Endocrine Physiology of Bone and Calcium Disorders

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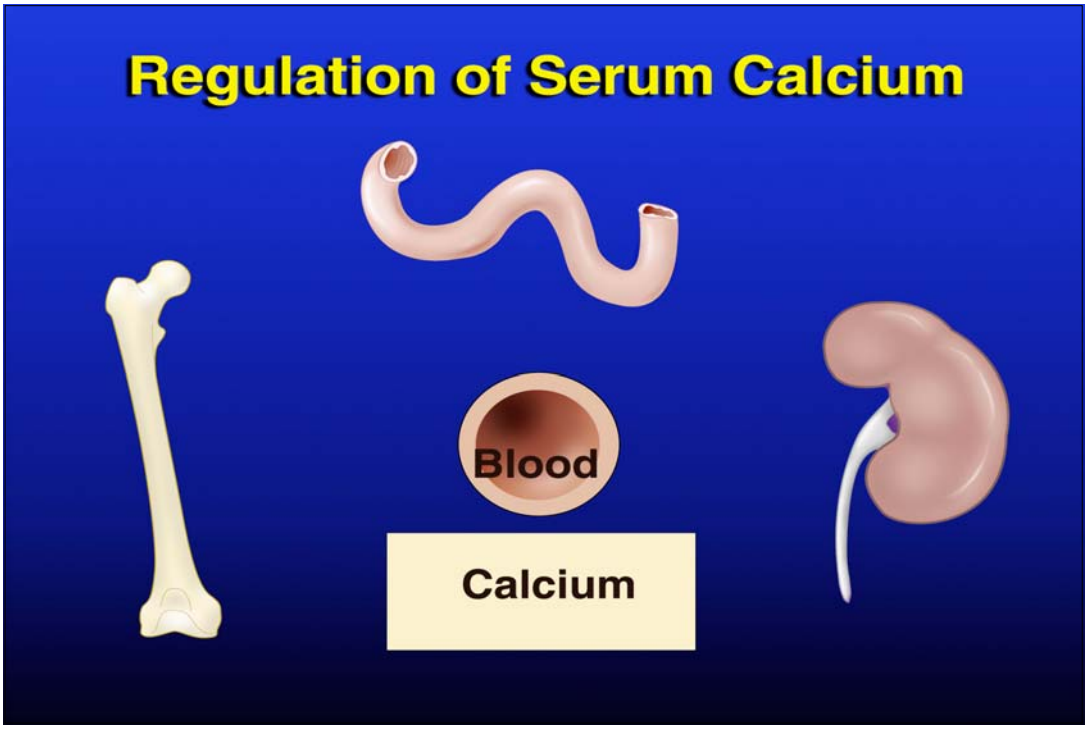
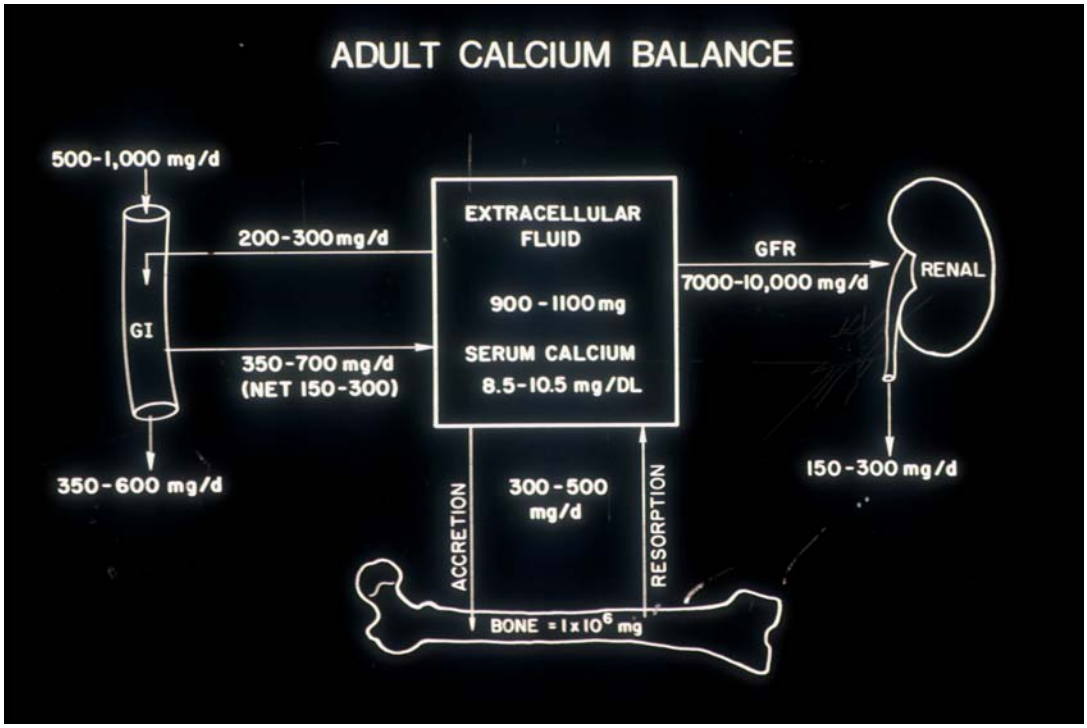
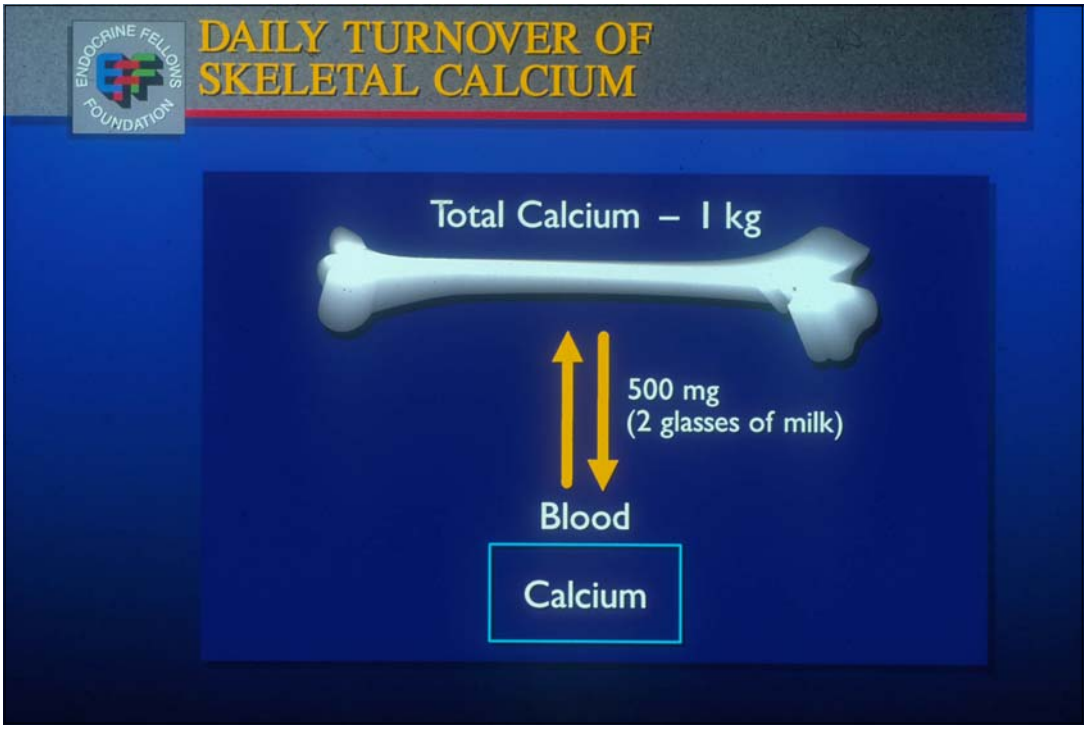
Wednesday, February 21, 2007

