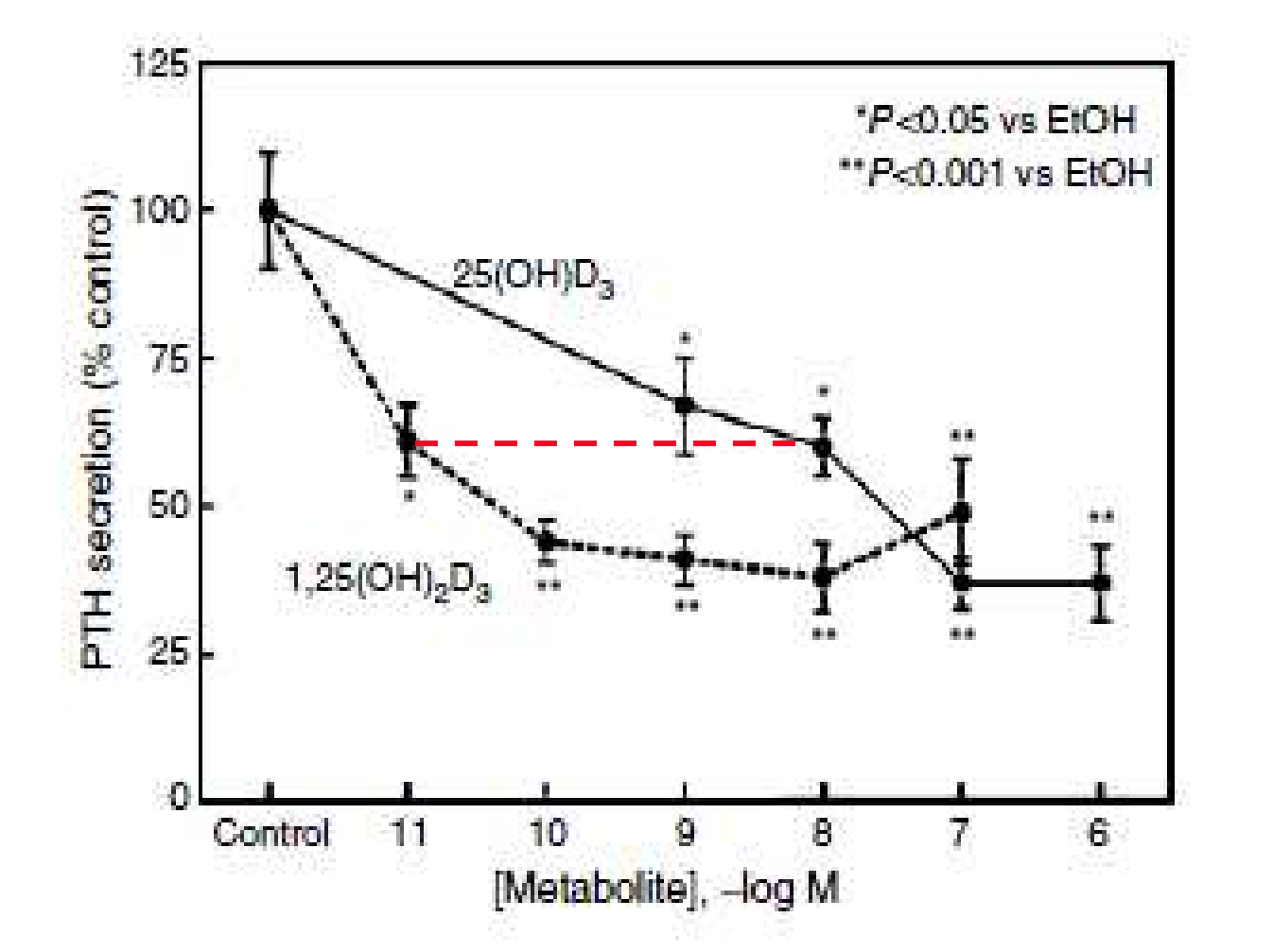
Segersten, J.Clin.Endocr.Metab.(2002) 87:2967

In proximal tubule uptake of 25(OH)D via Megalin



Nykjaer, Cell (1999) 96:507.

Suppression of PTH secretion by $25(OH)D_3$ and $1,25(OH)_2D_3$ in bovine parathyroid cell cultures



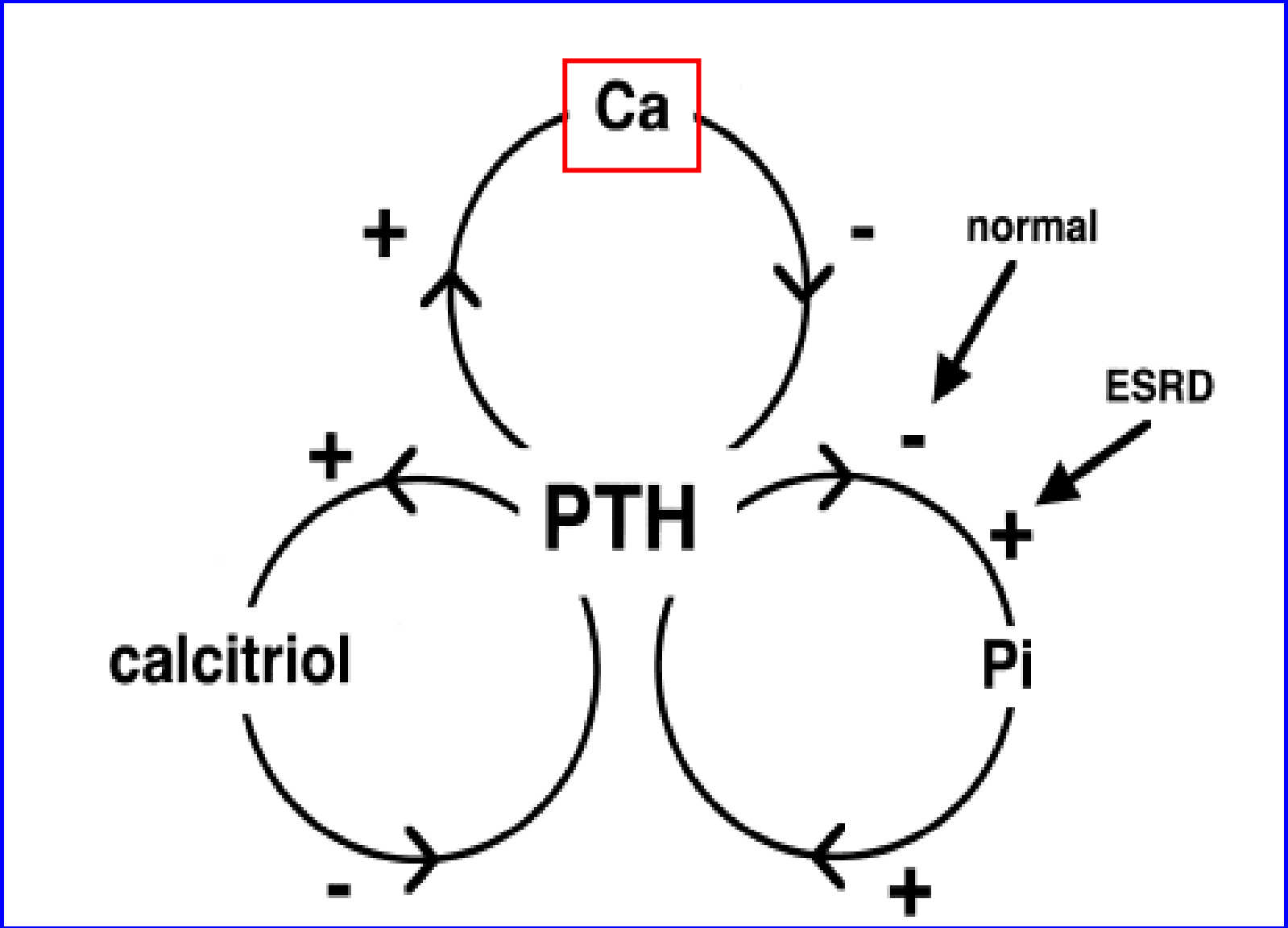
Ritter, Kidn.Intern.(2006) 70:654

What triggers (secondary) hyperparathyroidsim

- hyperphosphatemia → low ionised Ca^{++}
- lack of $1,25(OH)_2D_3$
- lack of 25(OH)D →

  local production of $1,25(OH)_2D_3$?
- ionised plasma Ca^{++}

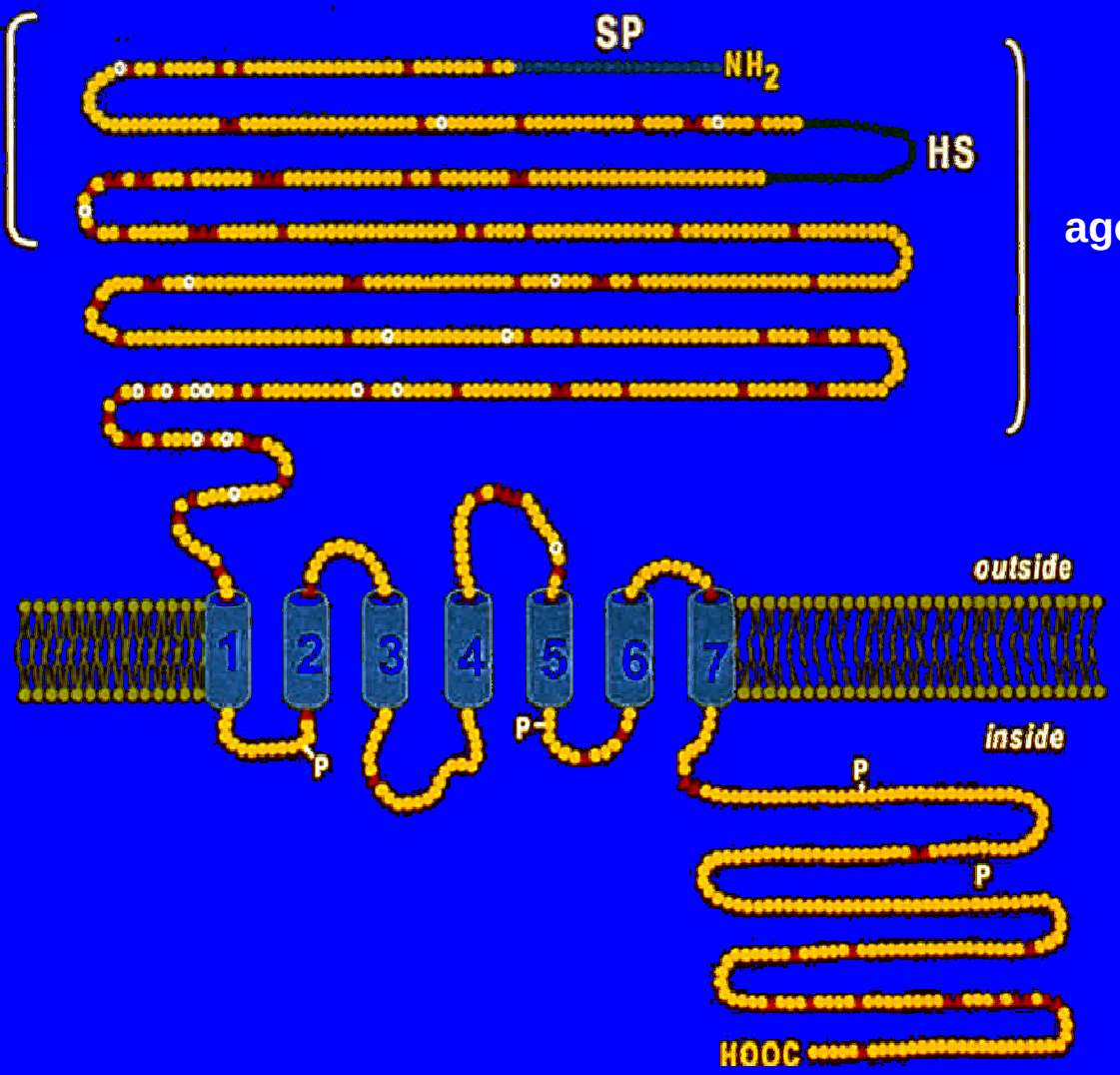
Pathogenesis of secondary hyperparathyroidism



Cunningham J., Kidn.Internat.(1999) 73, S59

Calcium sensing receptor (CaR)

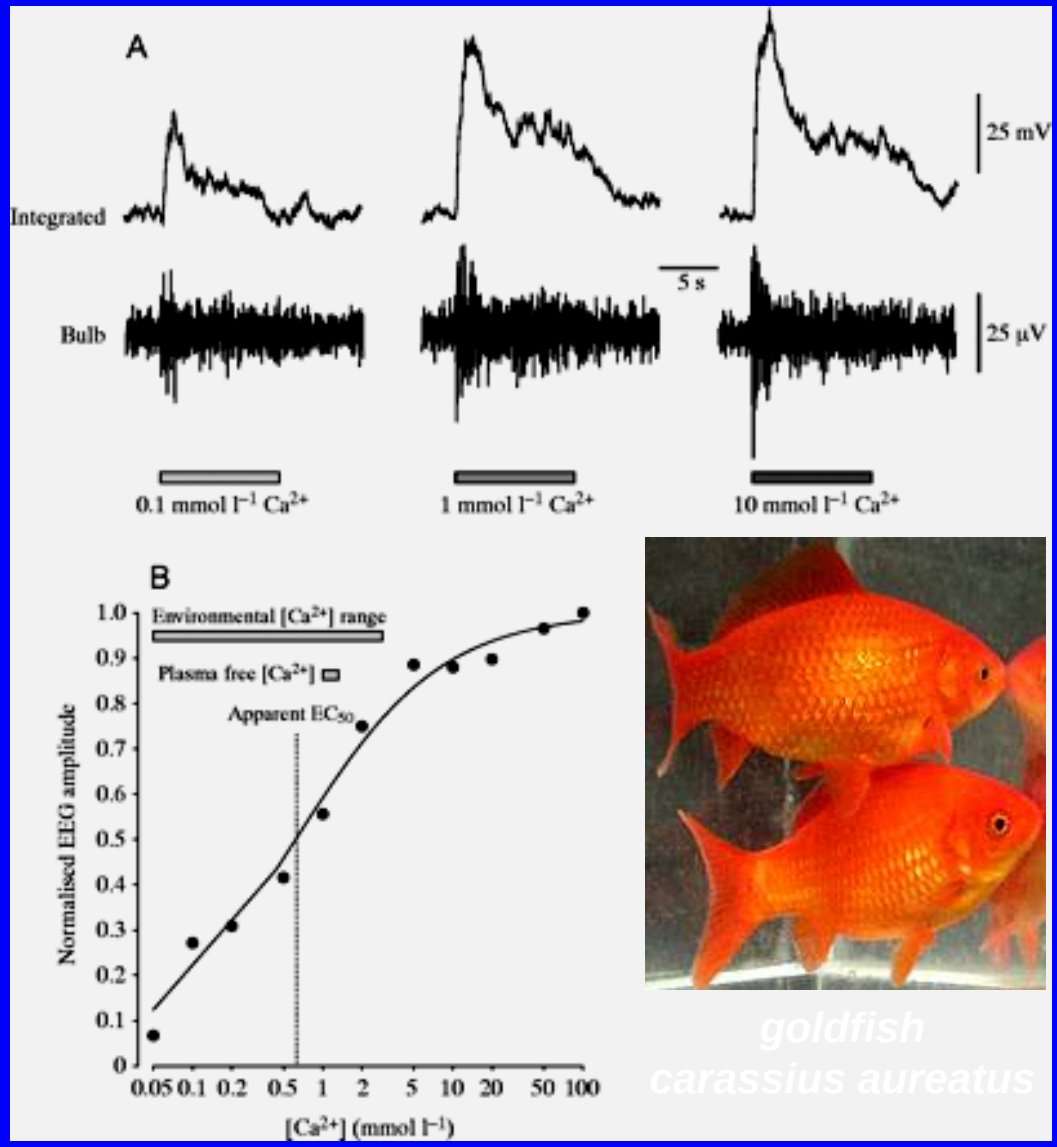
controls dimerization and normal receptor function



agonist binding

Caenorhabditis elegans

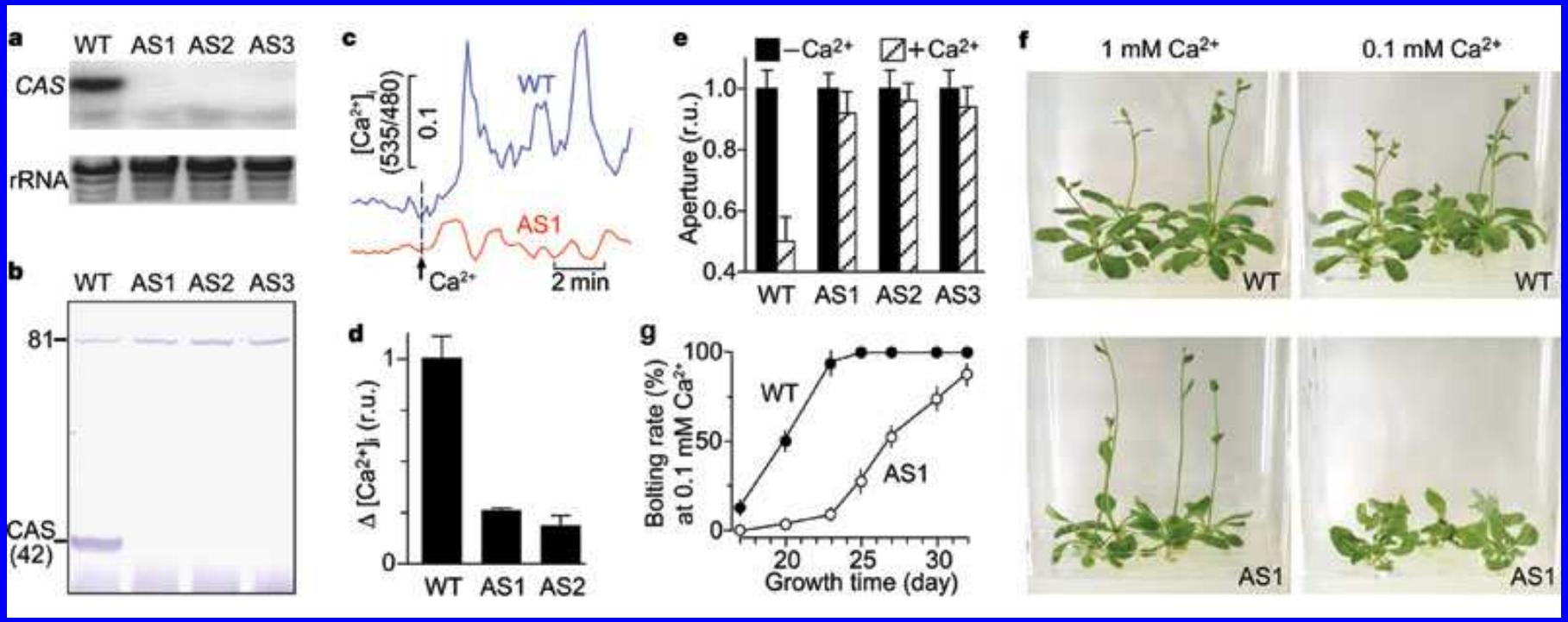
Olfactory sensing of Ca^{++} - by CaSr homologue