Outline of Lecture

- Normal calcium homeostasis
- Useful indices of calcium metabolism
- Hypercalcemia
- Hypocalcemia
- Osteoporosis


Regulation of Serum Calcium
Blood
Calcium


ADULT CALCIUM BALANCE
500-1,000 mg/d
200-300 mg/d
GI
350-700 mg/d
(NET 150-300)
350-600 mg/d
EXTRACELLULAR
FLUID
900 - 1100 mg
SERUM CALCIUM
8.5-10.5 mg/DL
GFR
7000-10,000 mg/d
RENAL
150-300 mg/d
ACCRETION
300-500
mg/d
RESORPTION
BONE = 1 x 10^6 mg



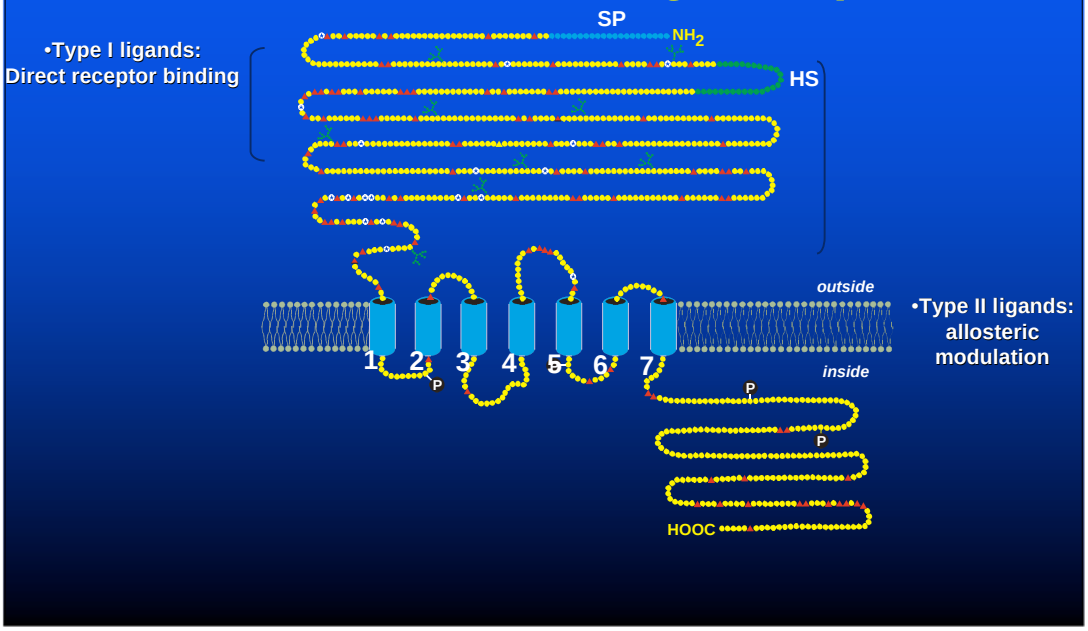
Two Major Calcium-Regulating Hormones

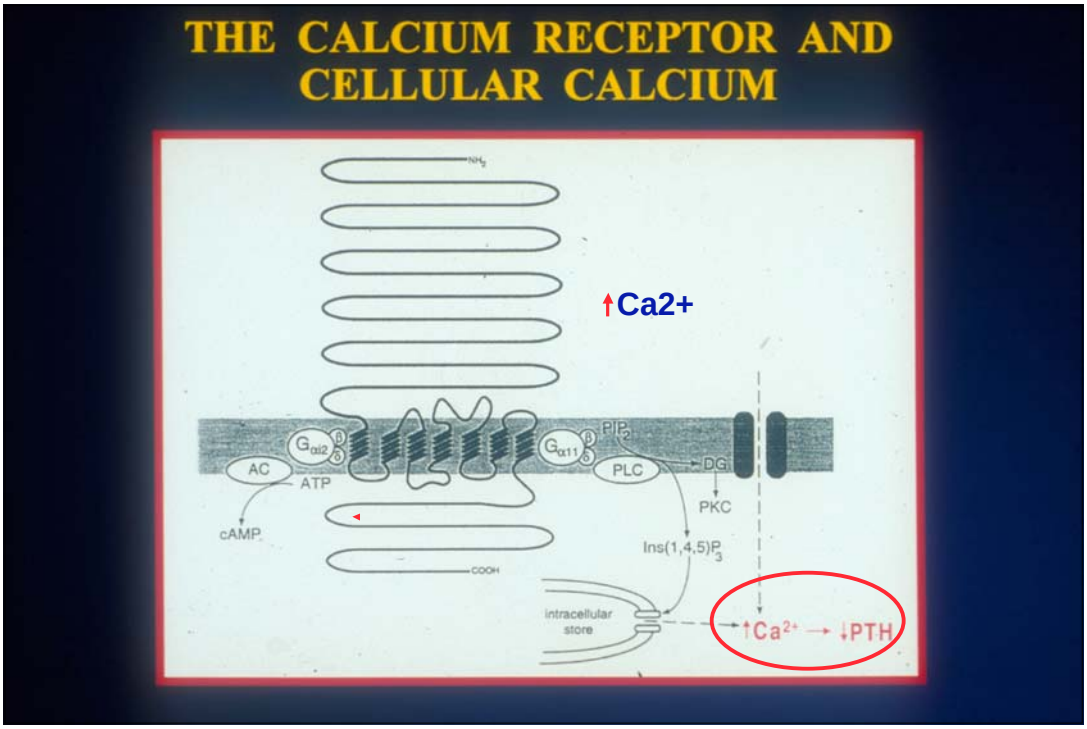
- **Parathyroid hormone**
- 1,25-dihydroxyvitamin D

Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D

The Calcium-Sensing Receptor



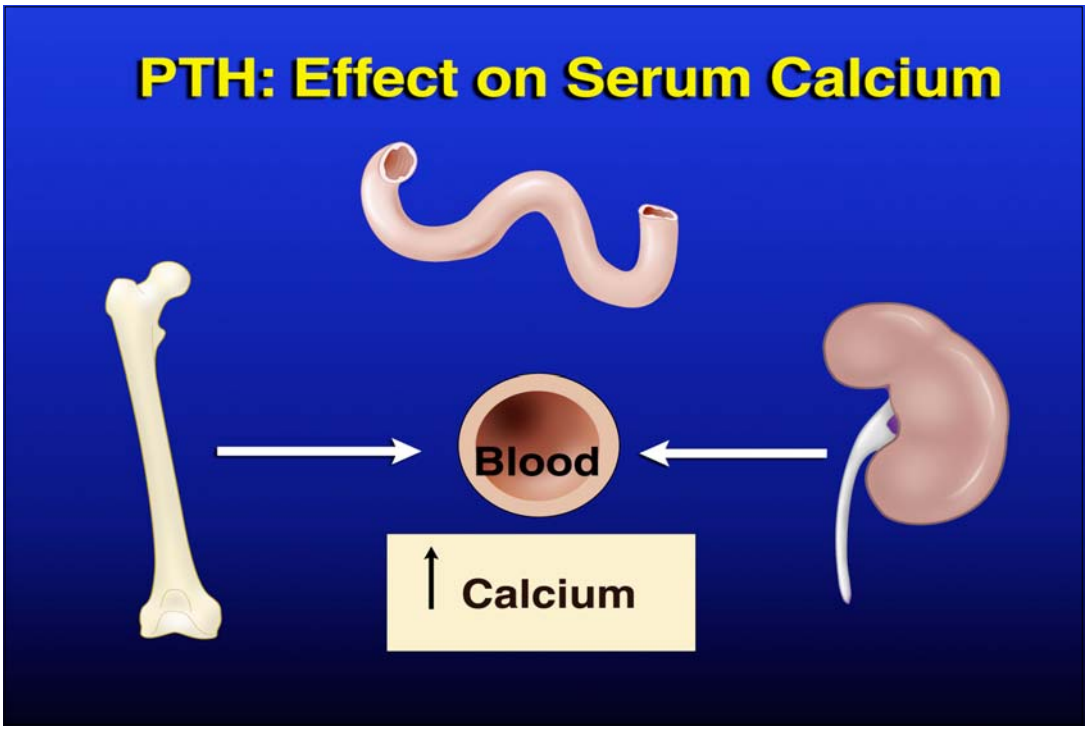


Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D

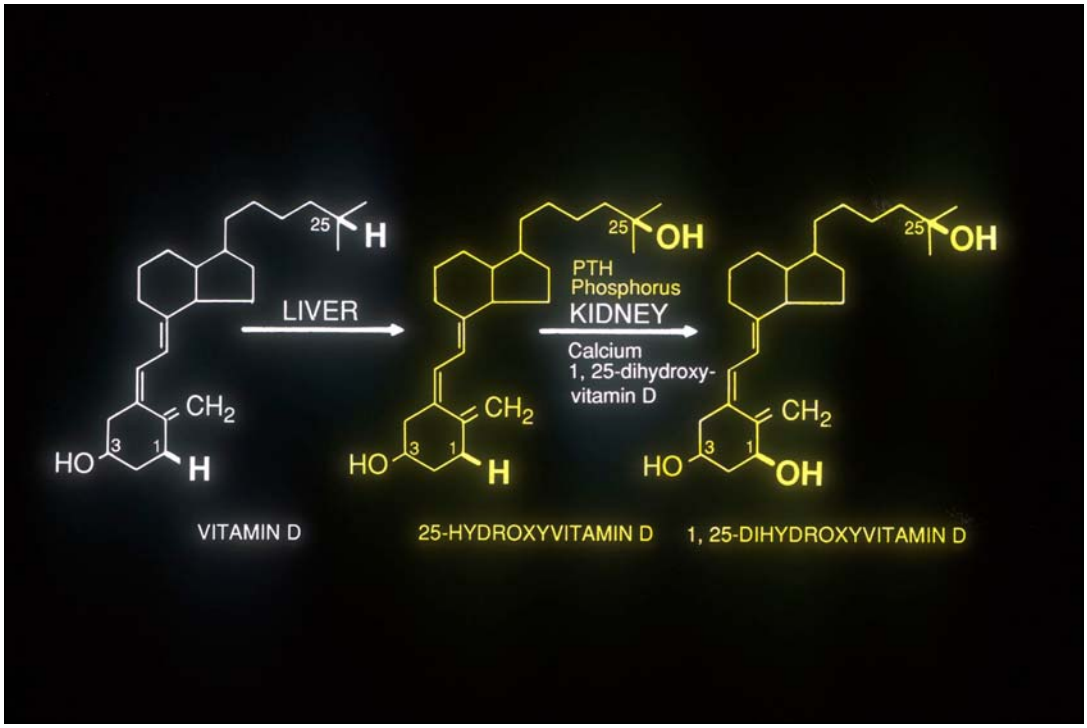
Major Functions of Parathyroid Hormone

- Regulation of serum calcium and phosphate
- Bone remodelling
- Regulation of 1,25-dihydroxyvitamin D levels



Two Major Calcium-Regulating Hormones

- Parathyroid hormone
- 1,25-dihydroxyvitamin D



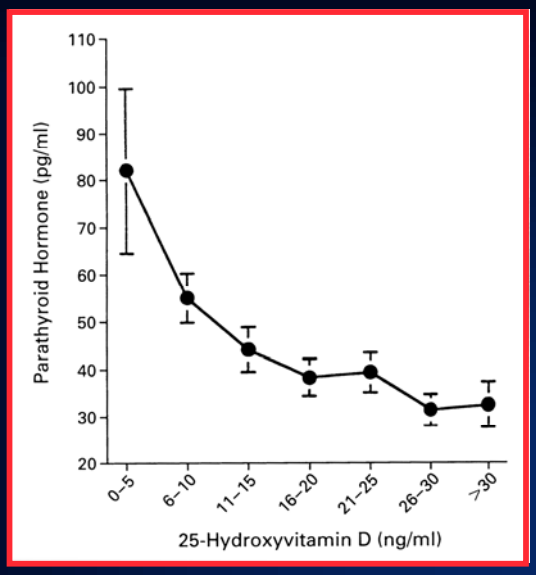
Major Functions of 1,25-dihydroxyvitamin D

- GI absorption of calcium and phosphate
- Bone remodelling
- Regulation of parathyroid hormone

Major Functions of 1,25-dihydroxyvitamin D

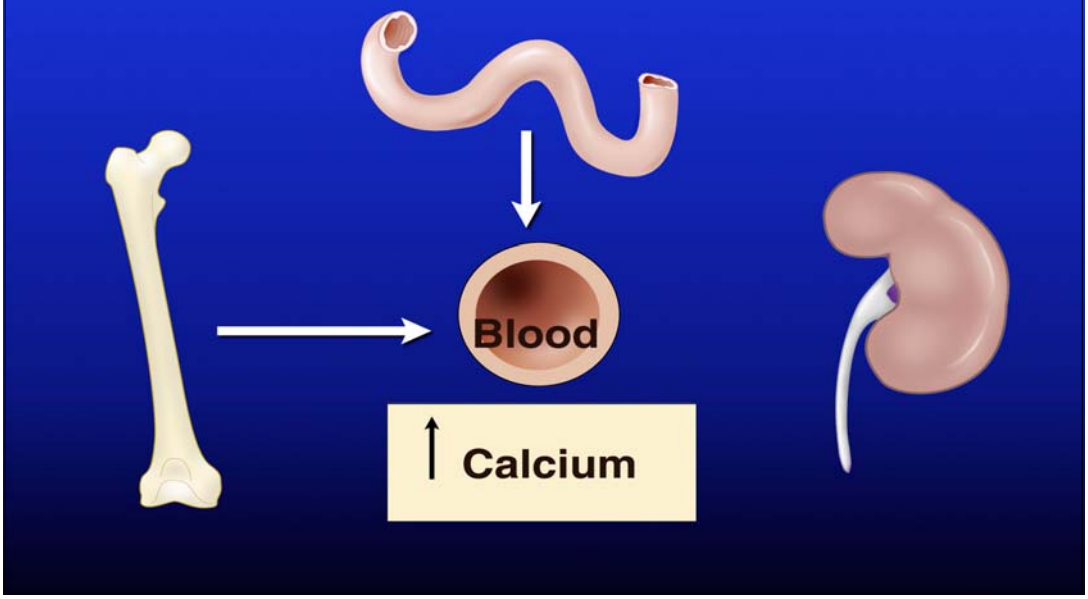
- GI absorption of calcium and phosphate
- Bone remodelling
- Regulation of parathyroid hormone

Relationship between 25-hydroxyvitamin D and PTH

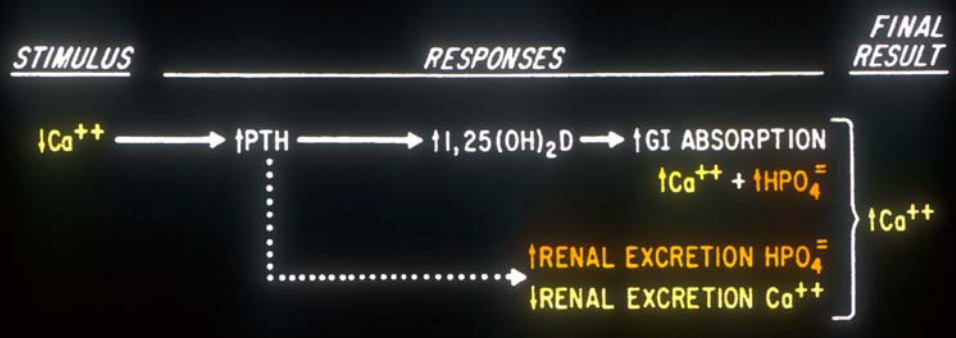


Thomas MK et al. N Eng J Med 1998;338:778-783

1,25(OH)$_2$D: Effect on Serum Calcium



HOW PTH AND 1,25(OH)$_2$D WORK TOGETHER TO CONTROL THE SERUM CALCIUM CONCENTRATION



Other Circulating Hormones that Influence Bone Metabolism

- Parathyroid hormone
- 1,25 $(OH)_2$ vitamin D
- Gonadal steroids
- Corticosteroids
- Thyroid hormone
- Growth hormone

Local Regulators of Bone Metabolism

- IGFs and IGF binding proteins
- TGF-β
- Bone morphogenic protein
- Platelet-derived growth factor, fibroblast growth factor
- Prostaglandins
- Interleukins (IL-1, IL-6)
- RANKL/osteoprotegerin

Raisz LG. *Clin Chem* 1999;45:1353-8.

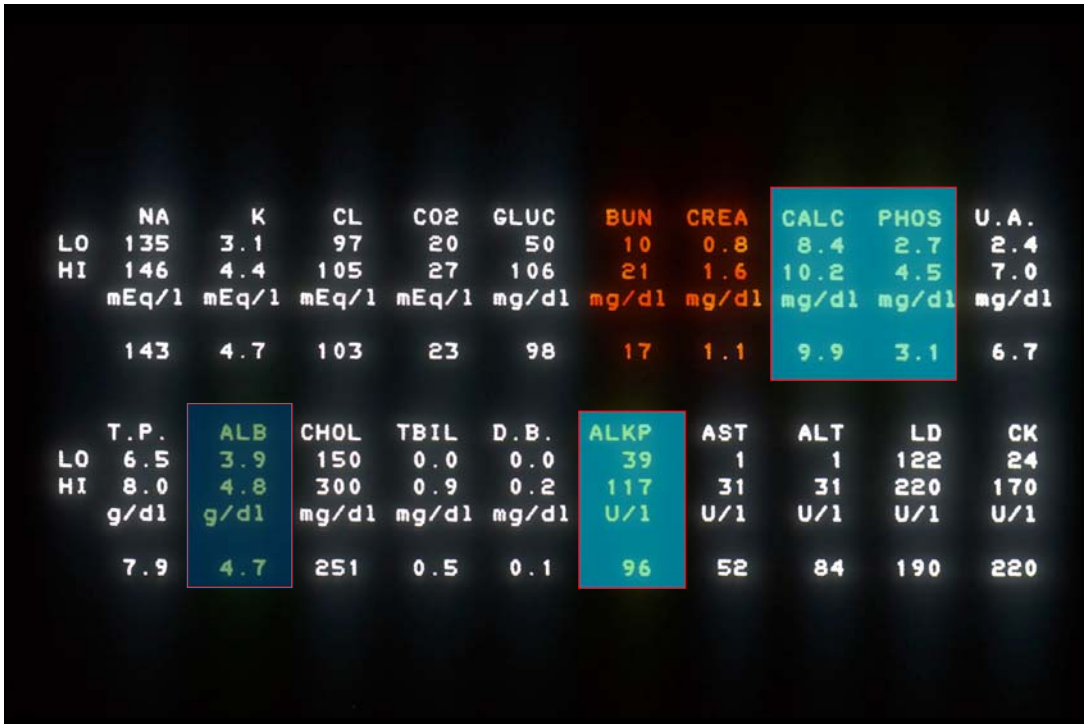
Outline of Lecture

- **Normal calcium homeostasis**
- **Useful indices of calcium metabolism**
- **Hypercalcemia**
- **Hypocalcemia**
- **Osteoporosis**

Useful indices of calcium metabolism as gleaned from the multichannel autoanalyzer

"THE HOLY TRINITY"

- **Calcium**
- **Phosphorous**
- **Alkaline phosphatase**

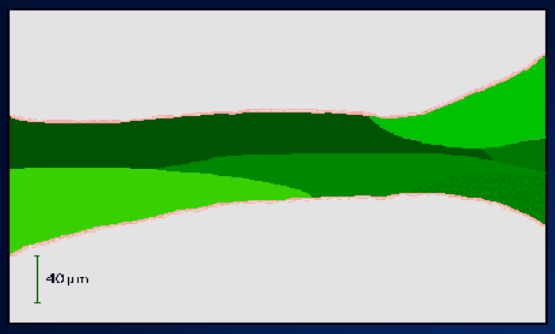


	NA	K	CL	CO2	GLUC	BUN	CREA	CALC	PHOS	U.A.
LO	135	3.1	97	20	50	10	0.8	8.4	2.7	2.4
HI	146	4.4	105	27	106	21	1.6	10.2	4.5	7.0
	mEq/l	mEq/l	mEq/l	mEq/l	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl
	143	4.7	103	23	98	17	1.1	9.9	3.1	6.7