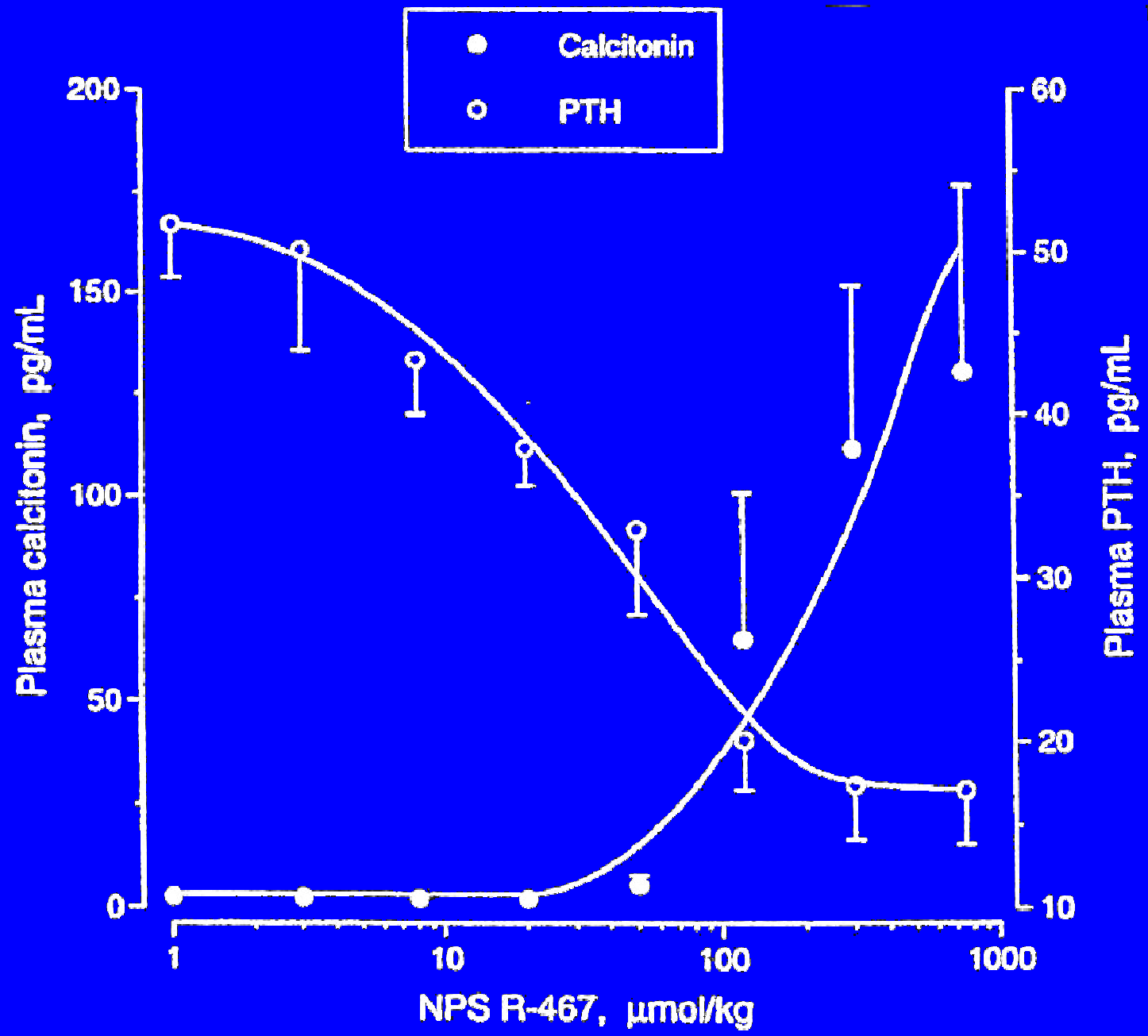
Hubbard, J.Experiment.Biol.(2002) 205:2755

Ca^{++} sensing protein in plants

(Arabidopsis guard cells)



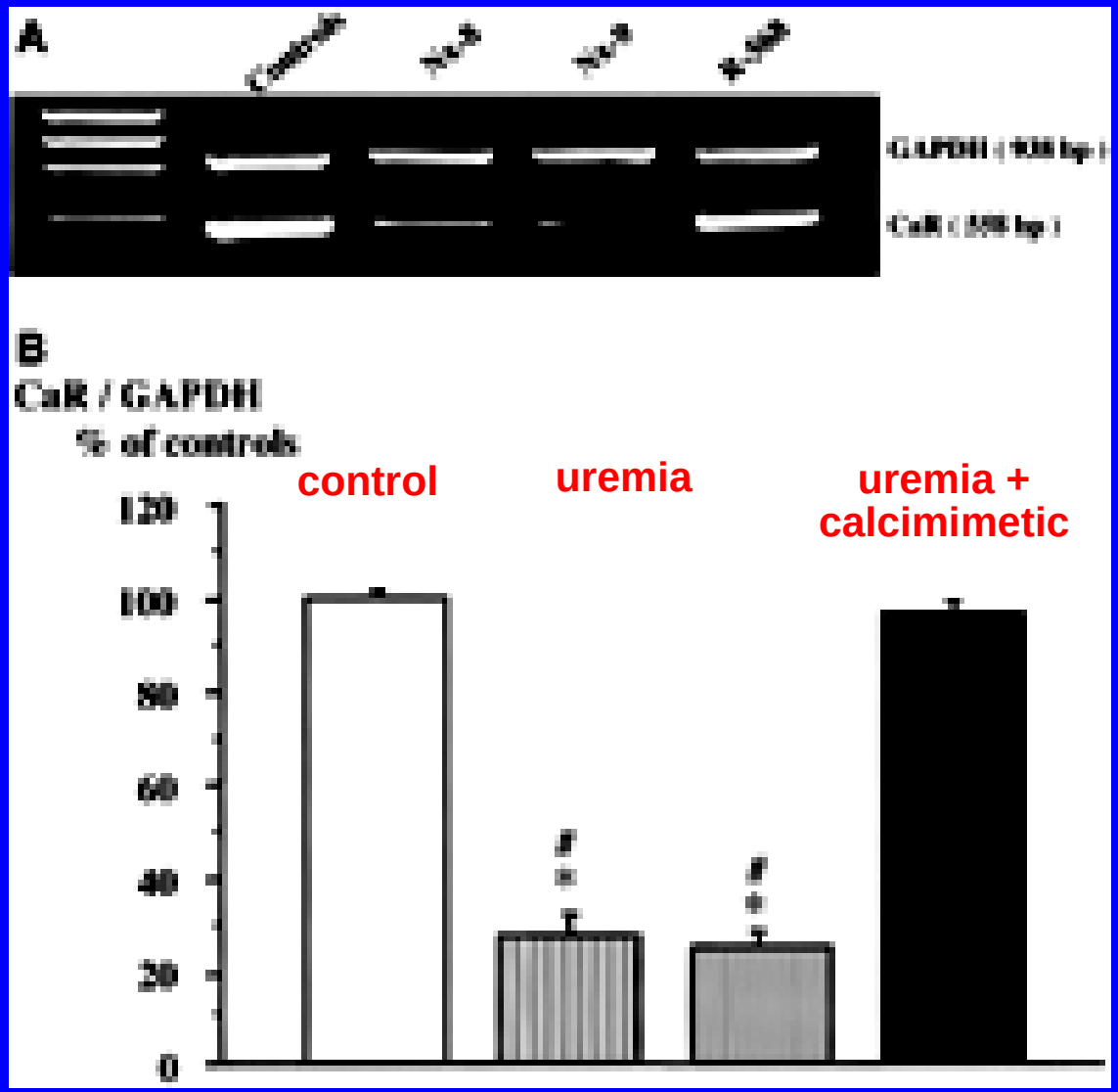
Han, Nature (2003) 425, 196


Calcitonin
PTH
Plasma calcitonin, pg/mL
Plasma PTH, pg/mL
NPS R-467, µmol/kg
200
150
100
50
0
60
50
40
30
20
10
1
10
100
1000

"**Calcimimetics** are a family of **small organic molecules** that **allosterically modulate calcium receptors** present on the surface of parathyroid cells and parafollicular cells of the thyroid glands to make them **more sensitive to serum Ca^{2+}** concentrations."

" trick the parathyroid into believing it were in a hypercalcemic milieu"

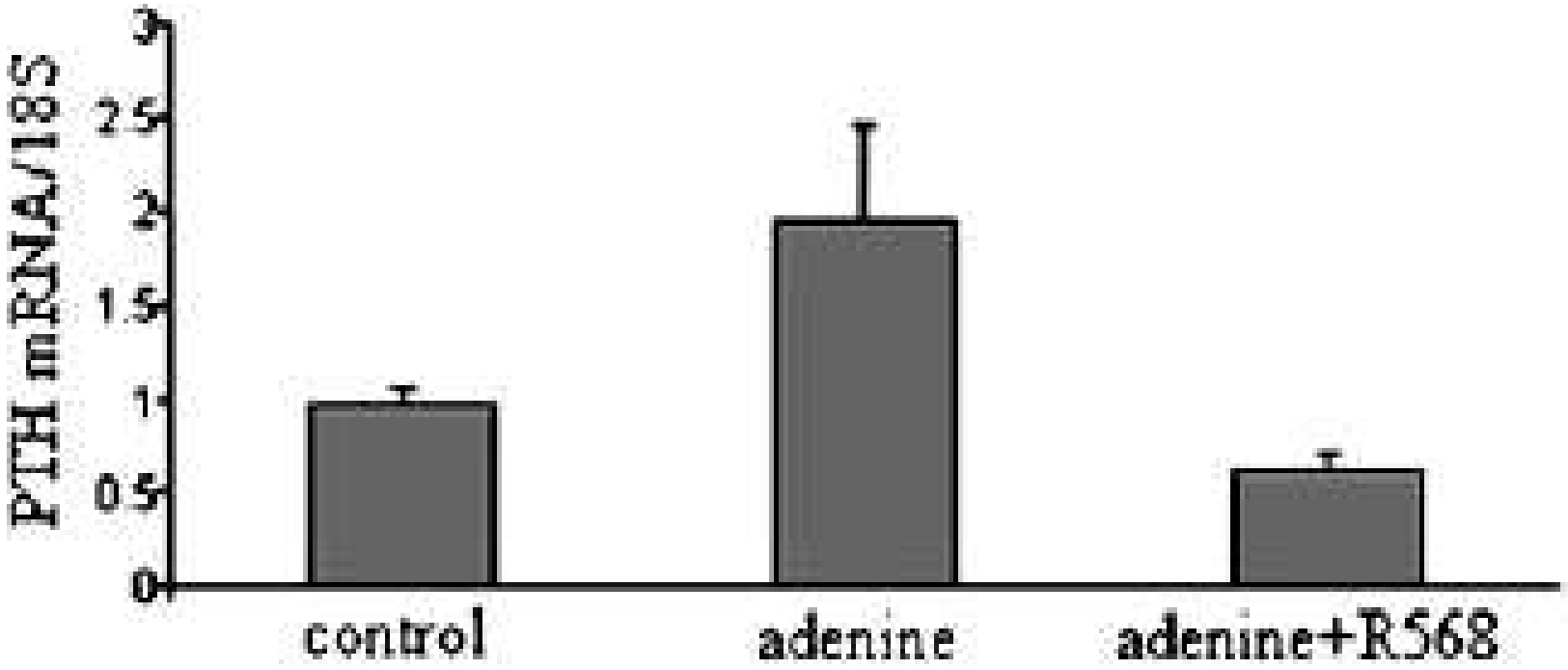
Calcimimetic upregulates Ca-receptor in renal failure



Mizobuchi, J.Am.Soc.Nephrol.(2004) 15:2579

Calcimimetics decrease PTHmRNA – posttranslational effect (AUF1) ~ high P_i

(model of adenine nephropathy)



Silver, J.Am.Soc.Nephrol.(2006) 17:107

Calcium sensing receptor is regulated by vitamin D, but not by calcium

Brown, Amer.J.Physiol.(1996) 270:F454

$1,25(OH)_2D_3$ increases Ca^{++} sensitivity of PTH secretion in HD patients

Delmez, J.Clin.Invest.(1989) 83:1349

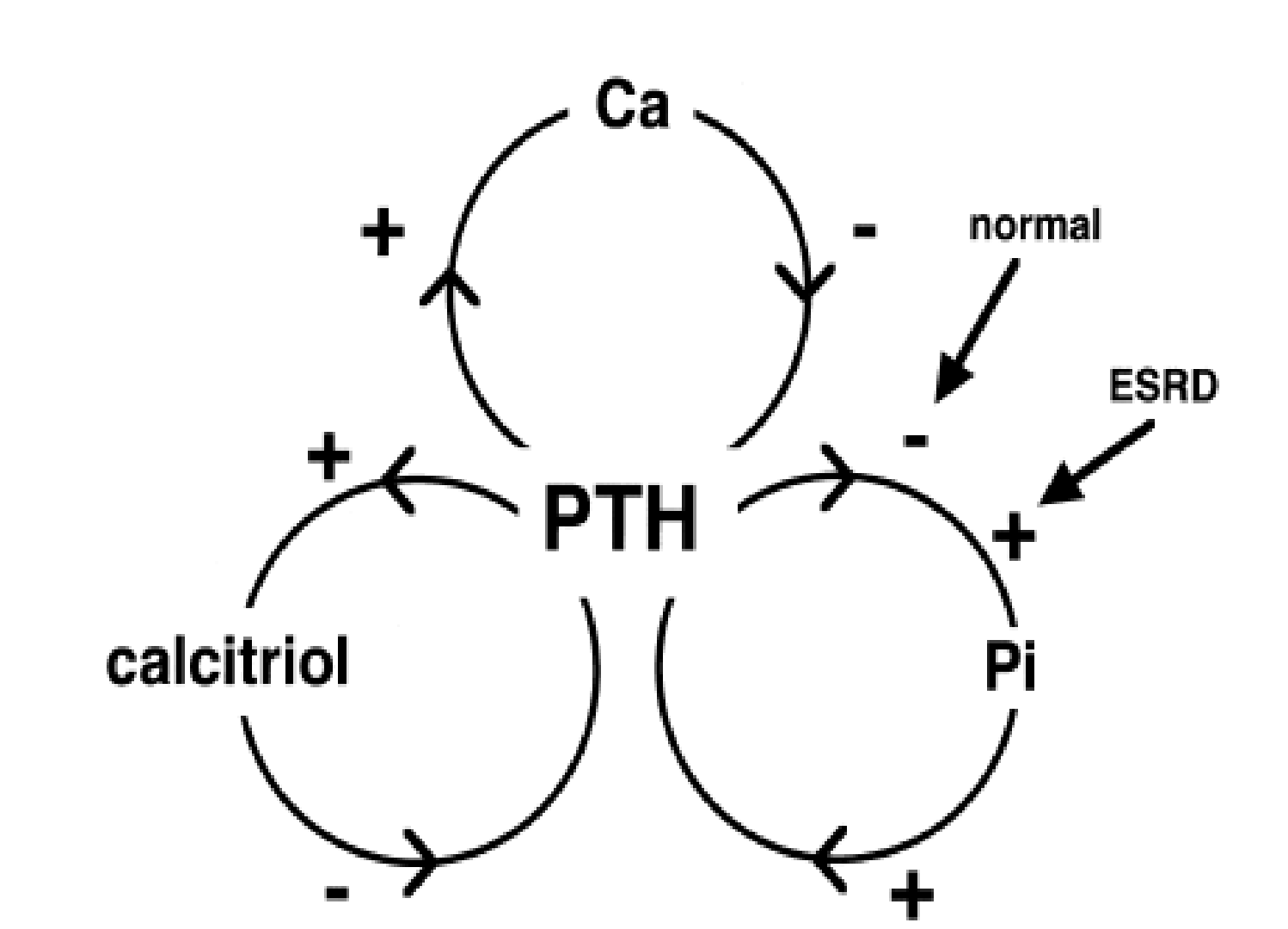
⇨ **- 1. increased Ca^{++} sensitivity of parathyroid**
- 2. reduced active intestinal Ca transport
argument for calcimimetic plus active vitamin D ?

What triggers (secondary) hyperparathyroidsim

- hyperphosphatemia → low ionised Ca^{++}
- lack of $1,25(OH)_2D_3$
- lack of 25(OH)D →

  local production of $1,25(OH)_2D_3$?
- ionised plasma Ca^{++}
- FGF23/klotho – new players

Pathogenesis of secondary hyperparathyroidism – not only a trio (rewrite the textbooks)



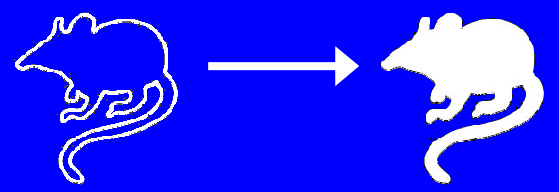
Cunningham J., Kidn.Internat.(1999) 73, S59