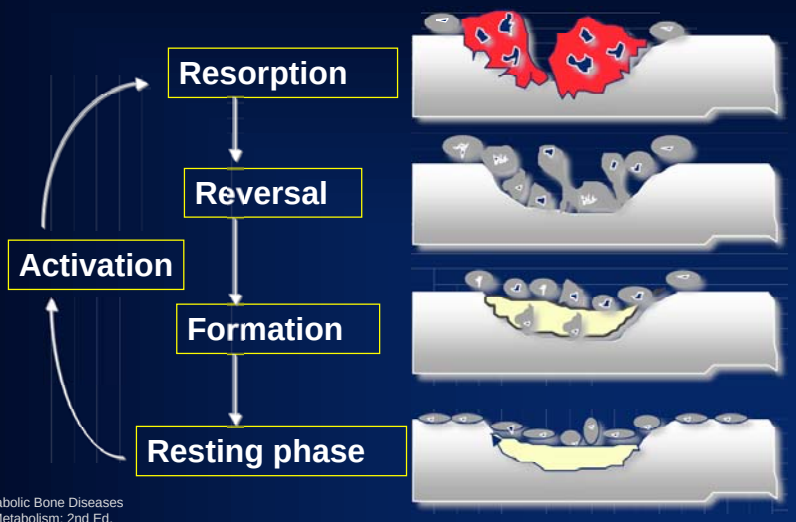
	T.P.	ALB	CHOL	TBIL	D.B.	ALKP	AST	ALT	LD	CK
LO	6.5	3.9	150	0.0	0.0	39	1	1	122	24
HI	8.0	4.8	300	0.9	0.2	117	31	31	220	170
	g/dl	g/dl	mg/dl	mg/dl	mg/dl	U/l	U/l	U/l	U/l	U/l
	7.9	4.7	251	0.5	0.1	96	52	84	190	220

Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
  - Bone formation
  - Bone resorption



Bone turnover in the adult skeleton



FROM: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism; 2nd Ed.

Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism

  Bone formation:

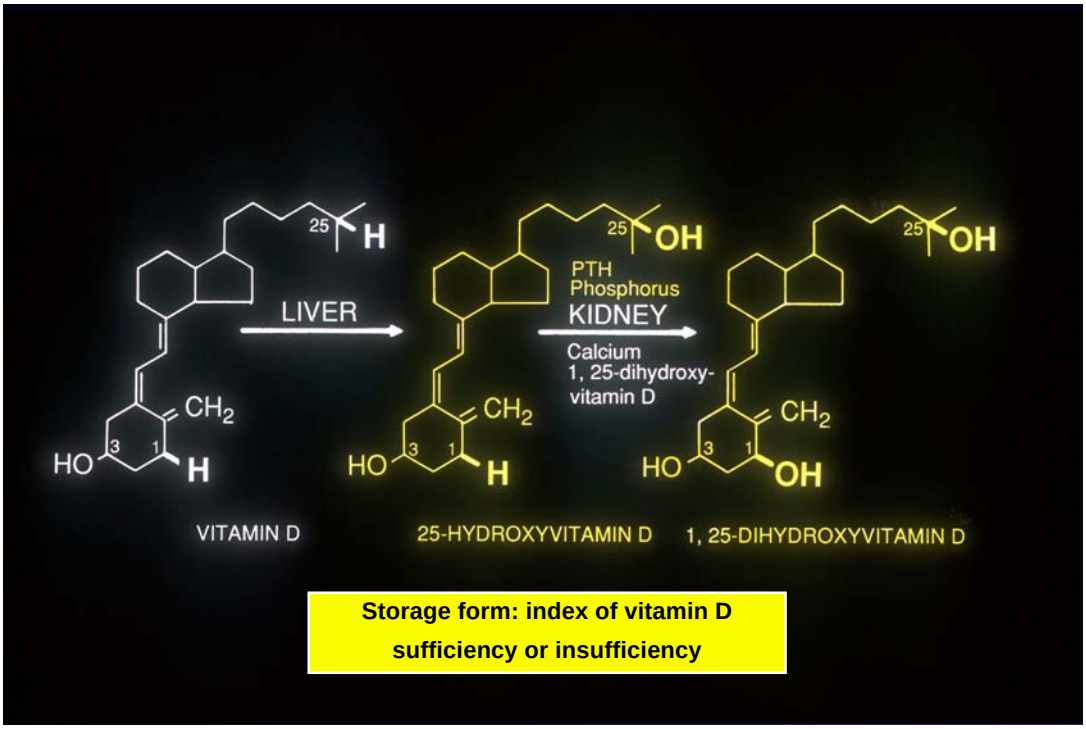
  Alkaline phosphatase (total and bone-specific), osteocalcin

  Bone resorption:

  N- or C- telopeptide of collagen and collagen crosslinks

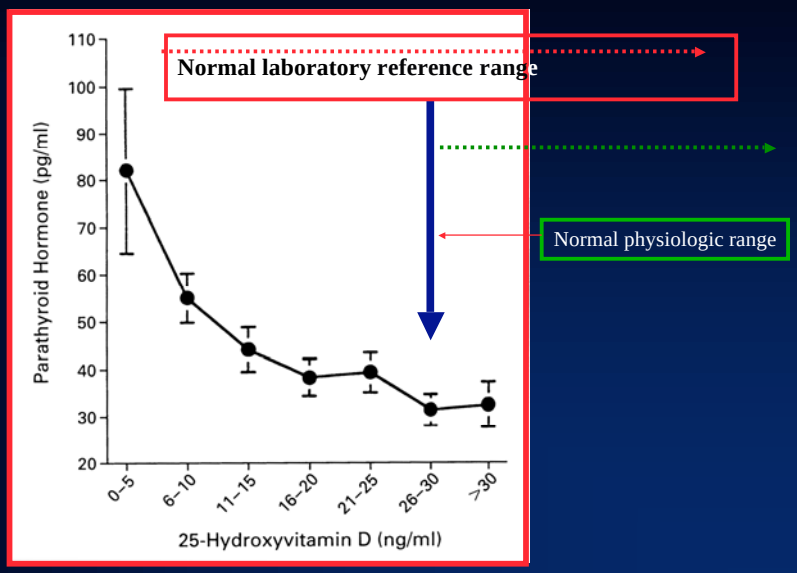
Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
- Calciotropic hormones
  - Parathyroid hormone
  - Vitamin D
    - 25-hydroxyvitamin D
    - 1,25-dihyhydroxyvitamin D



Storage form: index of vitamin D sufficiency or insufficiency

VITAMIN D DEFICIENCY IN MEDICAL INPATIENTS



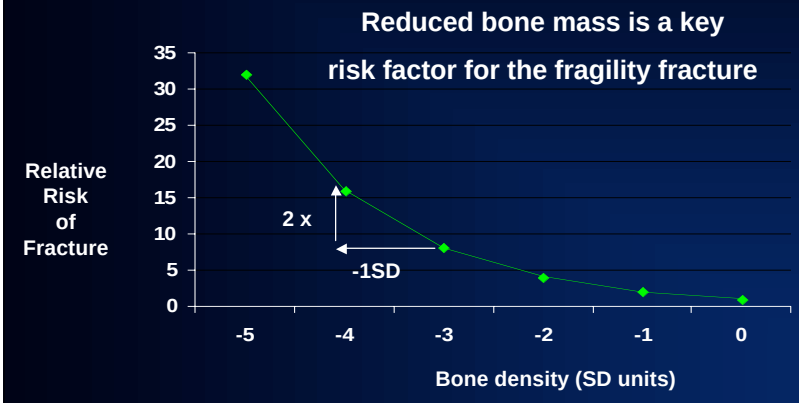
Thomas MK et al. N Eng J Med 1998;338:778-783

Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
- Calciotropic hormones
- Measurement of bone mass

REDUCED BONE MASS IS A KEY RISK FACTOR FOR FRACTURE

Relationship Between BMD and Fracture Risk in Untreated Patients



Dual Energy X-Ray Absorptiometry (DXA): Central Devices

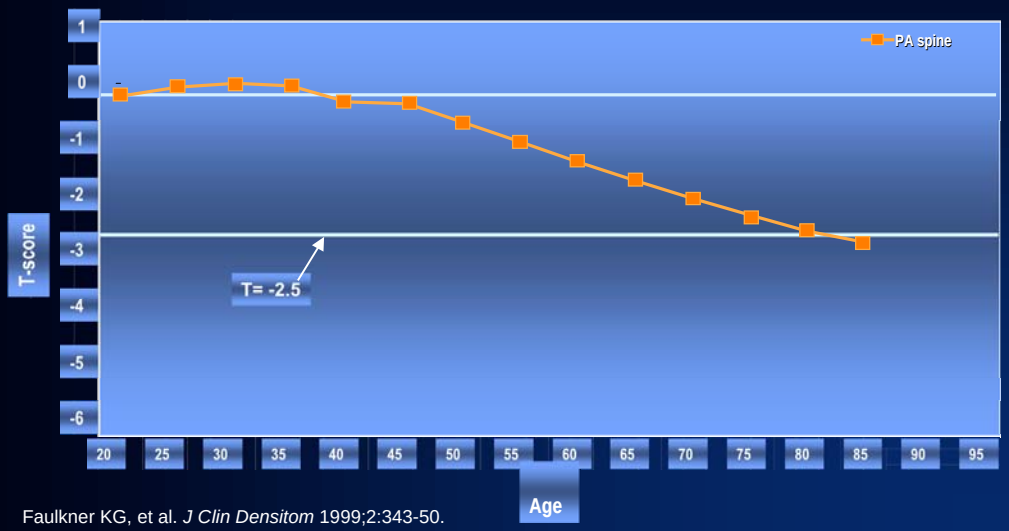
Hologic Delphi

GE Lunar Prodigy

Features of bone densitometry by DXA (dual energy X-ray absorptiometry)

- Safe
- Accurate
- Precise
- Normative population databases
- Correlates with fracture risk
- A diagnostic standard for osteoporosis

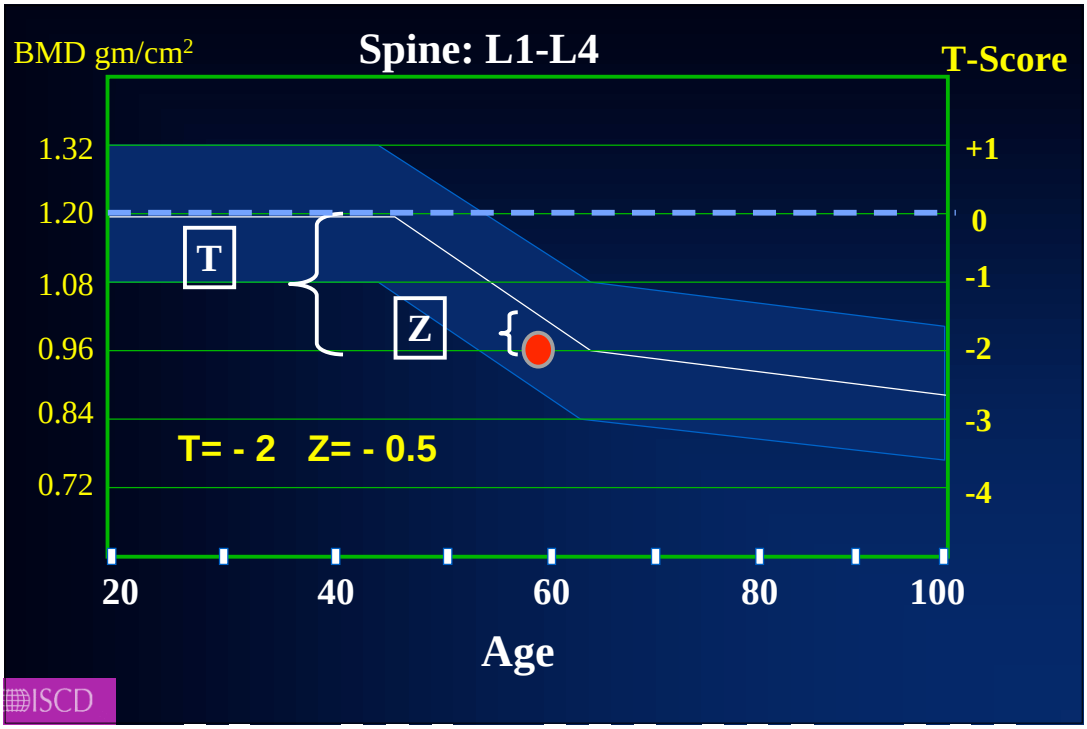
Bone loss as a function of age



Faulkner KG, et al. *J Clin Densitom* 1999;2:343-50.

Referents for comparisons of bone mass measurements

- **Z-score**: a measure of bone density in standard deviations from normal age- and sex-matched cohorts
- **T-score**: a measure of bone density in standard deviations from cohorts at peak bone mass (25-30 years old)

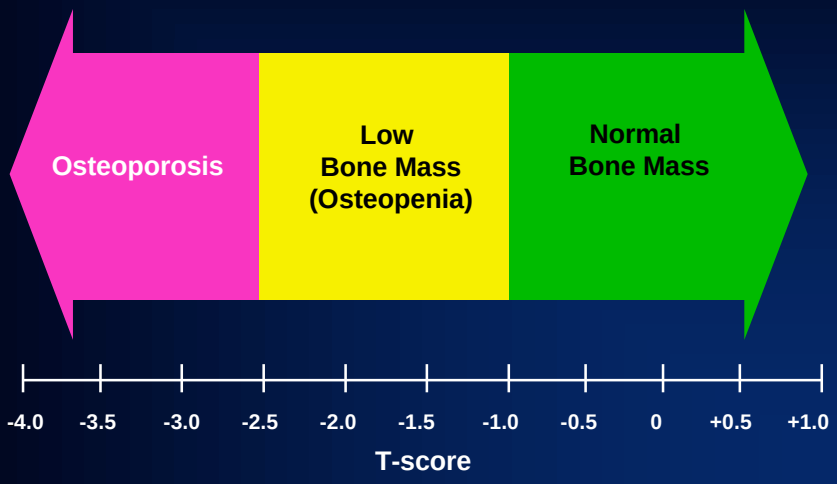


Diagnostic Standard

T-SCORE

Interpreting T-scores (World Health Organization)