Evidence of circulating factor

Nesbitt, J.Clin.Invest (1992) 89:1453

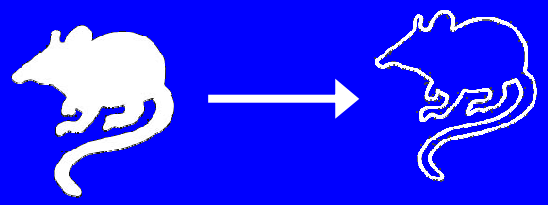
hyp mouse (genetic analogue of XLH) →
kidney transplantation

normal to hyp



→ phosphaturia

hyp to normal



→ unchanged phosphate excretion

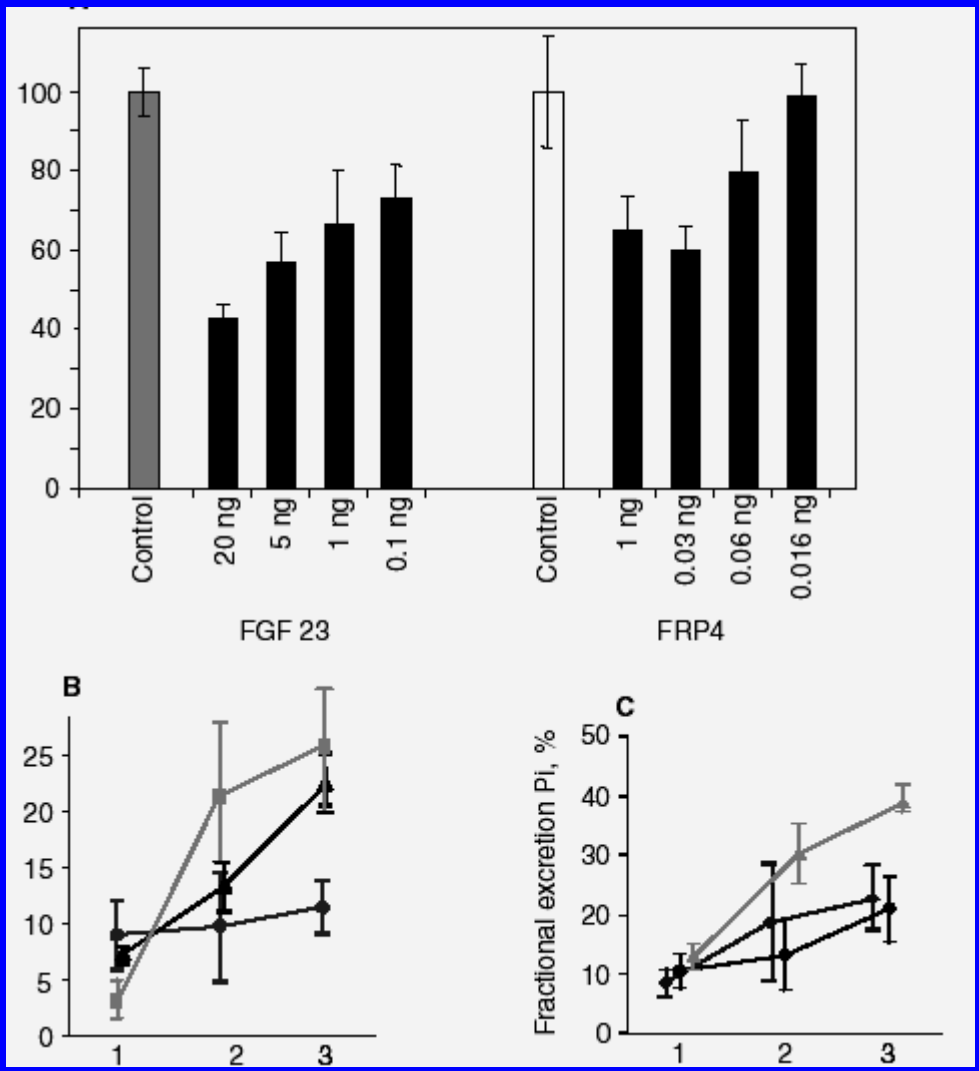
⇨ ***conclusion :***

not intrinsic defect of tubular epithelial cells, but circulating factor

Both FGF 23 and FRP 4 are phosphaturic

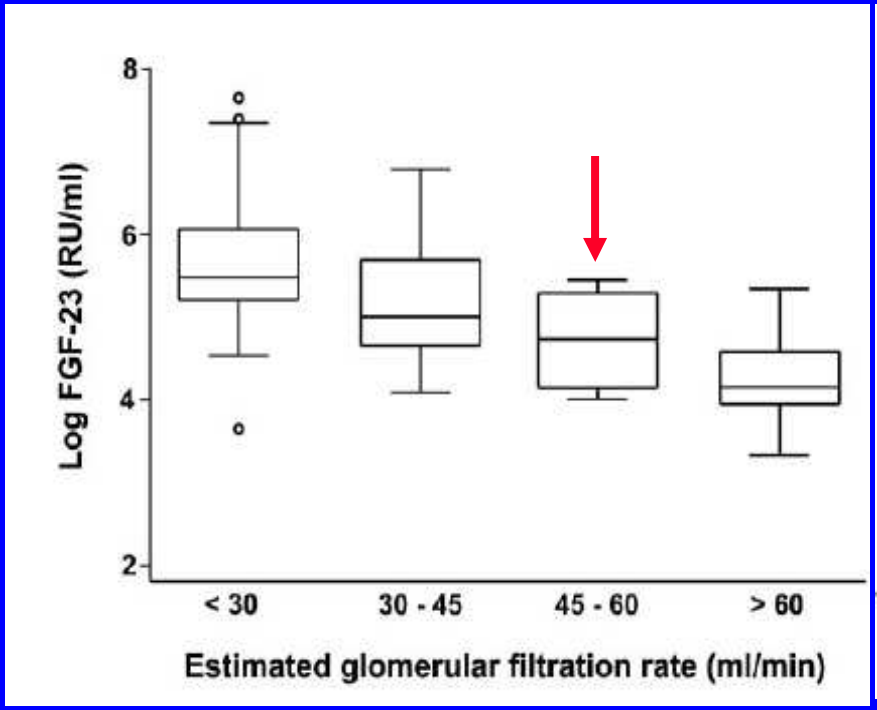
P uptake (%)

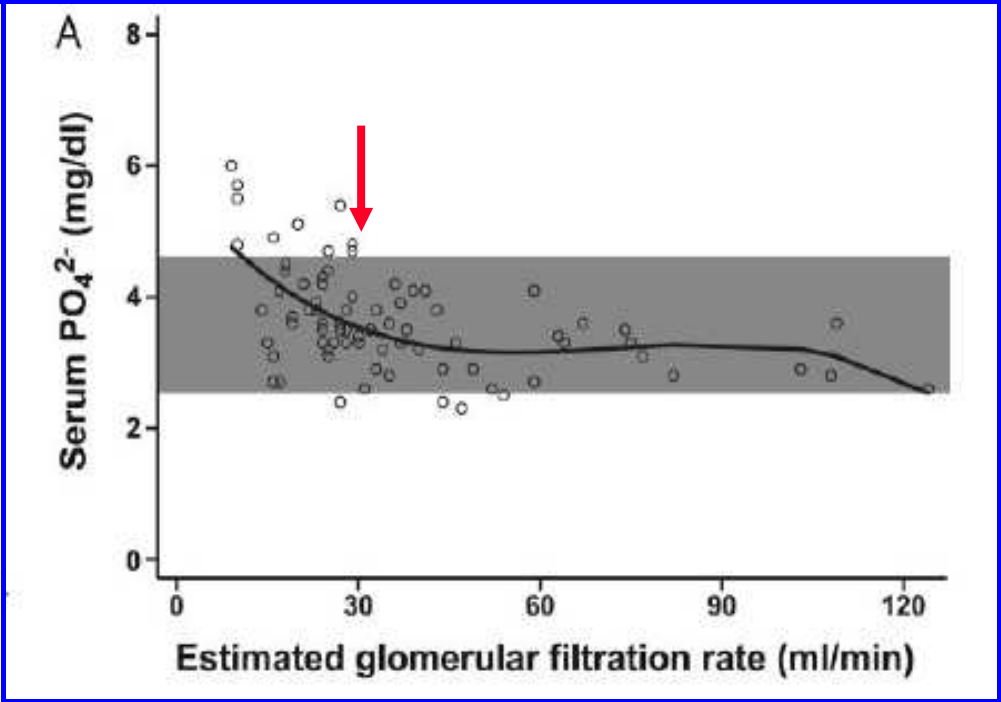
Fractional P excretion (%)



Schiavi and Kumar, Kidn.Intern. (2004) 65: 1

With decreasing GFR –
increasing FGF23
despite no early increase in S-phosphate





Guttierez, J.Am.Soc.Nephrol. (2005) 16: 2205

→ *conclusion :FGF23 mitigates hyperphosphatemia,*
but accentuates calcitriol deficiency

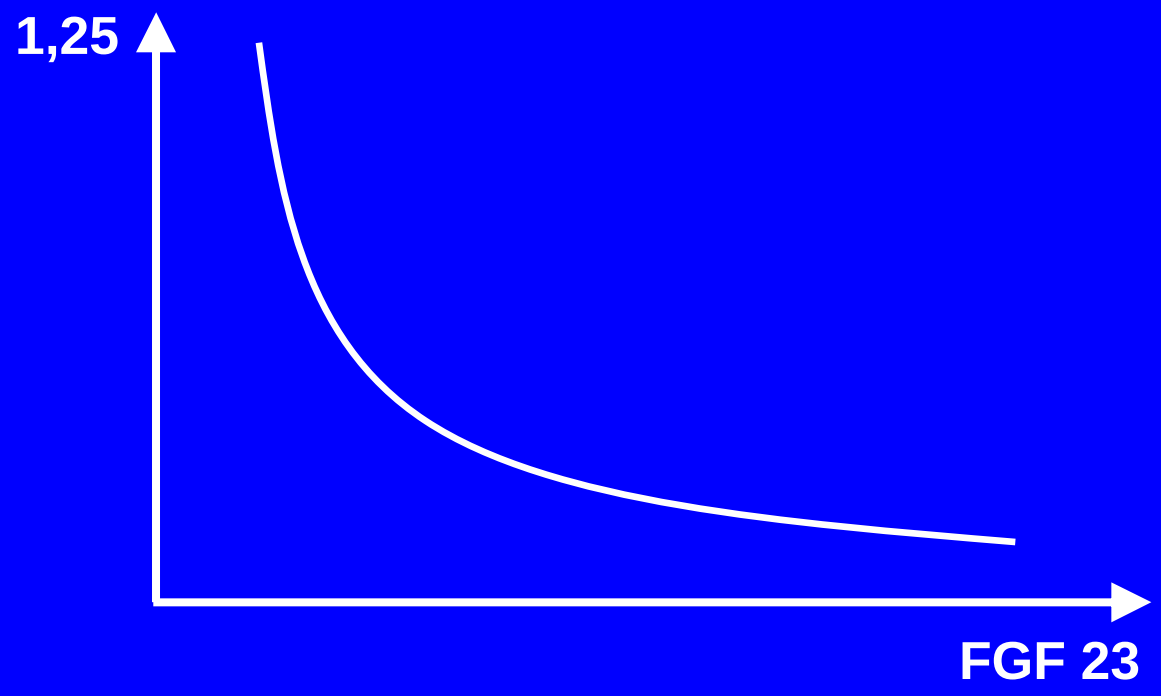
Role of FGF 23 in renal failure

elevated FGF 23 concentrations in renal failure

Jonsson,New Engl J Med(2003)348:1656
Jonsson,Kidn.Intern.(2003)64:2272

Anti-GBM-glomerulonephritis as model of chronic renal failure

FGF 23 ↑↑
inversely correlated to 1,25(OH)$_2$D$_3$ →
FGF23 inhibits 1$^{\alpha}$ hydroxylase



Shimada, 2003

Prevention of PTH increase by diminishing dietary phosphate in proportion to loss of GFR

60 days low P_i diet in patients with moderate renal failure

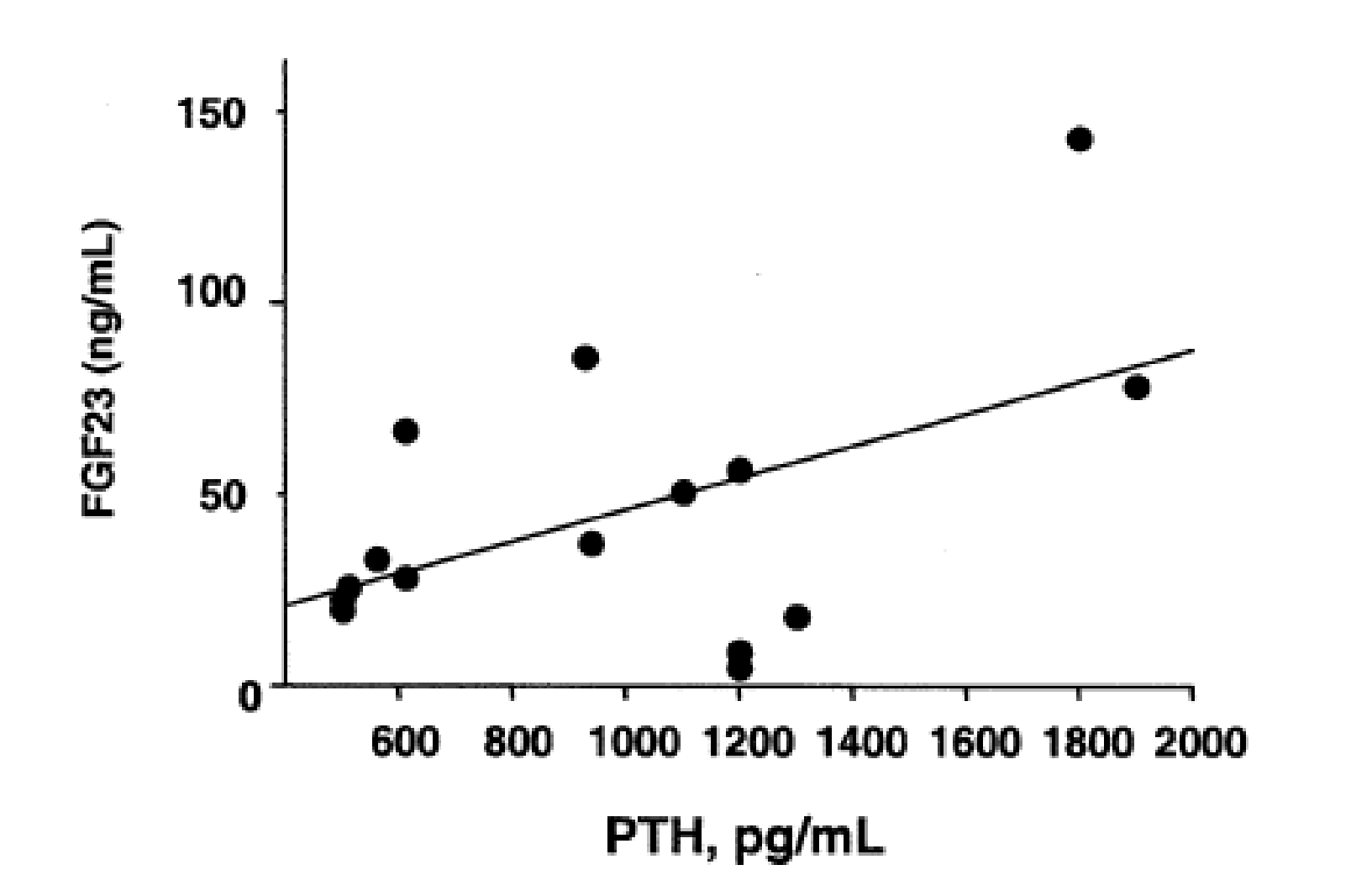
 # initially:

- *impaired intestinal calcium absorption*
- *reduced calcemic response to PTH*
- *low serum ionized calcium*
- *elevated PTH*

 # after the diet → all parameters returned to normal

Lllach and Massry, J.Clin.Endocr.Metab(1985) 61:601

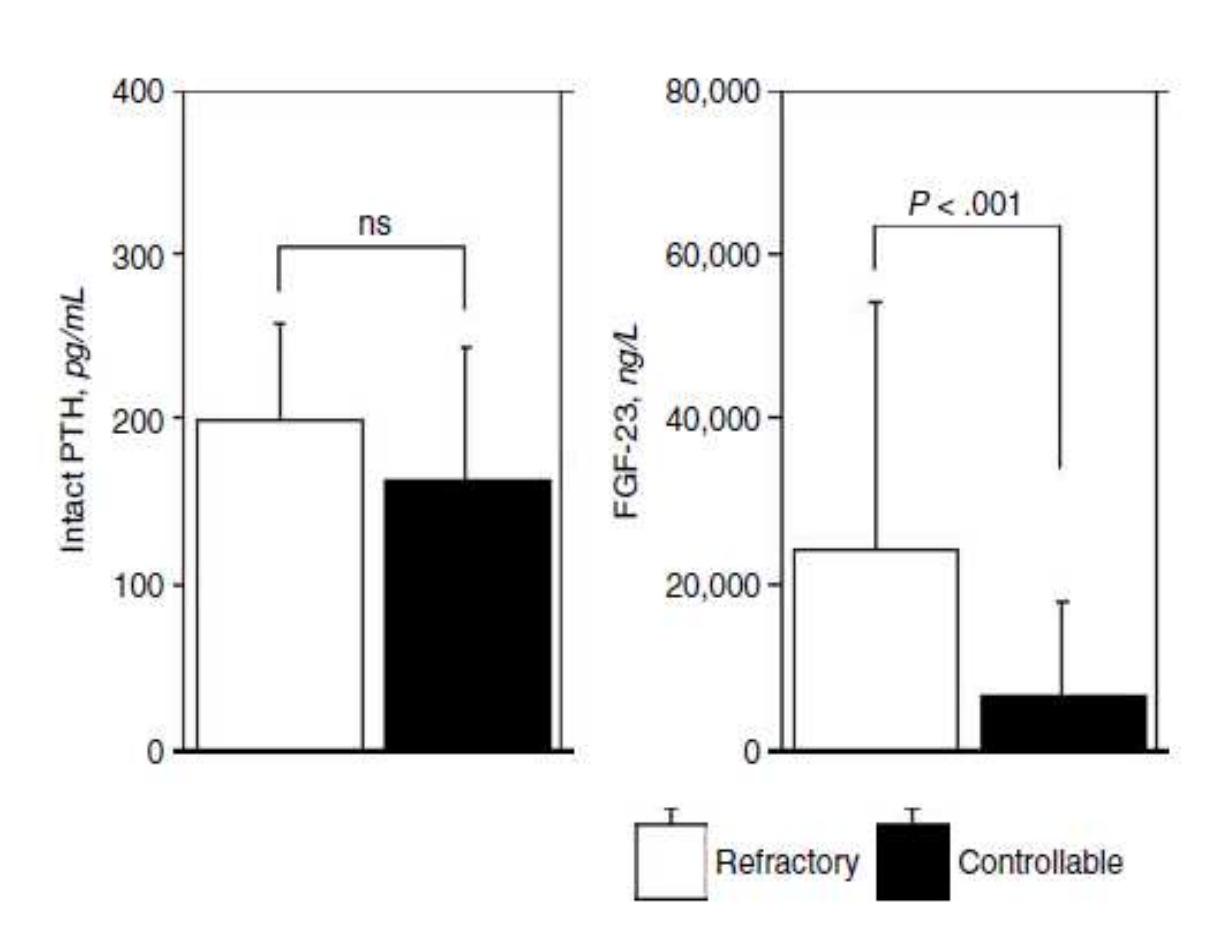
Prior to parathyroidectomy correlation PTH and FGF 23 concentrations



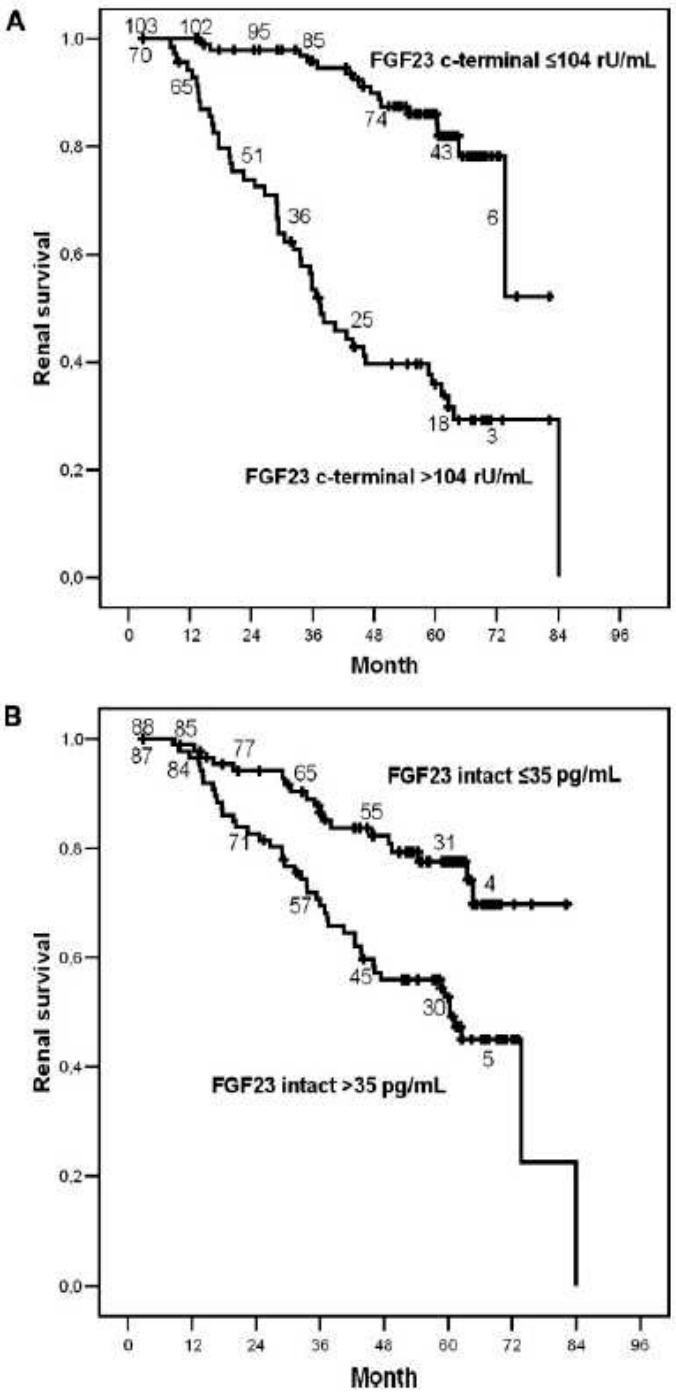
Sato, Am J Kidn Dis (2004) 44: 481

FGF23 predicts need of parathyroidectomy

= *refractory to conventional treatment*



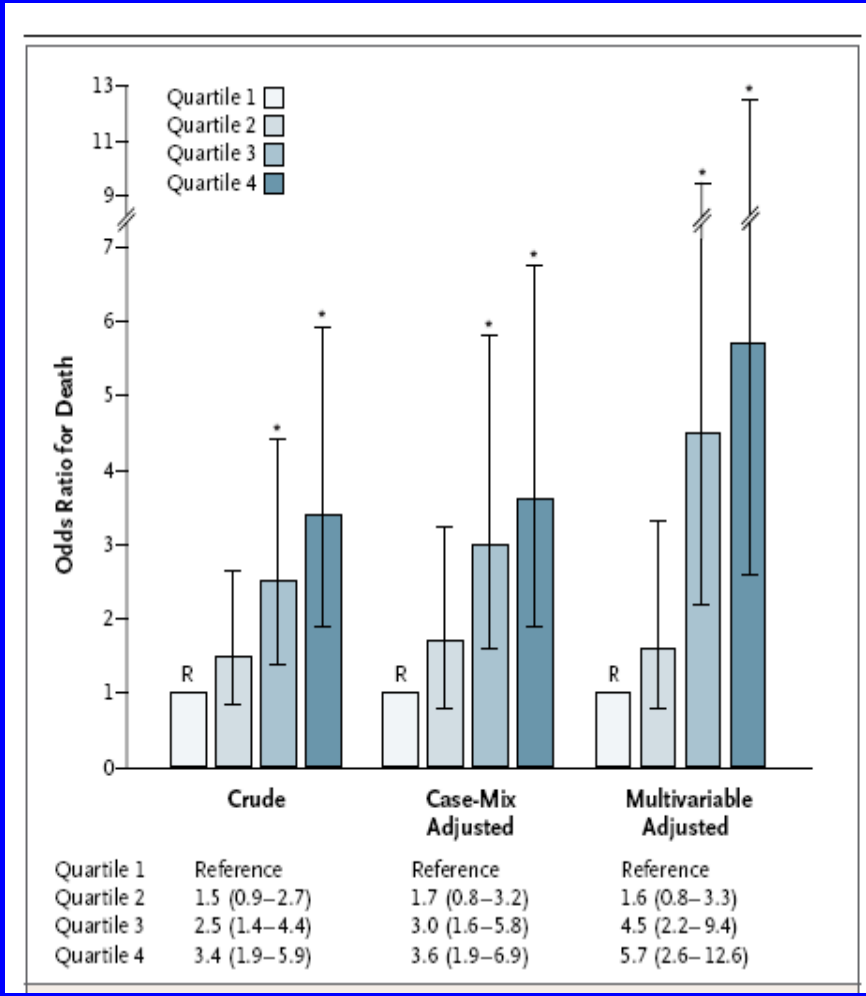
Nakanishi, Kidn.Internat.(2005) 67:1171



C-terminal and intact FGF23 predict renal survival

Fliser, J.Am.Soc.Nephrol.(2007) 18:2600

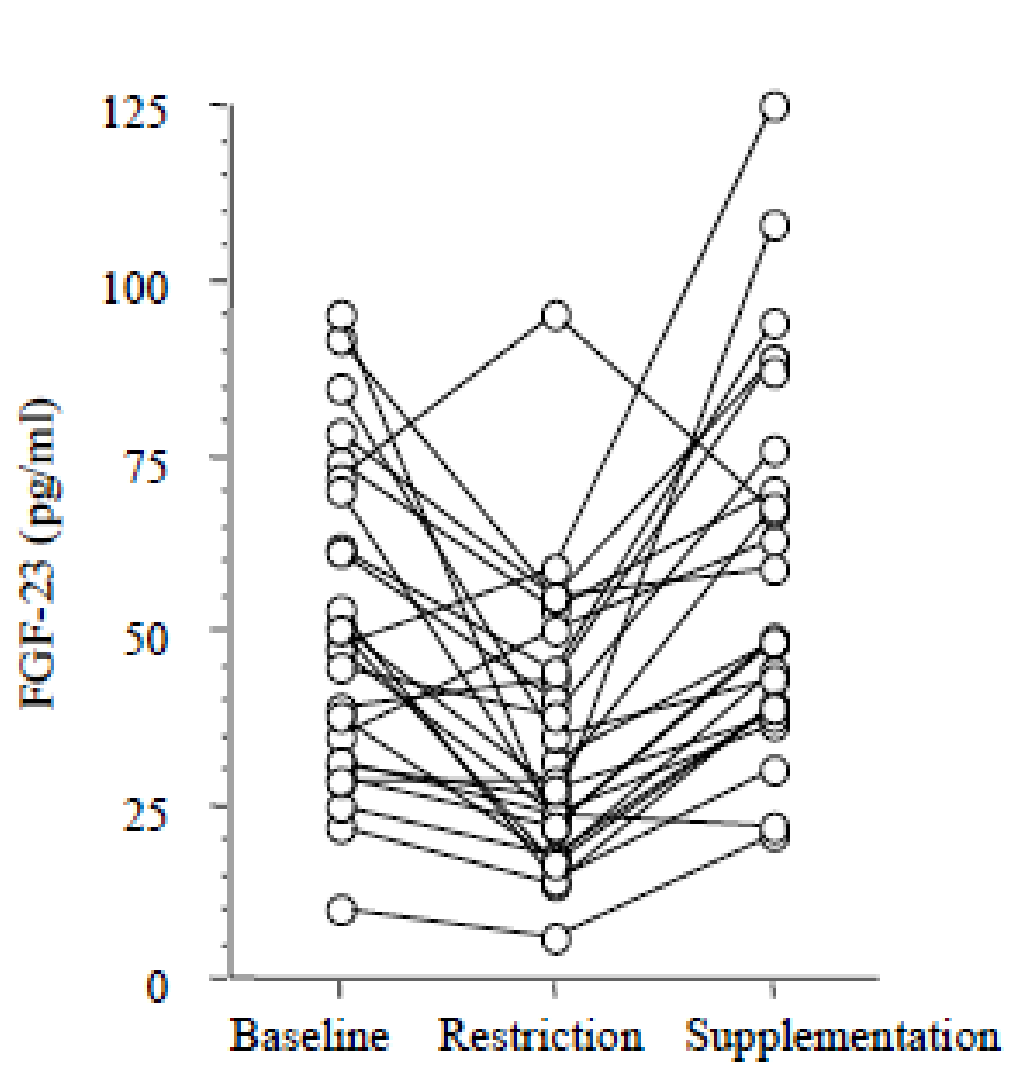
FGF23 predicts survival in dialysis patients



Gutiérez, New Engl.J.Med.(2008) 359:584

Can one modulate FGF 23 ?

FGF23 responds to P-restriction and supplementation in human volunteers



Ferrari, J.Clin.Endocr.Metab.(2005) 90:1519

Calcitriol iv ➡
PTH ↓,
FGF23 ↑↑

30 dialysis patients

3 x week 0.5-1.0 µg calcitriol iv for 6 months

- **PTH decreased ($p<0.001$)**
- **FGF23 gradually increased ($p<0.027$)**

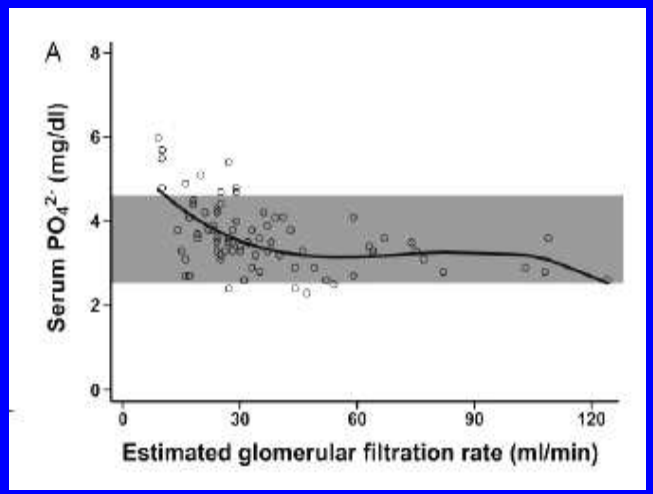
Δ FGF23 correlated to

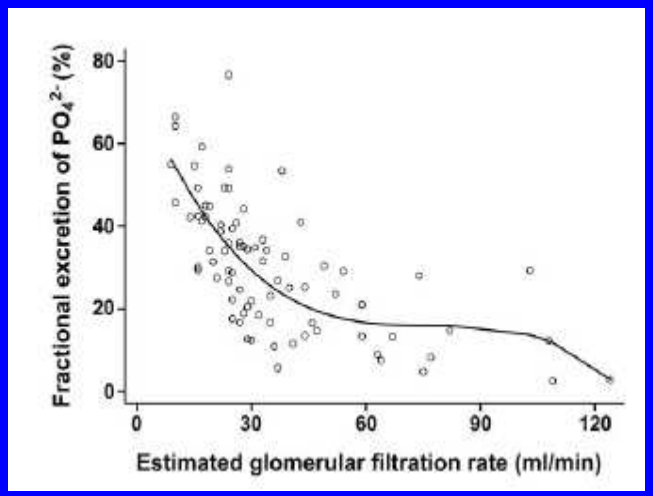
total calcitriol dose *(r^2 0.147;$p<0.036$)*

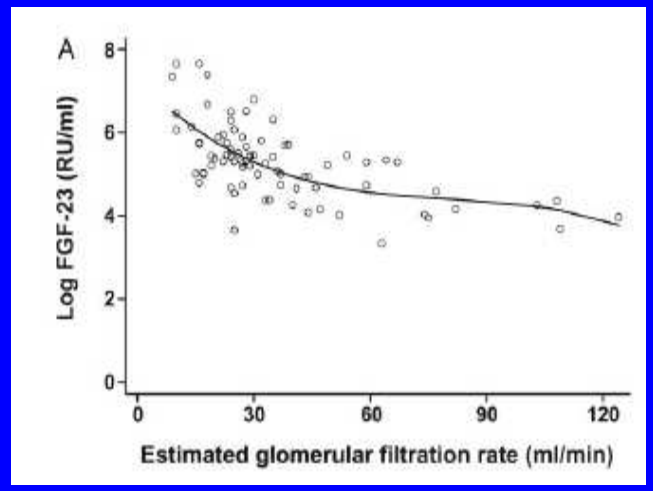
Nishi, Nephron Clin.Pract.(2005) c94

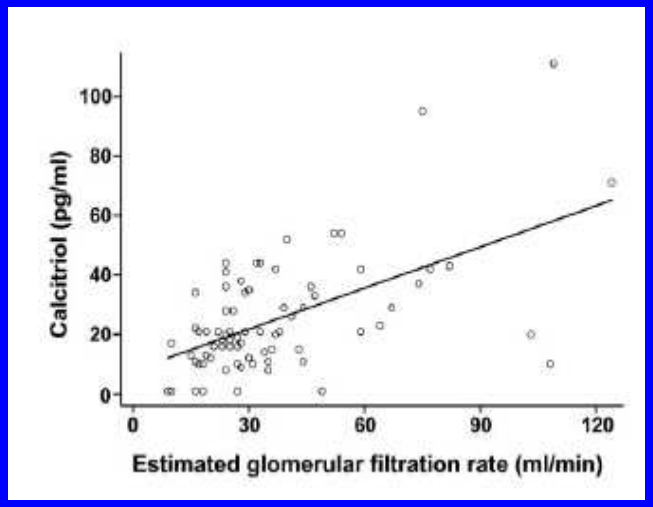
Scenario in CKD:

S-Pi kept normal by increased fractional excretion of Pi (FePi) via elevated FGF23 at the price of lowering calcitriol









Gutierrez, J.Am.Soc.Nephrol.(2005) 16:2205

FGF 23 –
beyond calcium-phosphate metabolism !

klotho mouse

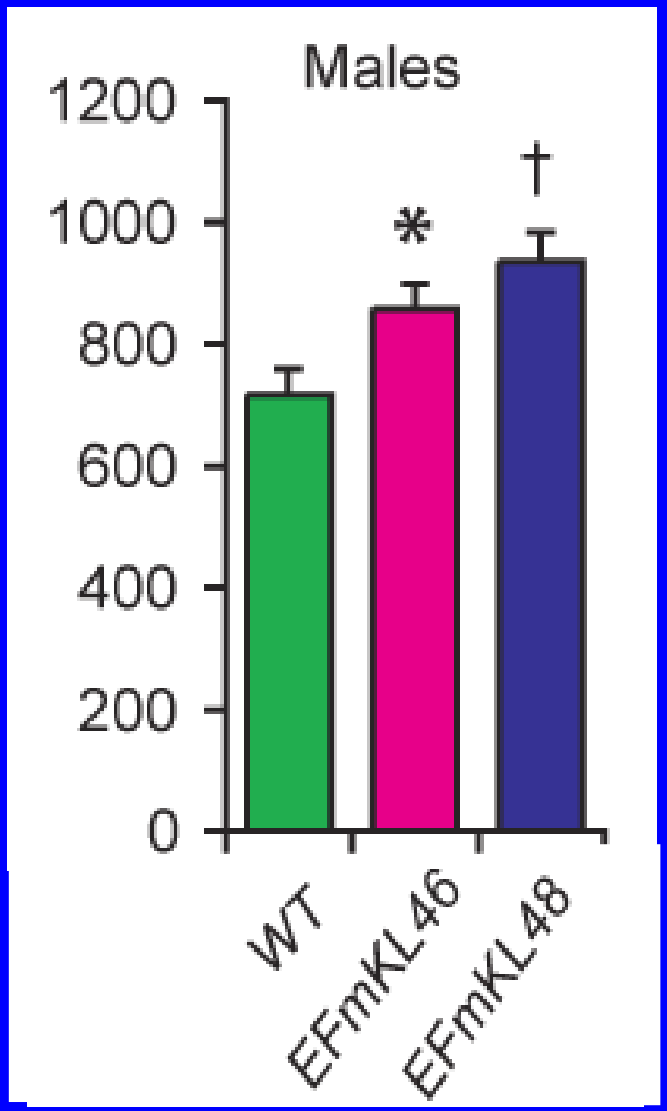
the first documented mammalian model for human aging that manifests multiple aging-like phenotypes in a single individual.

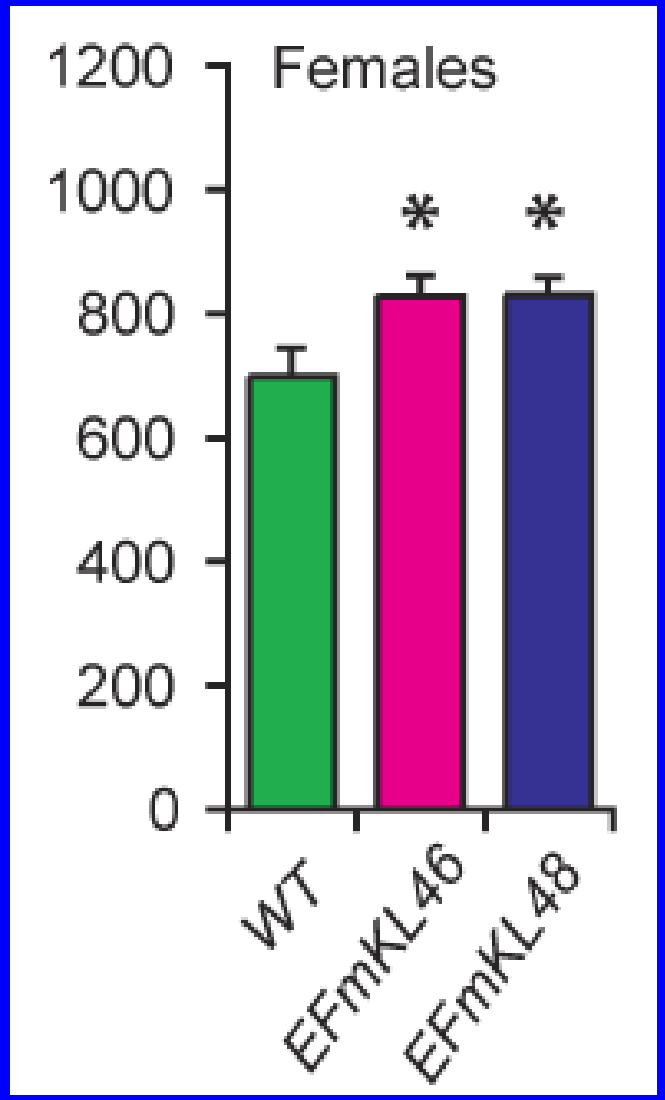
- **Short lifespan**
- **Growth retardation**
- **Infertility**
- **Premature thymic involution**
- **Skin atrophy**
- **Muscle atrophy**
- **Arteriosclerosis**
- **Osteoporosis**
- **Pulmonary emphysema**
- **Ectopic calcification**
- **Motor neuron degeneration**
- **Cognition impairment**
- **Hearing disorder**

***KL*$^{-/-}$**

Overexpression of Klotho prolongs life expectancy

***klotho* gene is "aging suppressor gene"**





Klotho

- **Mouse :**

  klotho -/- ageing

  klotho overexpression extension of lifespan

- **Humans :**

  polymorphisms of klotho gene correlated with

  lifespan

  osteoporosis

  stroke

  coronary disease

Arking, Am.J.Hum.Genet.(2003) 72:1154
Yamada, J.Mol.Med. (2005) 83:50

klotho -/- and FGF23 -/-
→ common signalling pathway ?

- *hyperphosphatemia*
- *hypercalciuria*
- *increased 1,25(OH)2D3*
- *increased 1$^{\alpha}$ hydroxylase*

Tsujikawa, Mol.Endocrinol.(2003) 17:2393

nature Vol 444 | 7 December 2006 | doi:10.1038/nature05315

LETTERS

Klotho converts canonical FGF receptor into a specific receptor for FGF23

Itaru Urakawa[1], Yuji Yamazaki[1], Takashi Shimada[1], Kousuke Iijima[1], Hisashi Hasegawa[1], Katsuya Okawa[1], Toshiro Fujita[2], Seiji Fukumoto[2] & Takeyoshi Yamashita[1]

Is hyperparathyroidism and disturbed Ca,Pi metabolism fully explained by known factors ?