Correlates with life time fracture risk for Caucasian Women



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- Normal calcium homeostasis
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- Hypercalcemia
- Hypocalcemia
- Osteoporosis

CAUSES OF HYPERCALCEMIA

- **Primary Hyperparathyroidism**
- **Malignancy**
- Other endocrinopathy
  - Hyperthyroidism
  - Pheochromocytoma
  - VIPoma
  - Adrenal insufficiency
- Medications
  - lithium
  - thiazide diuretics
  - thyroid hormone
  - Vitamin A
  - Vitamin D
- Vitamin D
  - Toxicity
  - Granulomatous disease
    - Tuberculosis
    - Sarcoidosis
    - Any other
- Lymphoma
- FHH
- Immobilization
- Acute or chronic renal disease

MAJOR CAUSES OF HYPERCALCEMIA

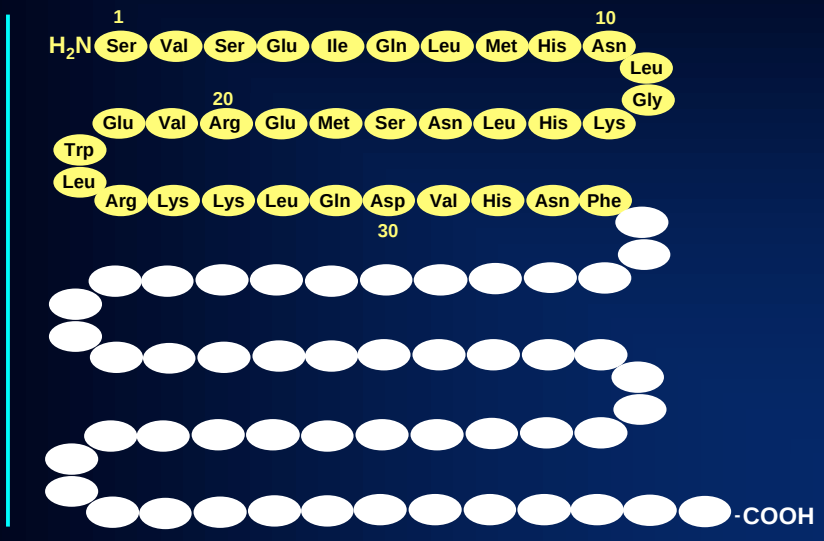
(From Mundy and Martin)

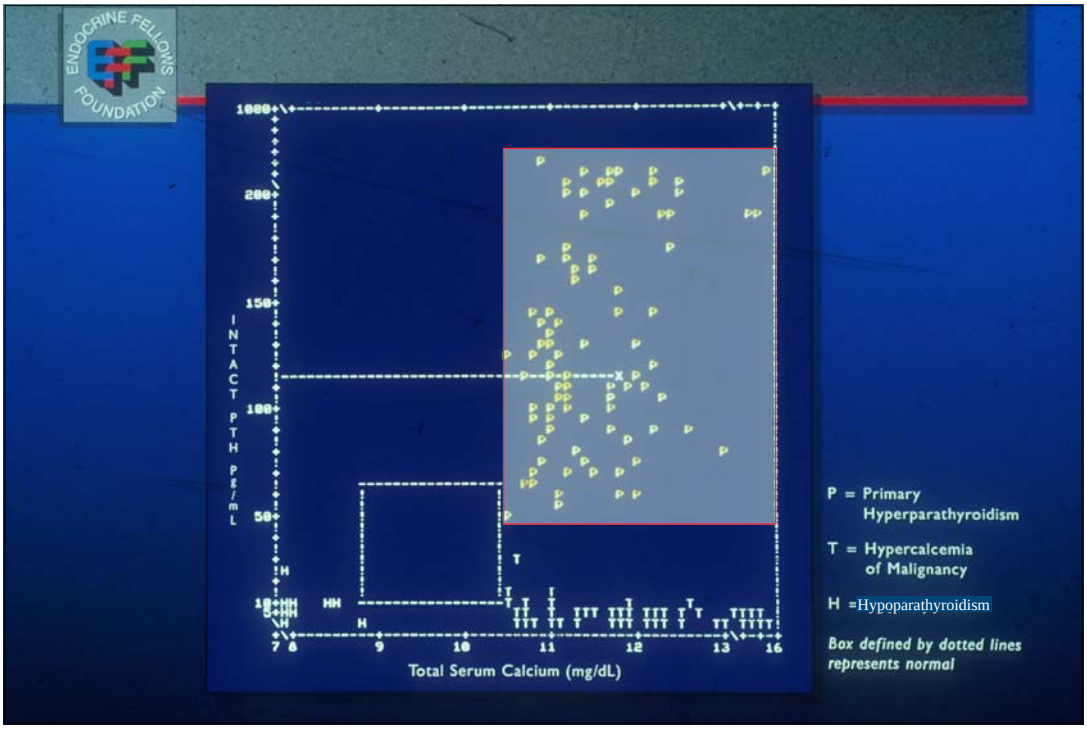
	# OF PATIENTS	% OF TOTAL
Primary Hyperparathyroidism	**111**	**54**
Malignancy	**72**	**35**
Others (sarcoid, thyroid, vit D, etc	12	6
Unknown	12	6

PRIMARY HYPERPARATHYROIDISM

- A common endocrine disorder characterized by incompletely regulated, excessive secretion of parathyroid hormone from one or more parathyroid glands.
- Primary Hyperparathyroidism is associated with hypercalcemia and elevated levels of parathyroid hormone.