⇨ **Further systemic and/or local factors operative in uremic bone disease**

PTH excess and 1,25(OH)2D3 deficiency do not fully explain bone disease

Subtotally NX and PTX rats, replacement doses of rat 1,34 PTH and 1,25(OH)2D3

	sham-op + solvent (n=8)	NX-PTX + solvent (n=8)	NX-PTX + PTH+1,25 (n=8)
osteoclasts (per mm_2)	*0.5 ± 0.3*	*0.28 ± 0.2*	*0.23 ± 0.2*
osteoblast surface (ObS/BS%)	*0.8 ± 1.2*	*0.54 ± 1.0*	*1.67 ± 2.4*
Osteoid thickness (µm)	*3.19 ± 3.3*	*7.7 ± 1.8*	*7.0 ± 3.6*
bone volume (BV/TV%)	*19.2 ± 9*	*19.3 ± 9.9*	*34.9 ± 7.9*

Szabo,Eur.J.Clin.Invest.(1999) 29:529

Thank you for your attention

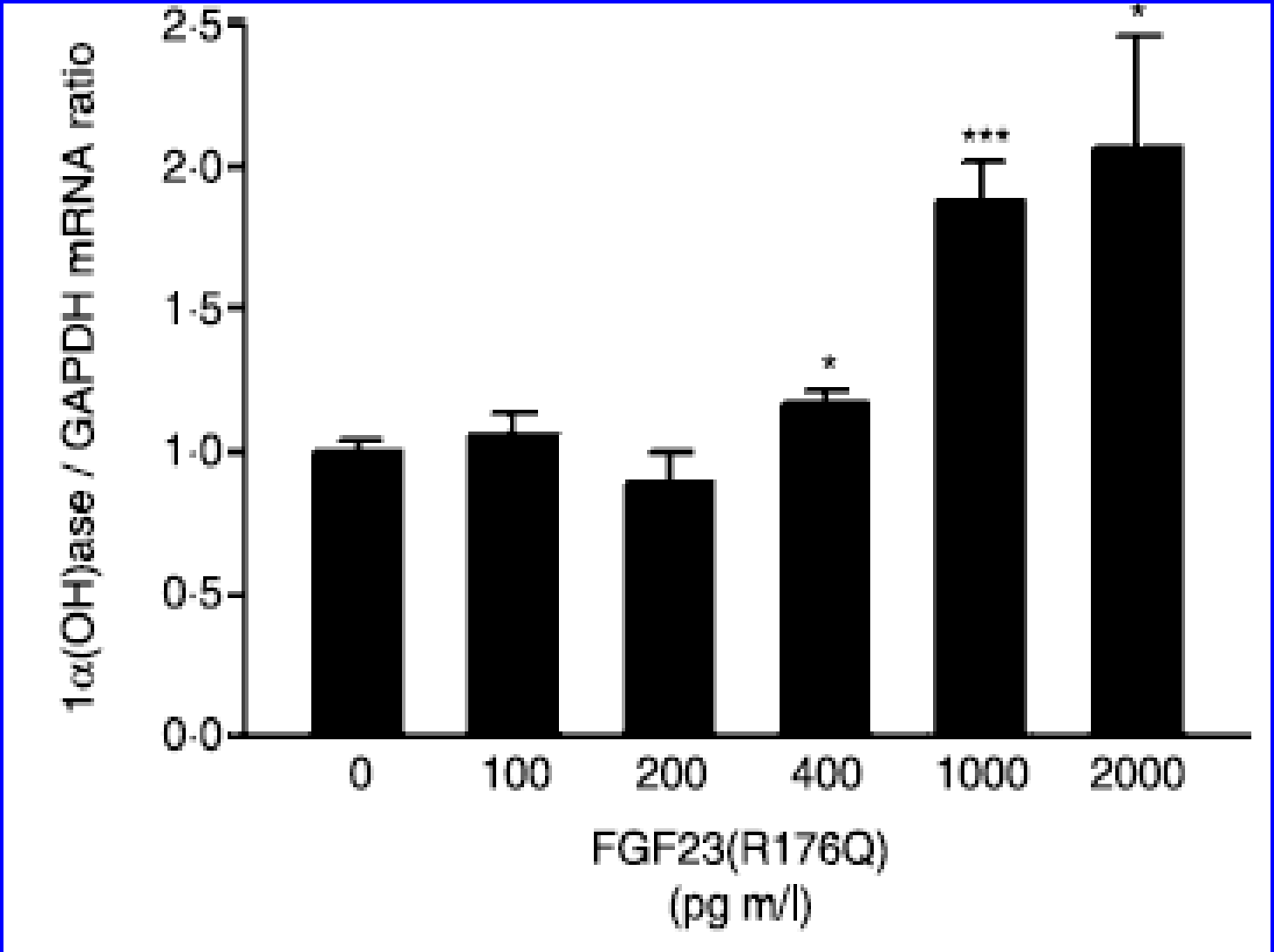
prof.e.ritz@t-online.de

Wer von allem etwas gibt,
wird allen etwas geben

(he who gives a bit of everything,
will give something to everyone)

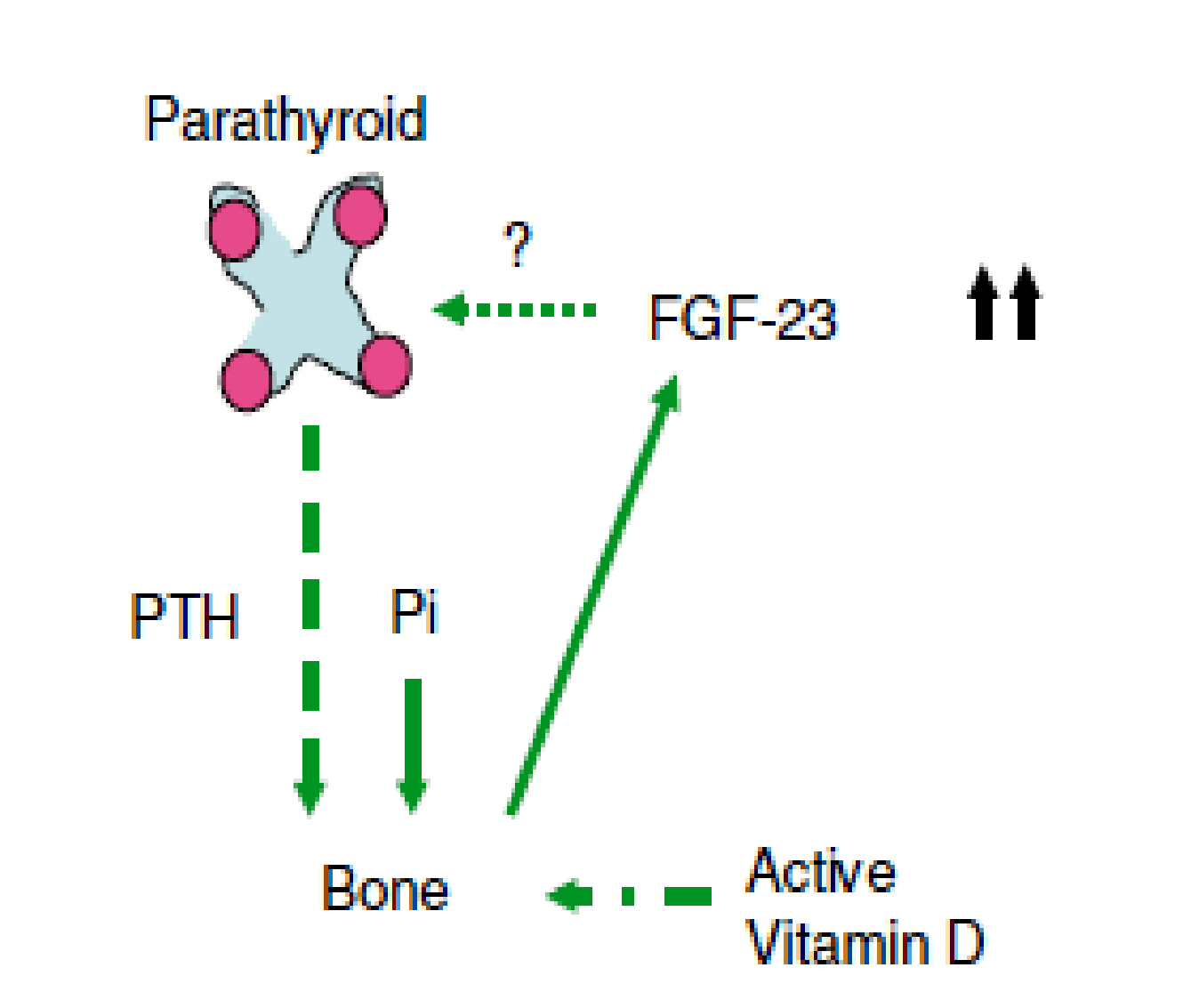
J.W. von Goethe
Faust
(Schauspieldirektor)

FGF23 increases 1(alpha) hydroxylase in parathyroid gland



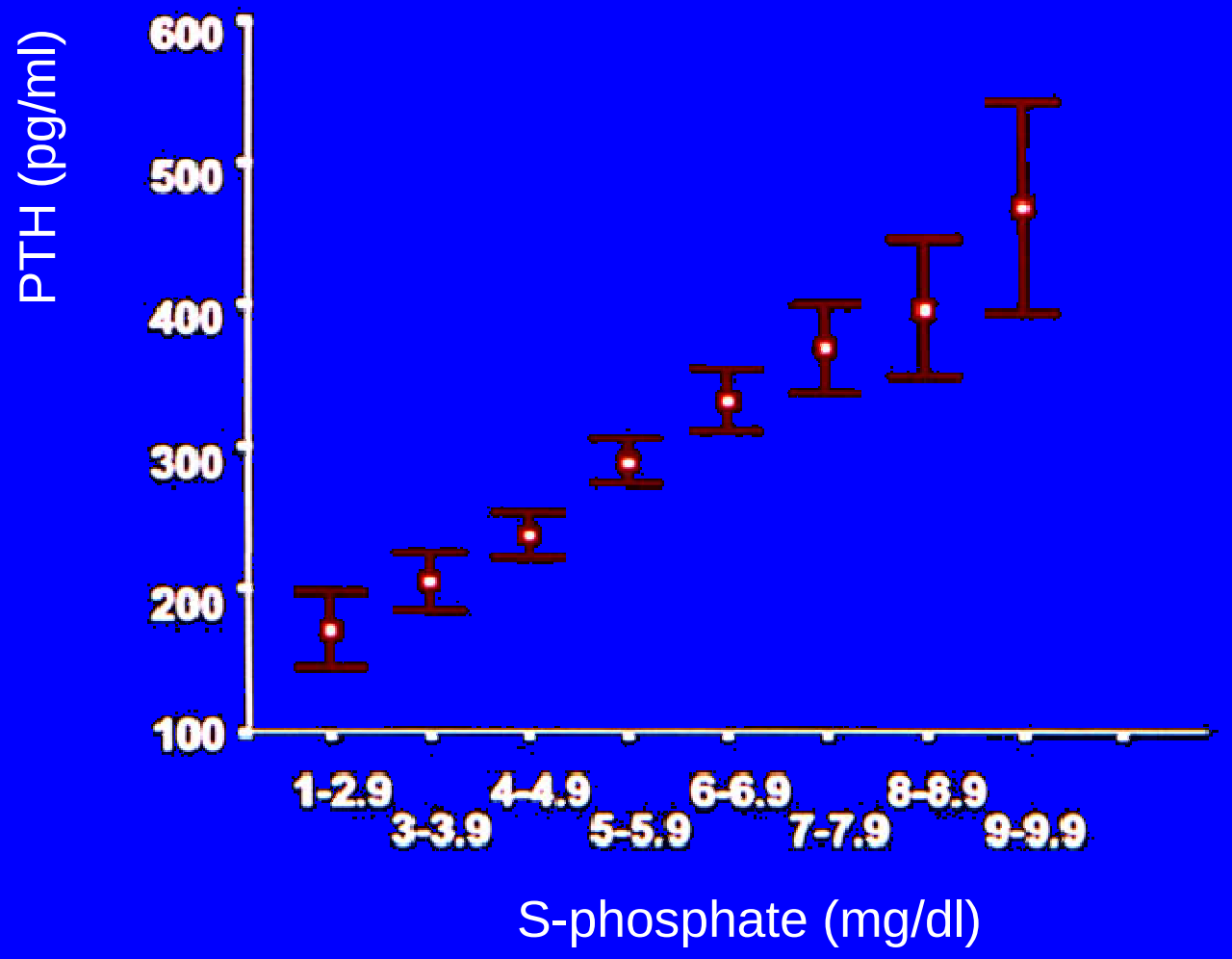
Krajisnik, J.Endocrinol.(2007) 195:125

A role of FGF23 in the genesis of hyperparathyroidism ?



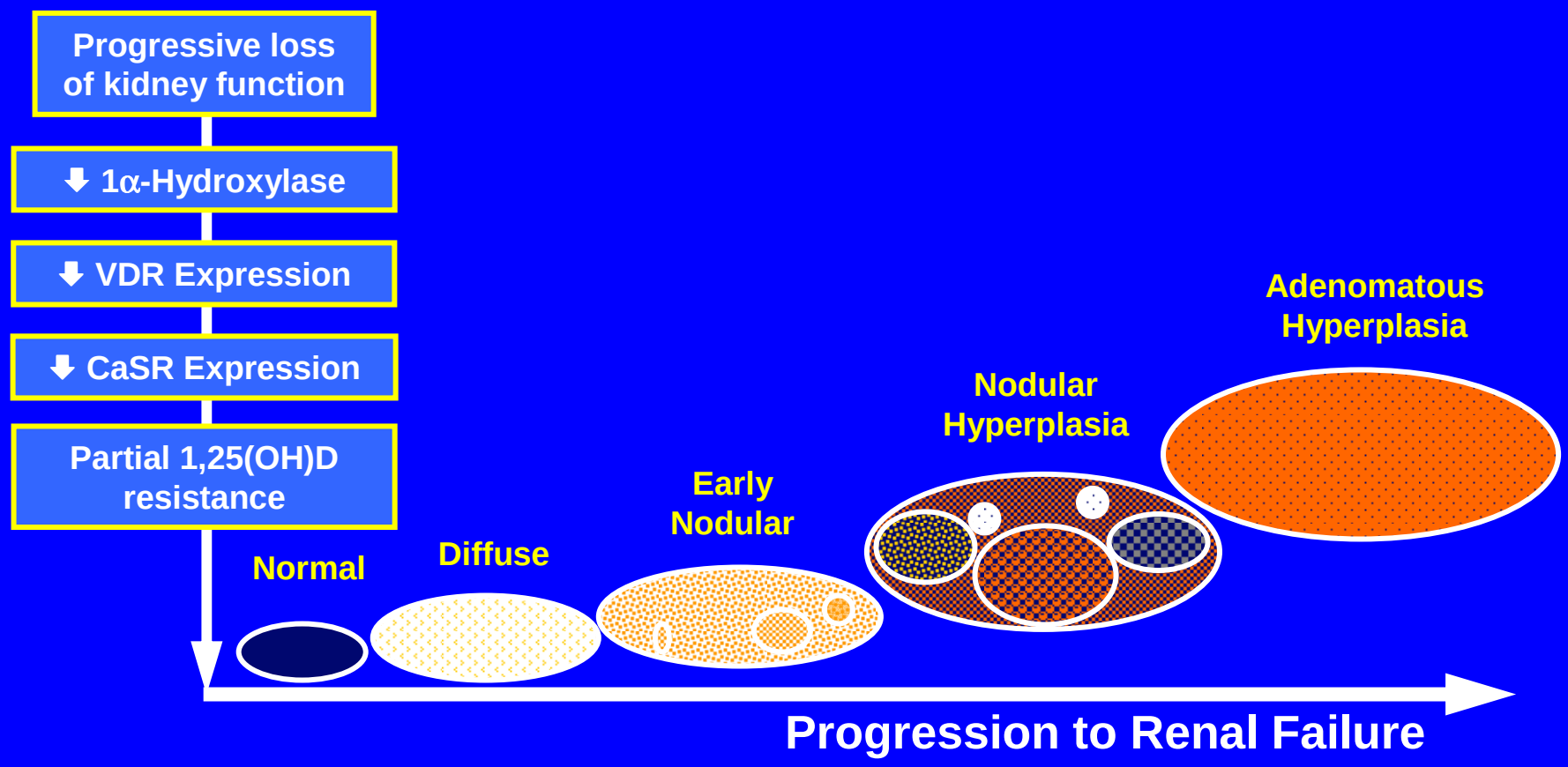
Fukagawa, Kidn.Intern.(2006) 70:S3

Relation between serum-phosphate and PTH – Spanish multicentre study



Cannata J, personal communication

Alteration of Parathyroid Gland Function



Fukagawa, J Nephrol (1996) 9:219

Guidance for Evaluating Elevated PTH Levels

- Is it due to excess PTH secretion ?
  - regulated by calcium via CaSR
  - hypocalcemia
- Is it due to excess PTH gene transcription ?
  - regulated by vitamin D
  - regulated by calcium
  - serum calcitriol (1,25$(OH)_2$D) levels
  - vitamin D nutrition (25(OH)D)
  - serum calcium concentration
- Is it due to parathyroid gland enlargement from tissue hyperplasia ?
  - regulated by calcium via CaSR
  - phosphorus via TGFα and p21

What triggers (secondary) hyperparathyroidsim

- hyperphosphatemia → low ionised Ca^{++}
- lack of $1,25(OH)_2D_3$
- lack of 25(OH)D →

  local production of $1,25(OH)_2D_3$
- ionised plasma Ca^{++}
- klotho

Plasma $1,25(OH)_2D_3$ – independent predictor of coronary calcium by EBCT

- 283 high risk subjects
- $1,25(OH)_2D_3$ by radioimmunoassay, coronary Ca by EBCT
- $1,25(OH)_2D_3$ inversely correlated to calcium mass ($r=-0.19$; $p<0.001$)

Doherty, Circulation (1997) 96:1477

Calcium sensing receptor is regulated by vitamin D, but not by calcium

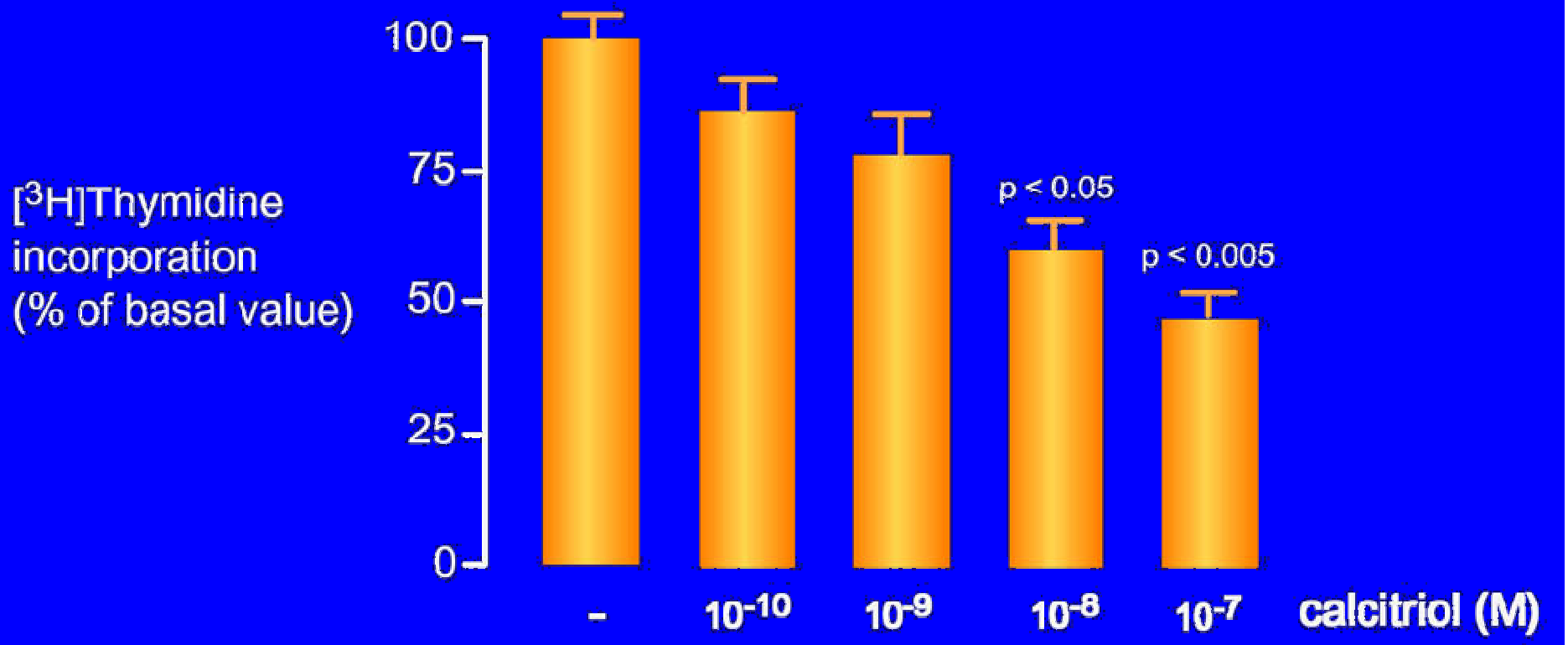
Brown, Amer.J.Physiol.(1996) 270:F454

$1,25(OH)_2D_3$ increases Ca^{++} sensitivity of PTH secretion in HD patients

Delmez, J.Clin.Invest.(1989) 83:1349

⇨ **- increased Ca^{++} sensitivity of parathyroid**
- reduced active intestinal Ca transport
argument for calcimimetic plus active vitamin D ?

Effect of calcitriol on parathyroid cell proliferation index in vitro

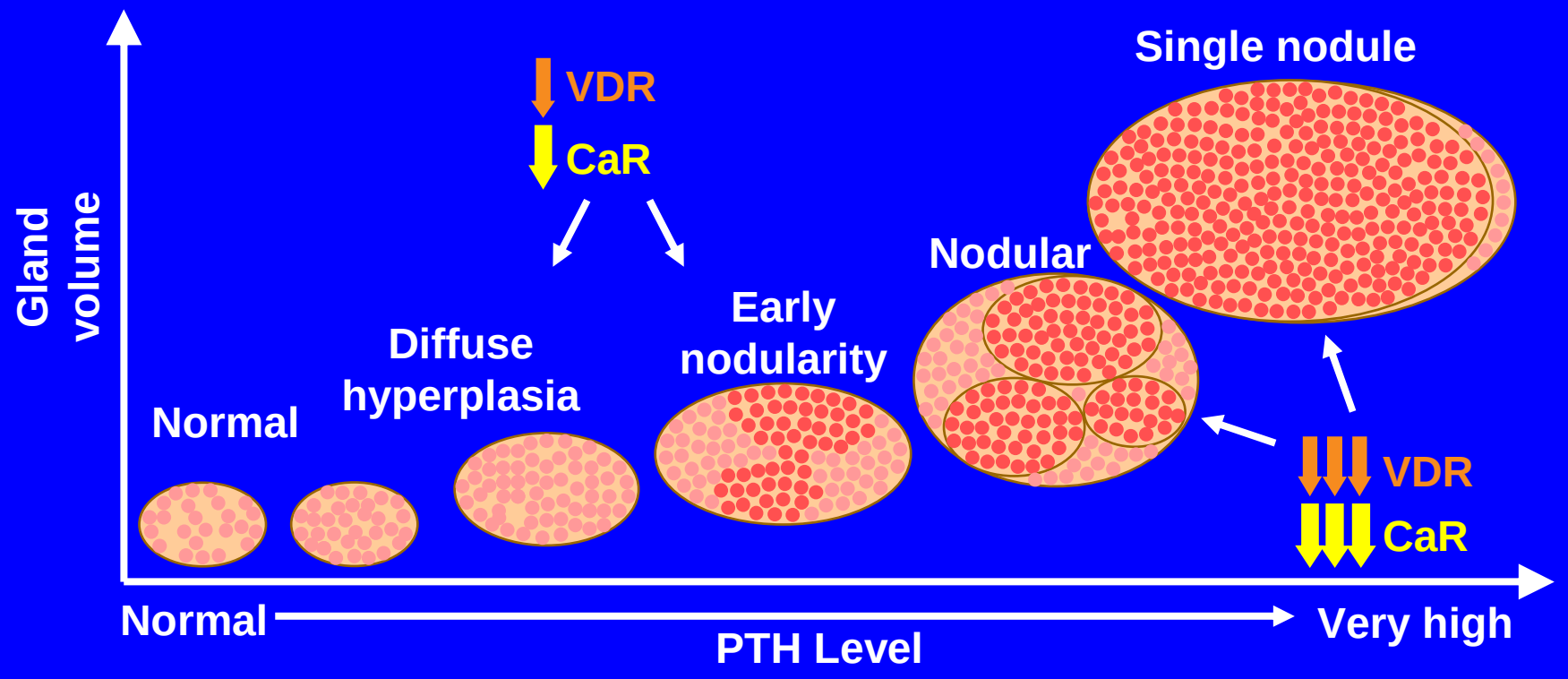


Naveh-Many, JCI (1995) 96: 1786

Progression of secondary HPT -

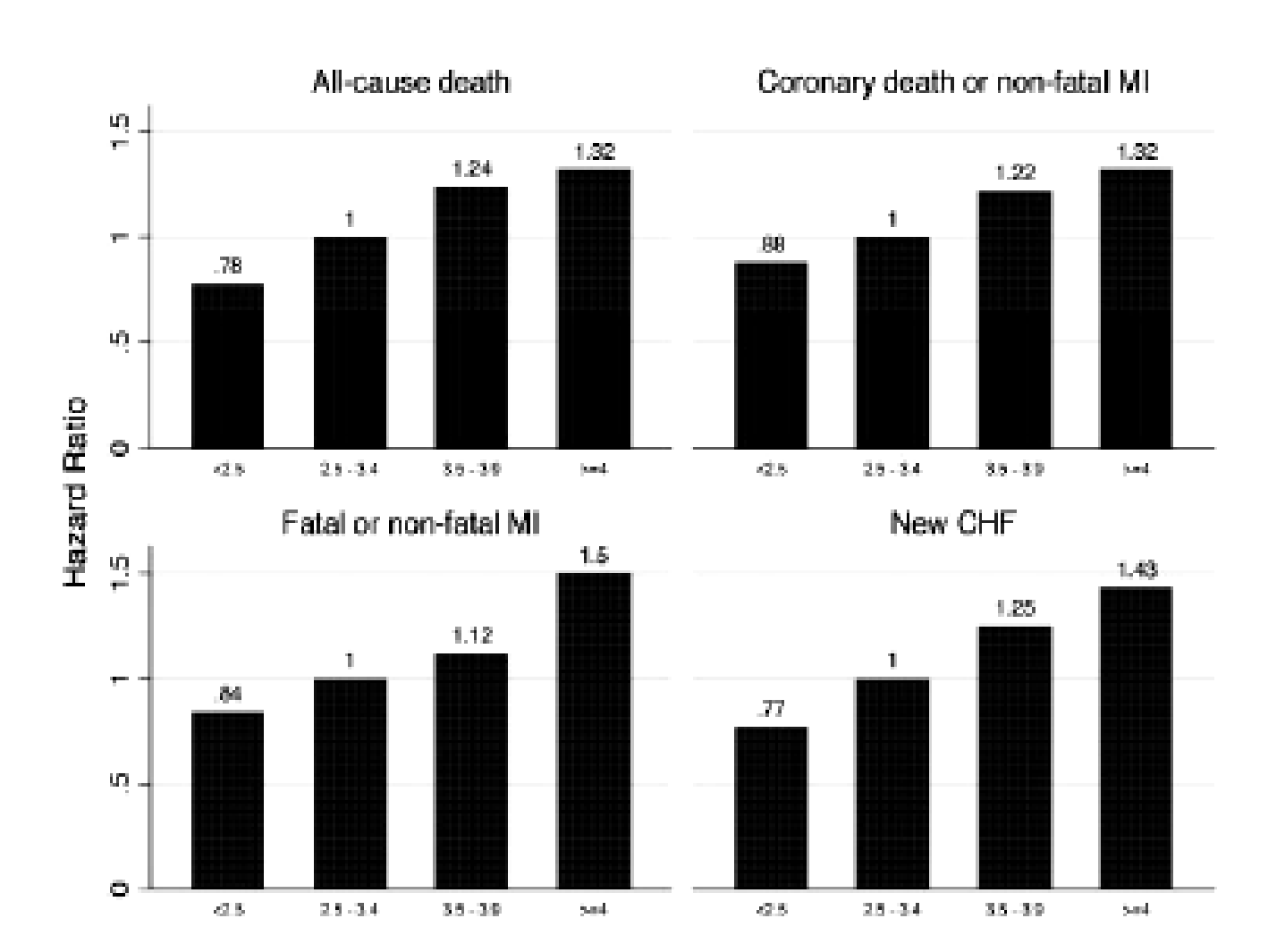
⇨ progressively higher doses of vitamin D required

(decrease of vitamin D receptors)



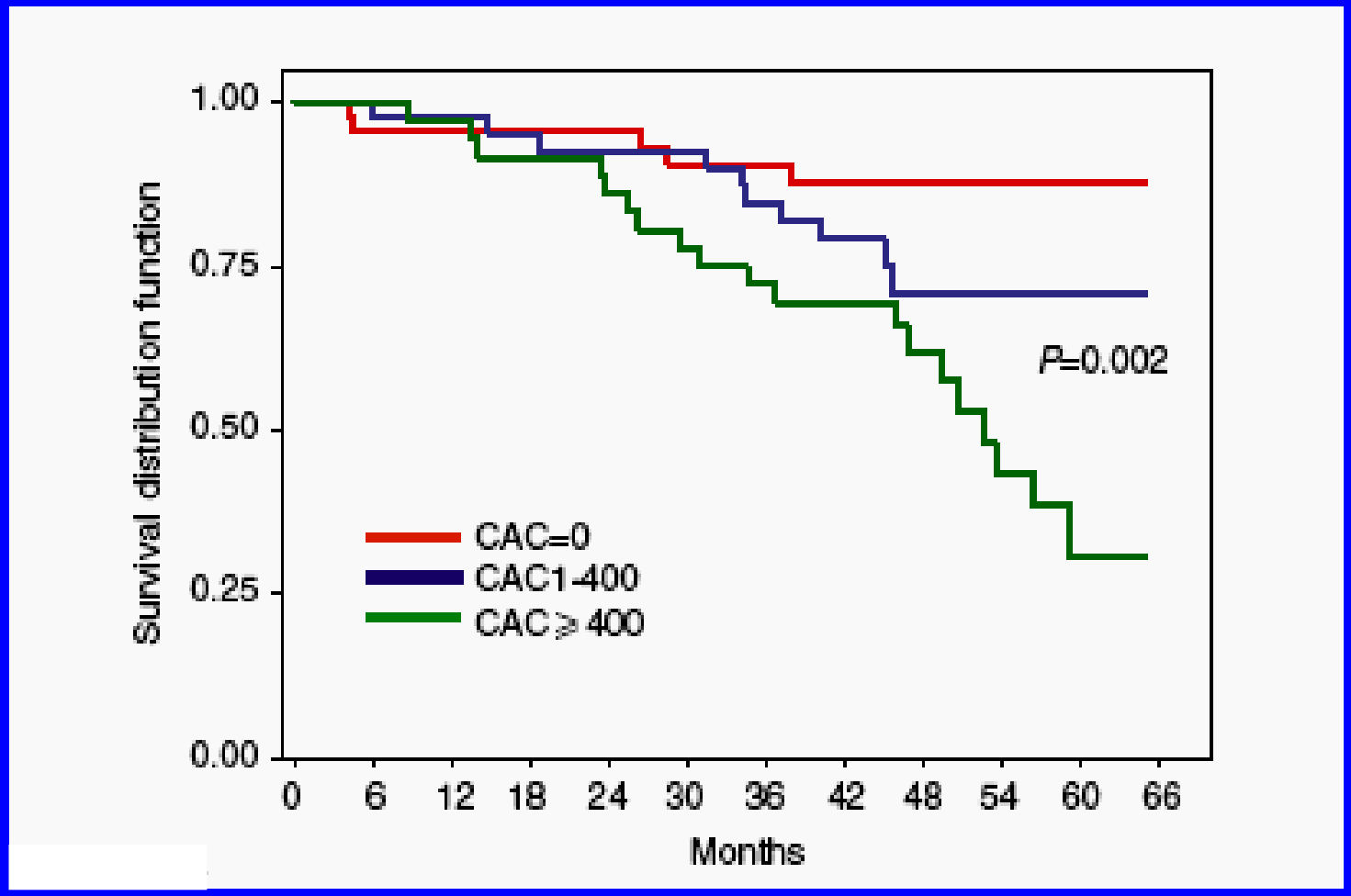
Tominaga, Curr Opin Nephrol Hypertens (1996)5:336

Correlation: serum phosphate and cardiovascular disease – patients without chronic kidney disease



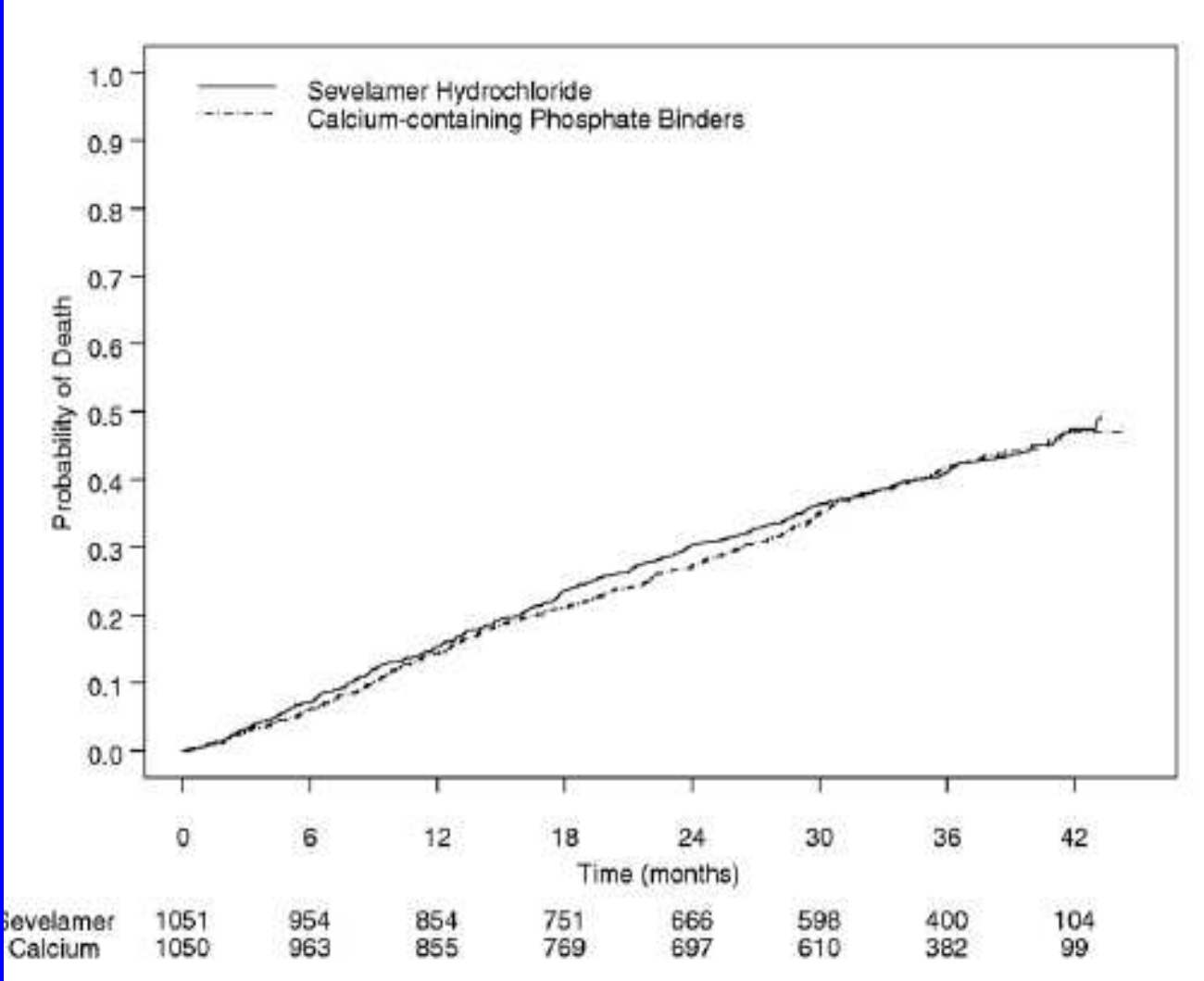
Tonelli, Circulation (2005) 112: 2627

Baseline coronary calcification score predicts survival in incident dialysis patients



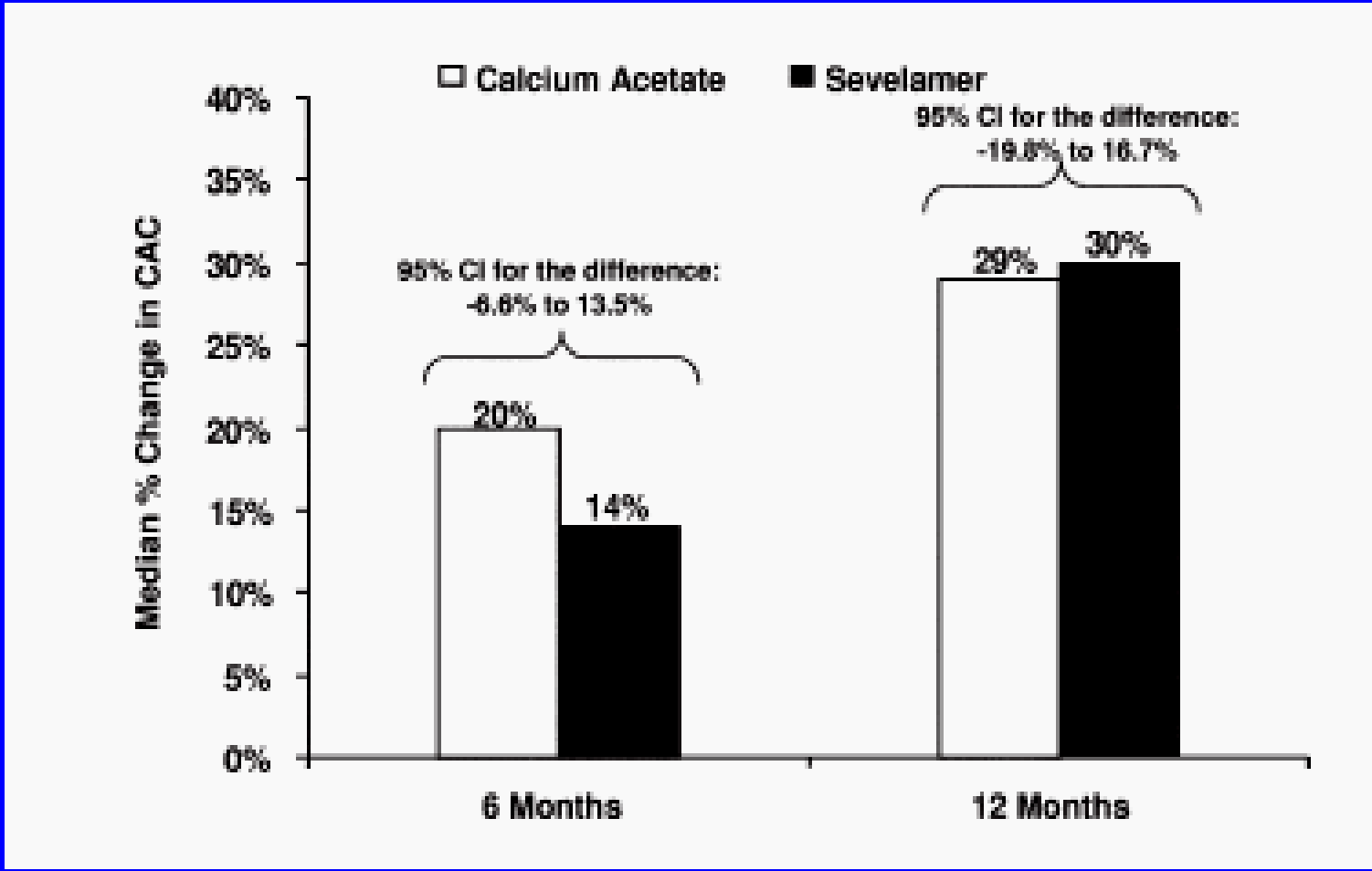
Block, Kidn.Internat.(2007) 71: 438

Sevelamer vs calcium carbonate – similar outcomes



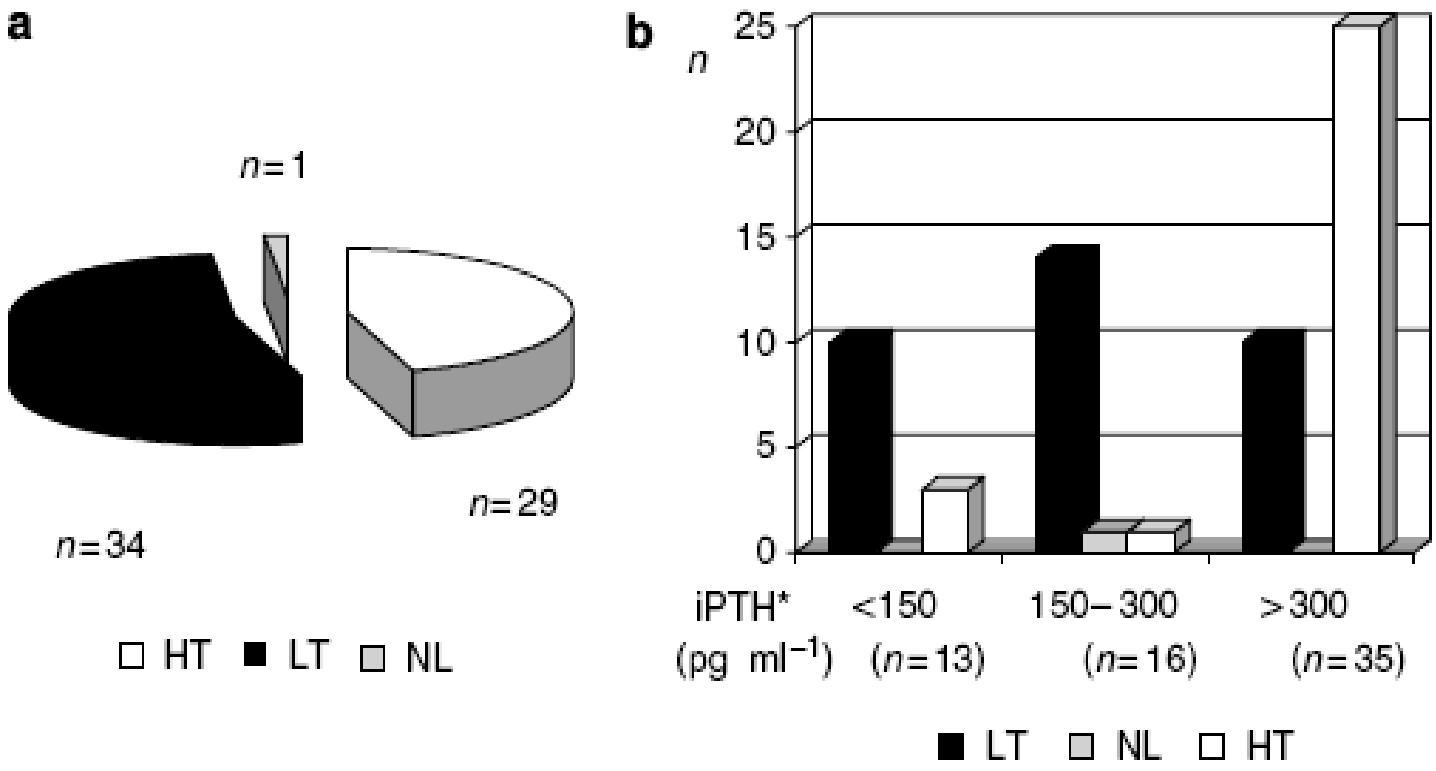
St.Peter, Am.J.Kidn.Dis.(2008) 51:445

Change of coronary calcium in dialysis patients – similar with statin and sevelamer : is it cholesterol or phosphate ?



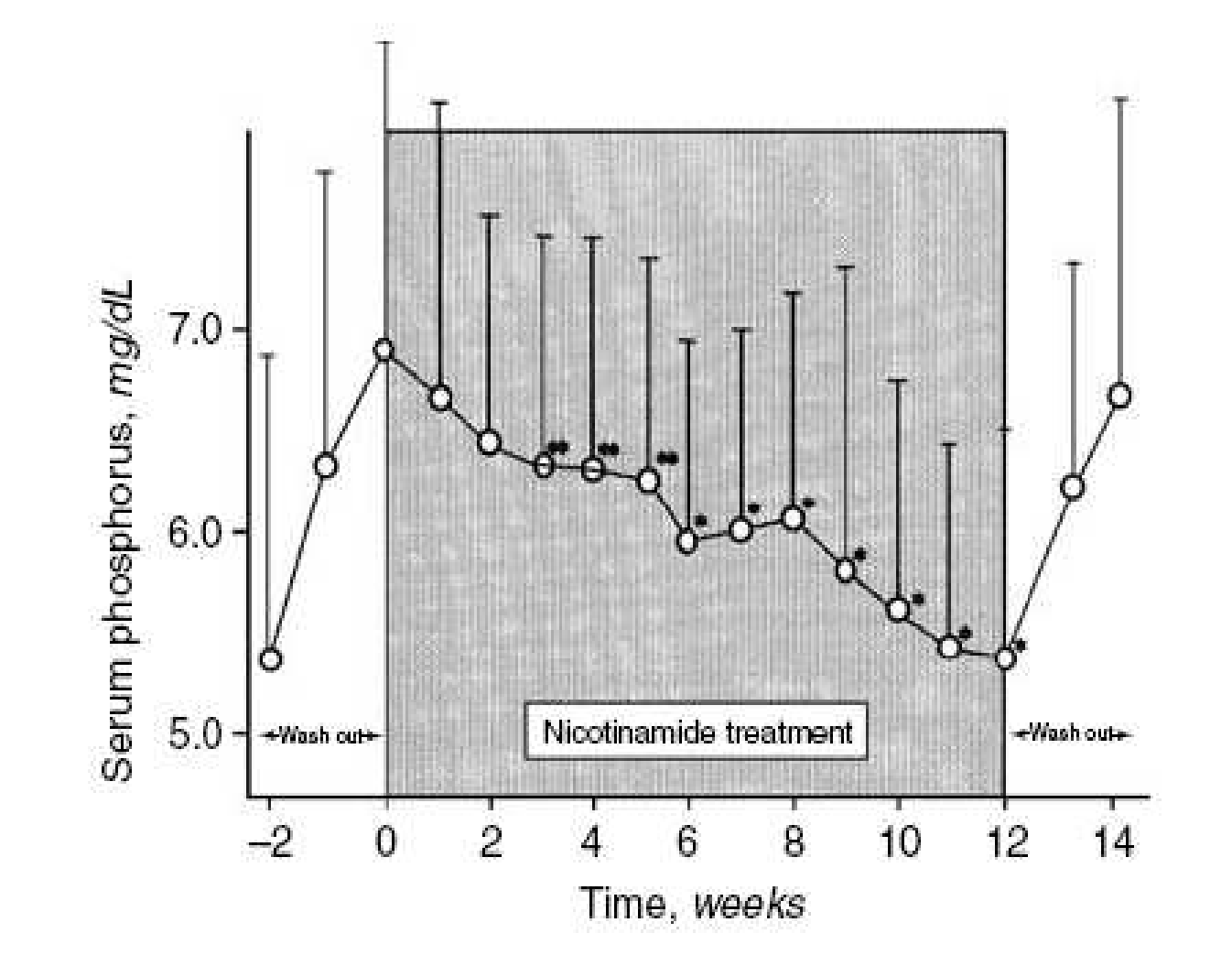
Qunibi, Am.J.Kidn.Dis.(2008) 51:952

DOQI guidelines (iPTH 150-300 pg/ml) do not gurantee normal bone turnover

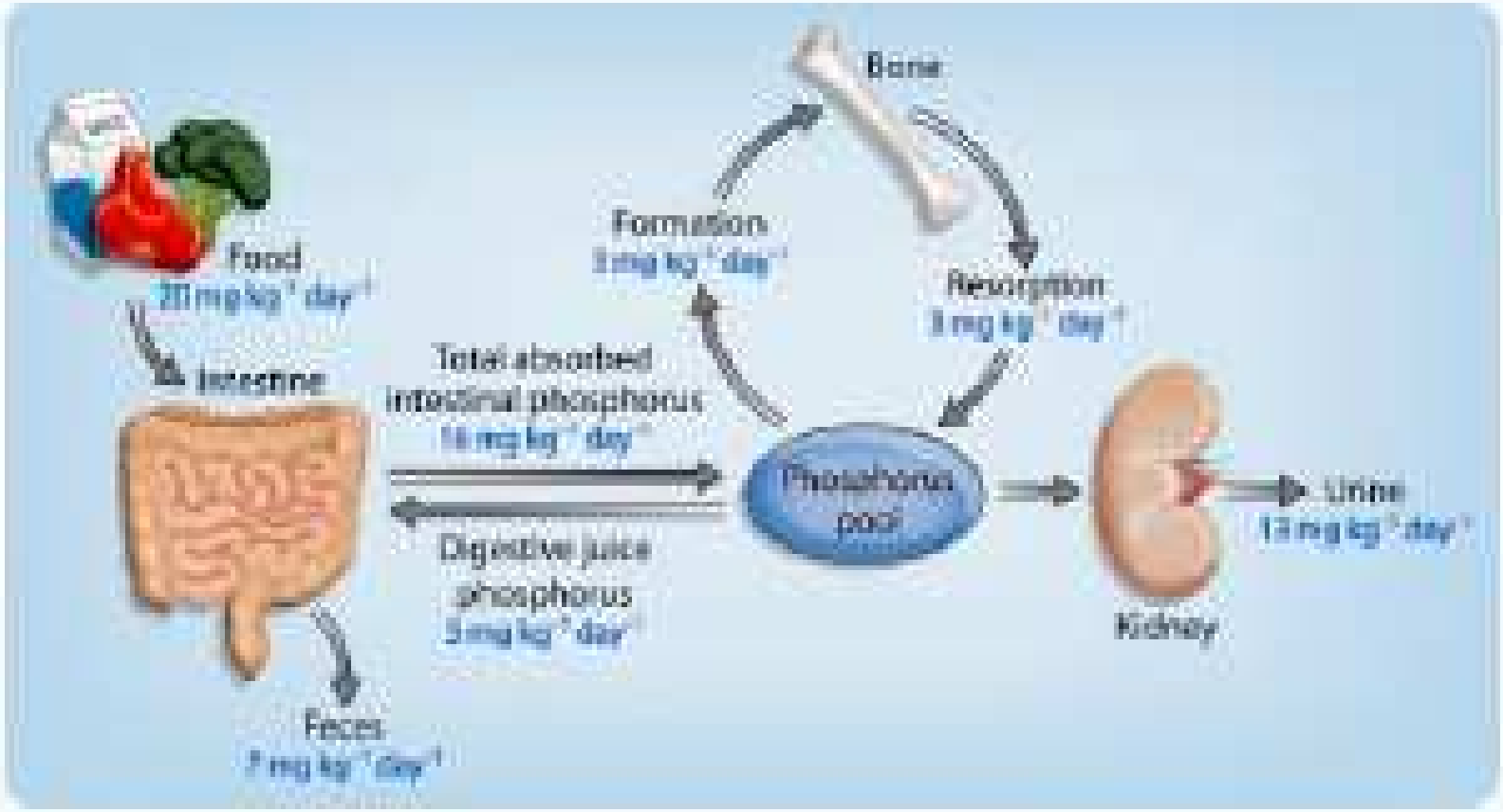


Barreto, Kidn.Internat.(2008) 73:771

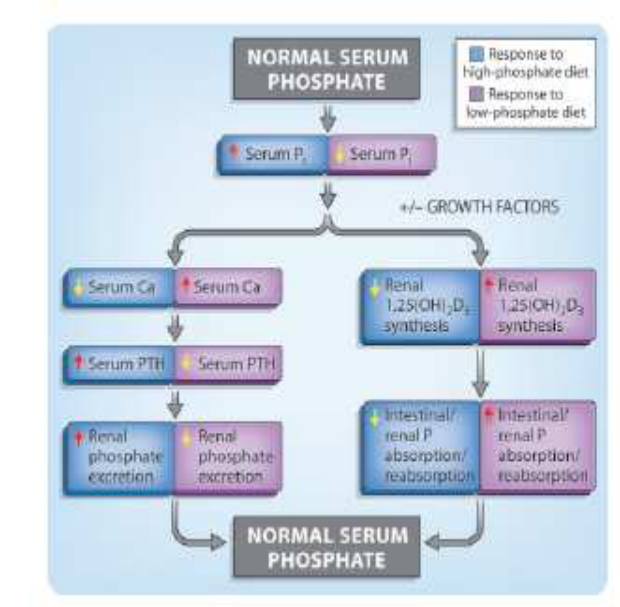
Treatment with nicotinamide lowers S-phosphate in hemodialysis patients



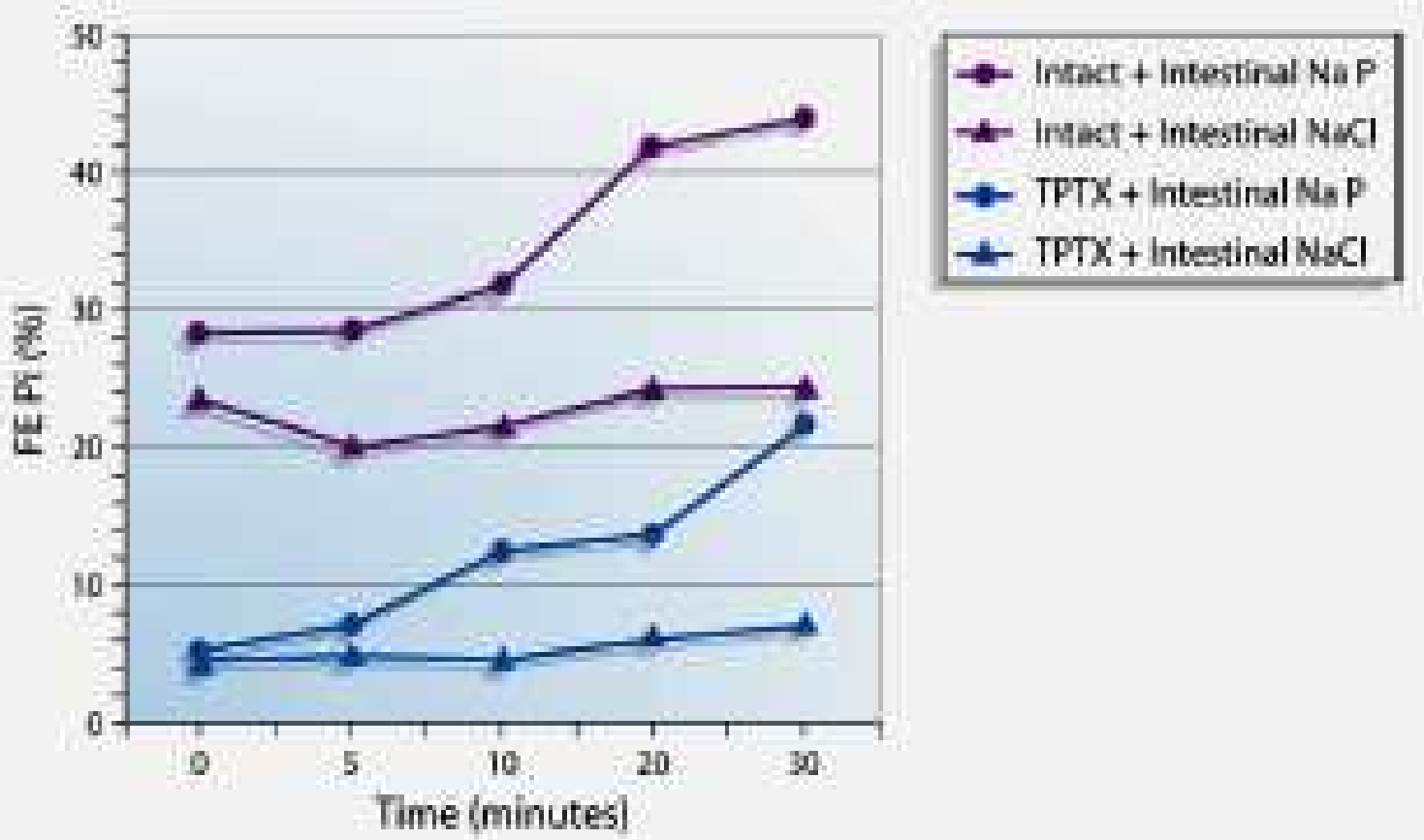
Takahashi, Kidn.Internat.(2004) 65:1099



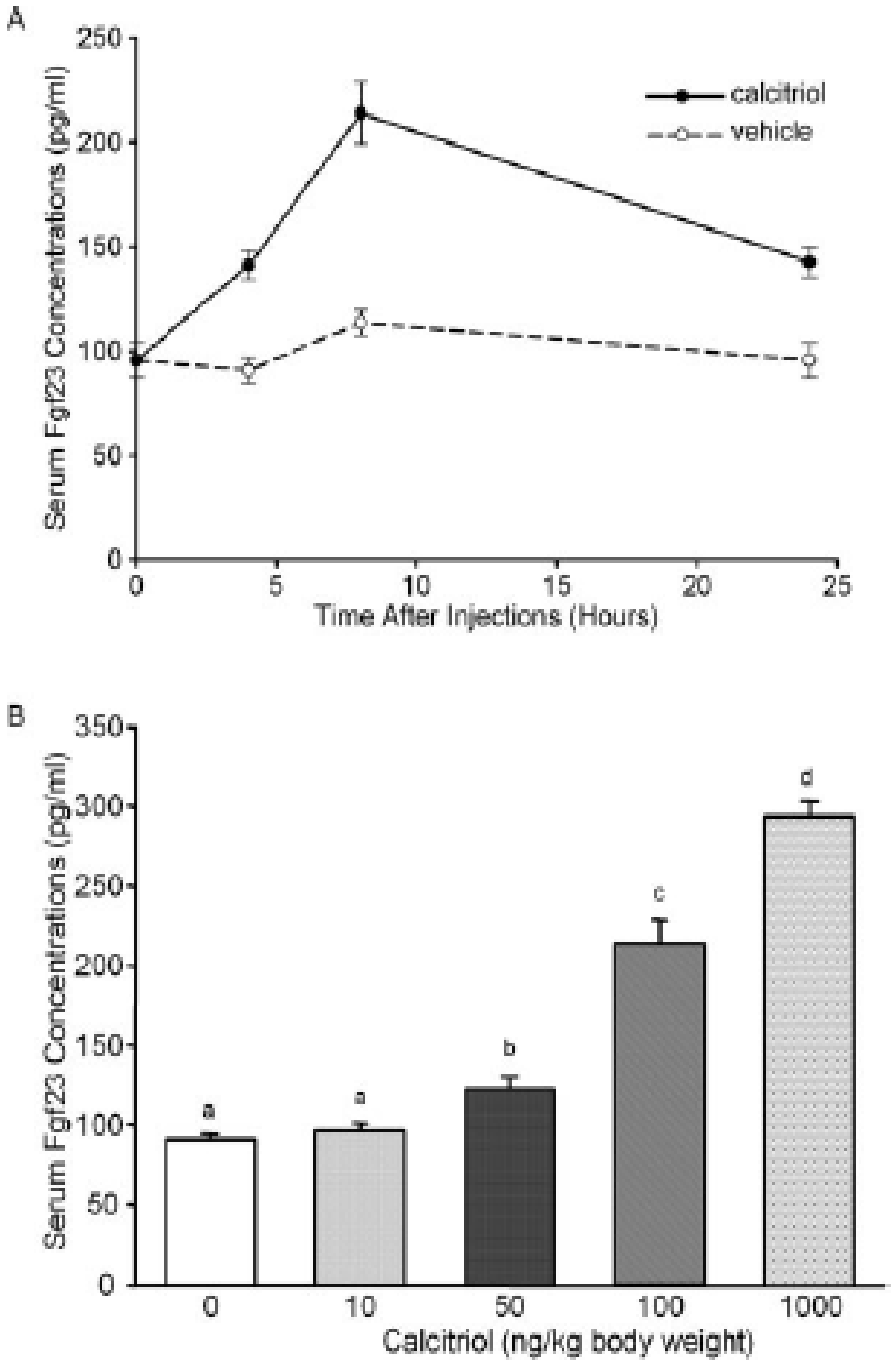
Thomas, J.Am.Soc.Nephrol.(2008) 19:207



Thomas, J.Am.Soc.Nephrol.(2008) 19:207



Thomas, J.Am.Soc.Nephrol.(2008) 19:207

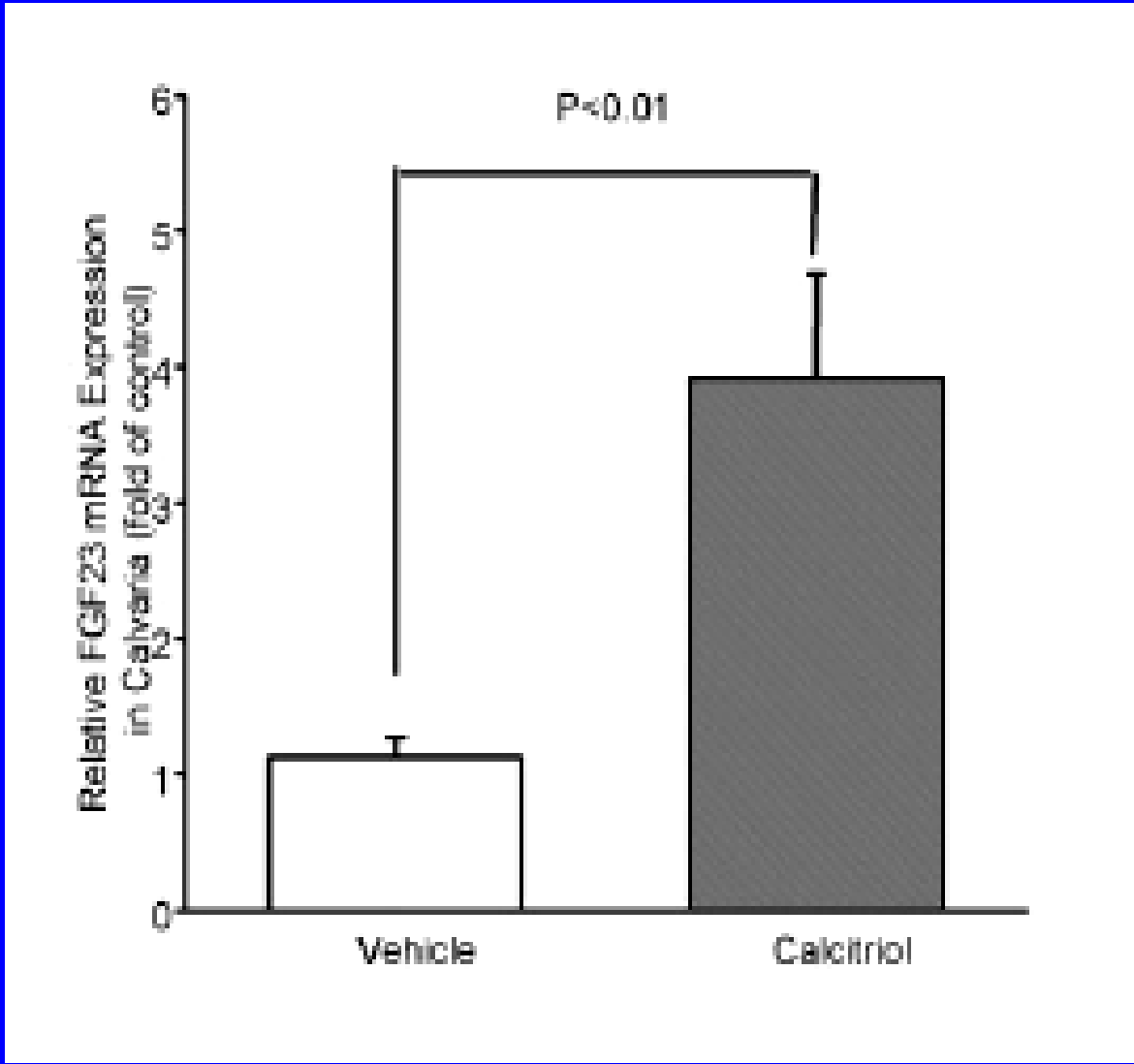


$1,25(OH)_2D_3$ is an important regulator of serum FGF_{23}

Liu,

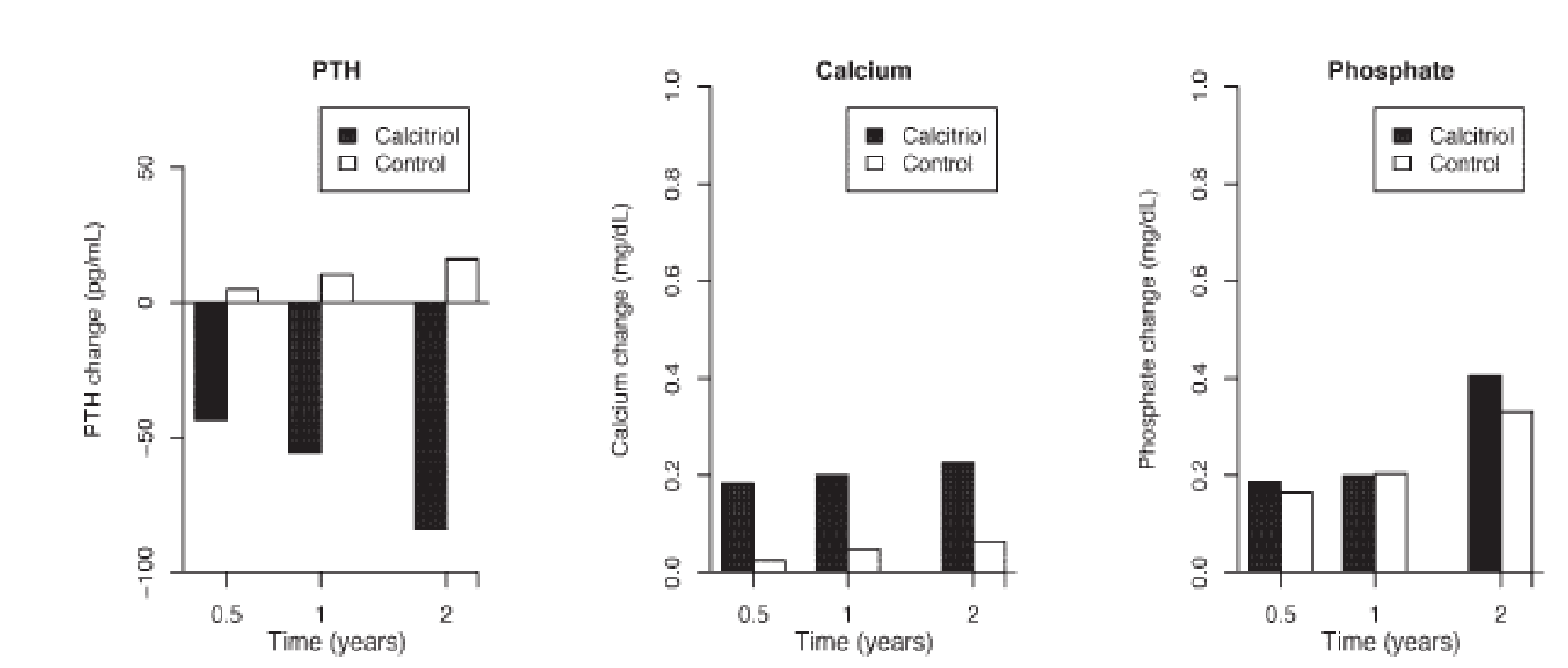
J.Am.Soc.Nephrol. (2006) 17:1305

1,25(OH)2D3 is an important regulator of FGF23 synthesis by osteblasts



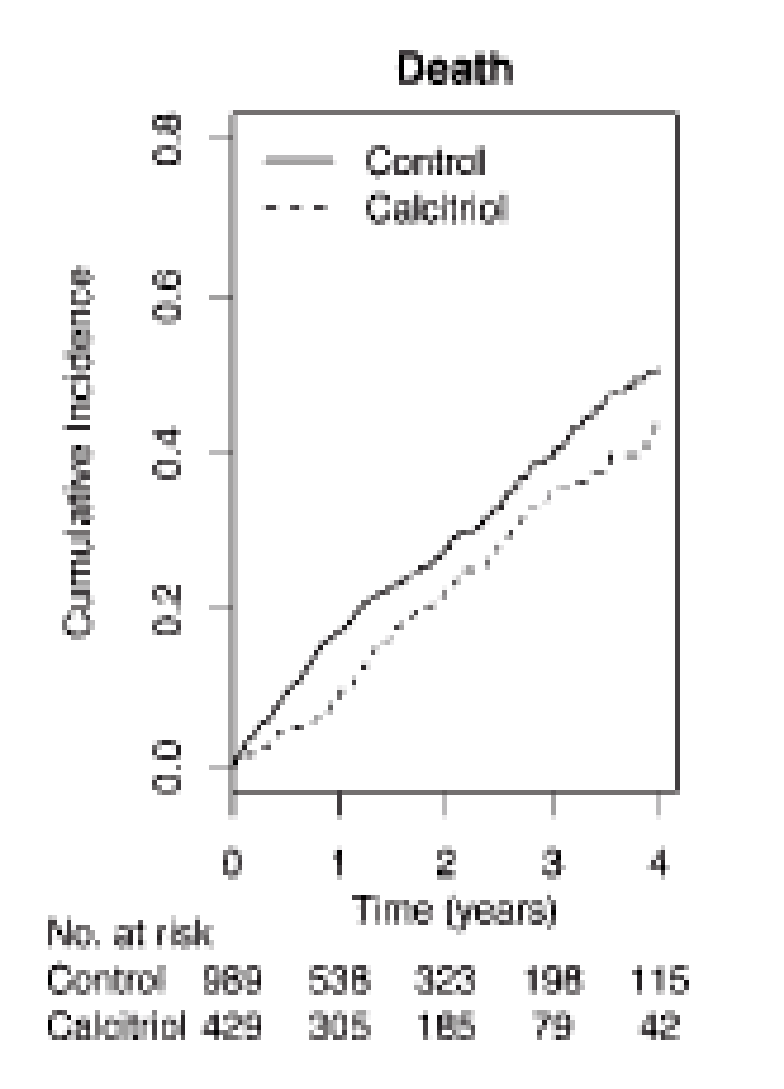
Liu, J.Am.Soc.Nephrol. (2006) 17:1305

Calcitriol in patients not yet on hemodialysis – change of parameters of Ca,P metabolism



Shoben, J.Am.Soc.Nephrol.(2008) 16: 1613

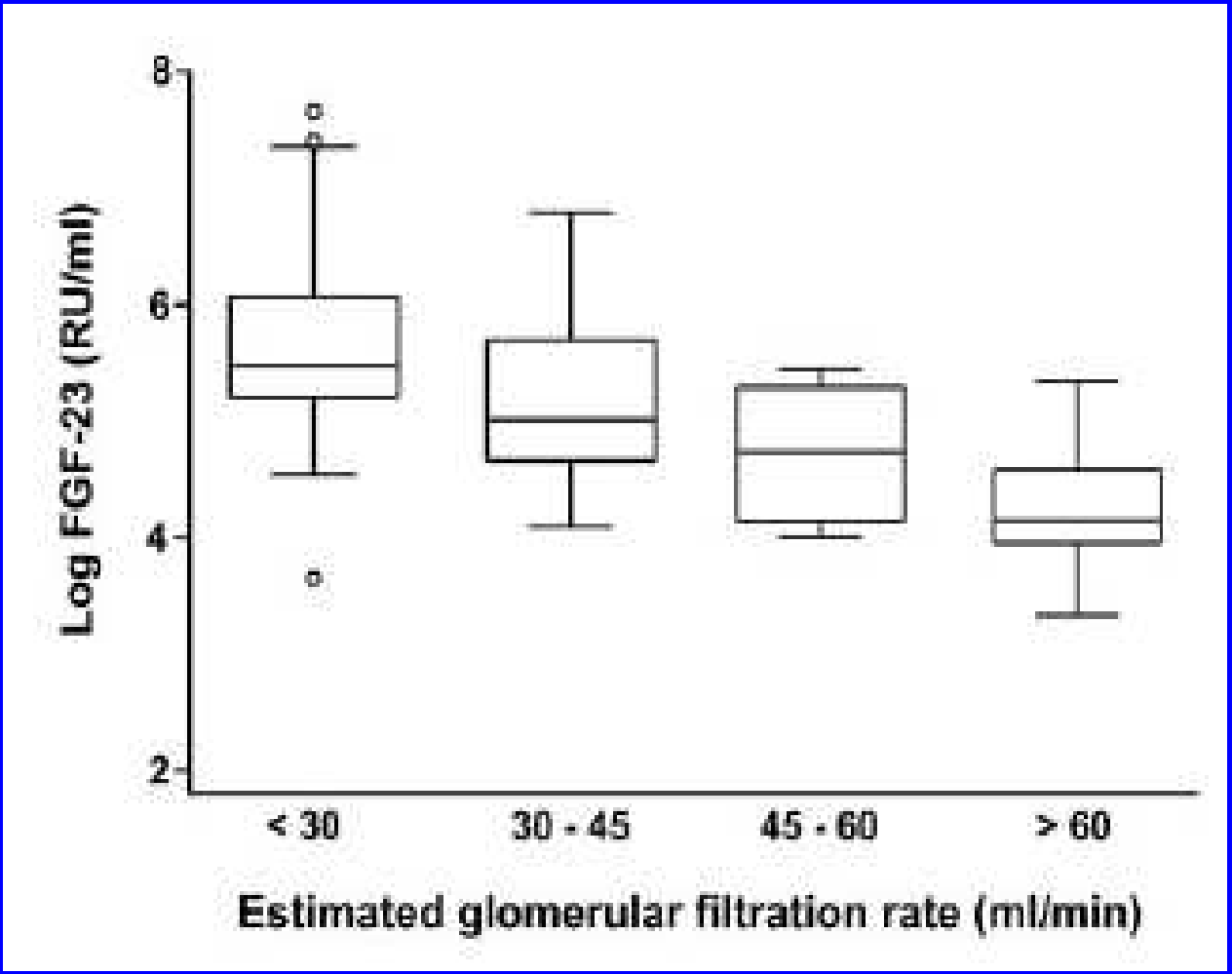
Calcitriol reduces mortality in patients not yet on hemodialysis



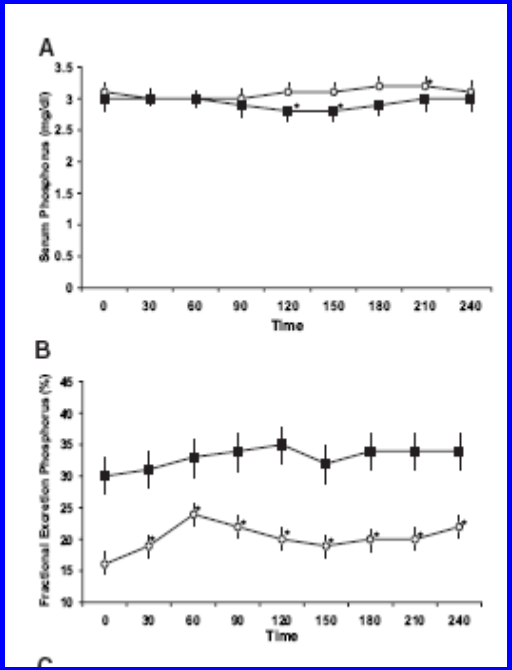
1418 VA patients with CKD3 or 4 and hyperparathyroidism
1.9 year follow-up
26% lower risk of death
(95%CI 5-42; p=0.016)

Shoben, J.Am.Soc.Nephrol.(2008) 16: 1613

FGF23 concentrations increase as GFR values decrease



Gutierrez, J.Am.Soc.Nephrol.(2005) 16:2205


A
Serum Phosphorus (mg/dl)
3.5
3
2.5
2
1.5
1
0.5
0
0
30
60
90
120
150
180
210
240
Time
B
Fractional Excretion Phosphorus (%)
45
40
35
30
25
20
15
10
0
30
60
90
120
150
180
210
240
Time