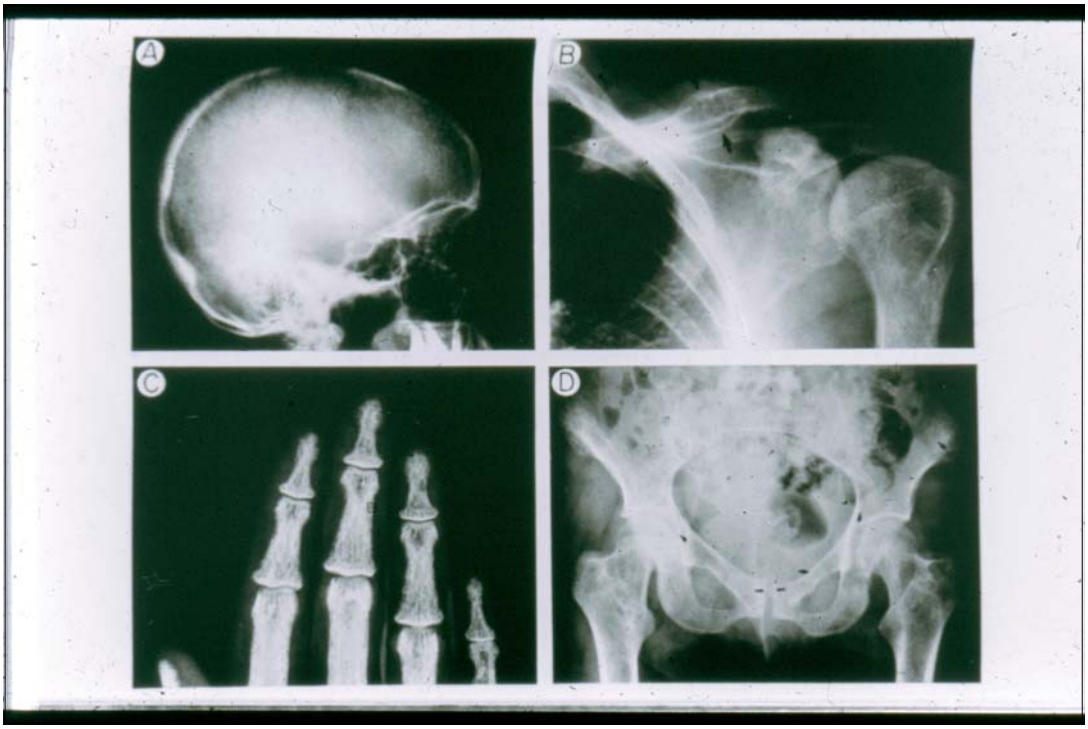
Human Parathyroid Hormone





PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans



CHANGING CLINICAL PROFILE OF PRIMARY HYPERPARATHYROIDISM

	Cope et al. 1930-1965	Heath et al. 1965-1974	Mallette et al. 1965-1974	Silverberg, Bilezikian et al. 1984-2007
Nephrolithiasis	57%	51%	37%	17%
Hypercalciuria	Not reported	36%	40%	39%
Overt Skeletal Disease	23%	10%	14%	1.4%
Asymptomatic	0.6%	18%	22%	80%

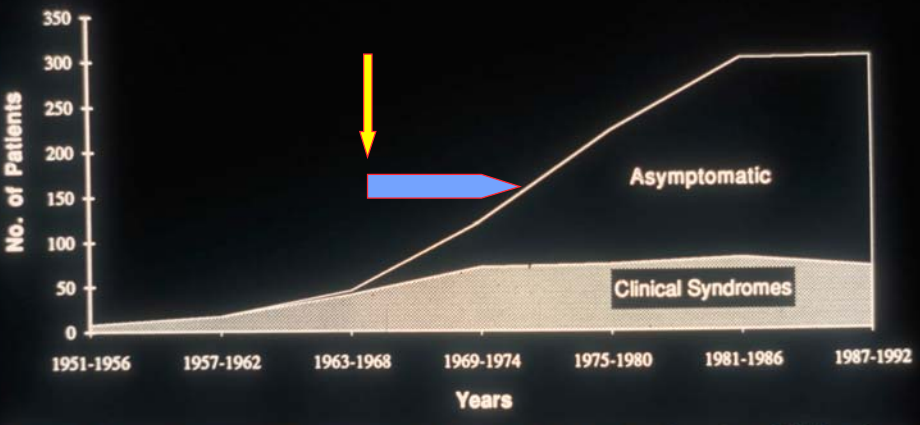


Figure 2 Changing proportion of asymptomatic patients with clinical manifestations of HPT at 6 year intervals.

Biochemical and hormonal profile in Primary Hyperparathyroidism

Index	Patients	nl range
• Calcium (mg/dl)	10.7±0.1	8.4-10.2
• Phosphorus (mg/dl)	2.9±0.1	2.5-4.5
• Alk Phos (IU/l)	114±4	<100
• PTH (pg/ml)	121±7	10-65
• 25-OH Vit D (ng/ml)	21±1	9-52
• 1,25-OH_2 Vit D (pg/ml)	59±2	15-60
• Urinary calcium (mg)	248 ± 12	250-300
• DPD (nmol/mmol Cr)	17 ± 6	4-21

PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans

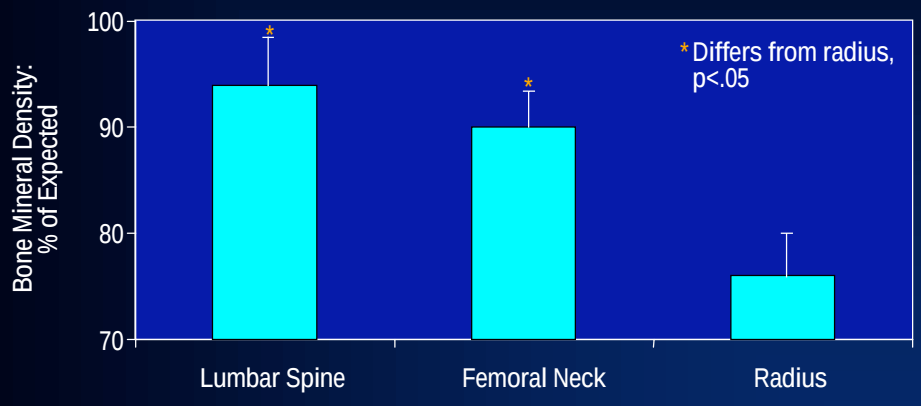
Since 1970: A disease of asymptomatic hypercalcemia

BONE MASS MEASUREMENTS IN PRIMARY HYPERPARATHYROIDISM

Bone and stone disease in primary hyperparathyroidism: 1965-2007

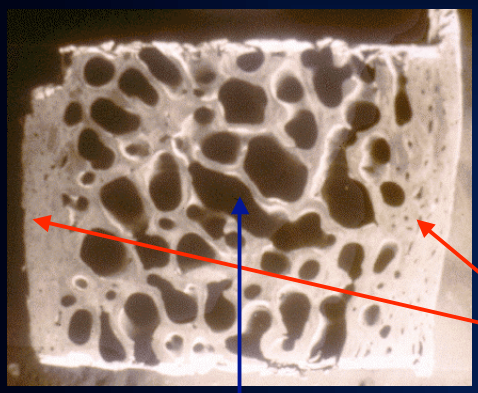
	Mallette, Bilezikian Heath & Aurbach 1965-1972 n=57	Silverberg, Bilezikian et al. 1984-2007 n=121
Nephrolithiasis	37%	17%
Bone disease (Radiological)	**14%**	**1.4%**

BMD in Postmenopausal Women With Primary Hyperparathyroidism



Silverberg, Bilezikian et al. JBMR, 1989

Normal Bone



Skeletal Site	Cancellous	Cortical
Lumbar spine	***	*
Total Hip Femoral neck	**	**
Radius (1/3 site)	*	***

Densitometric and Histomorphometic Characteristics of Bone in Primary Hyperparathyroidism

- Cancellous bone (lumbar spine): relatively well preserved
- Cortical bone (distal radius): preferentially affected

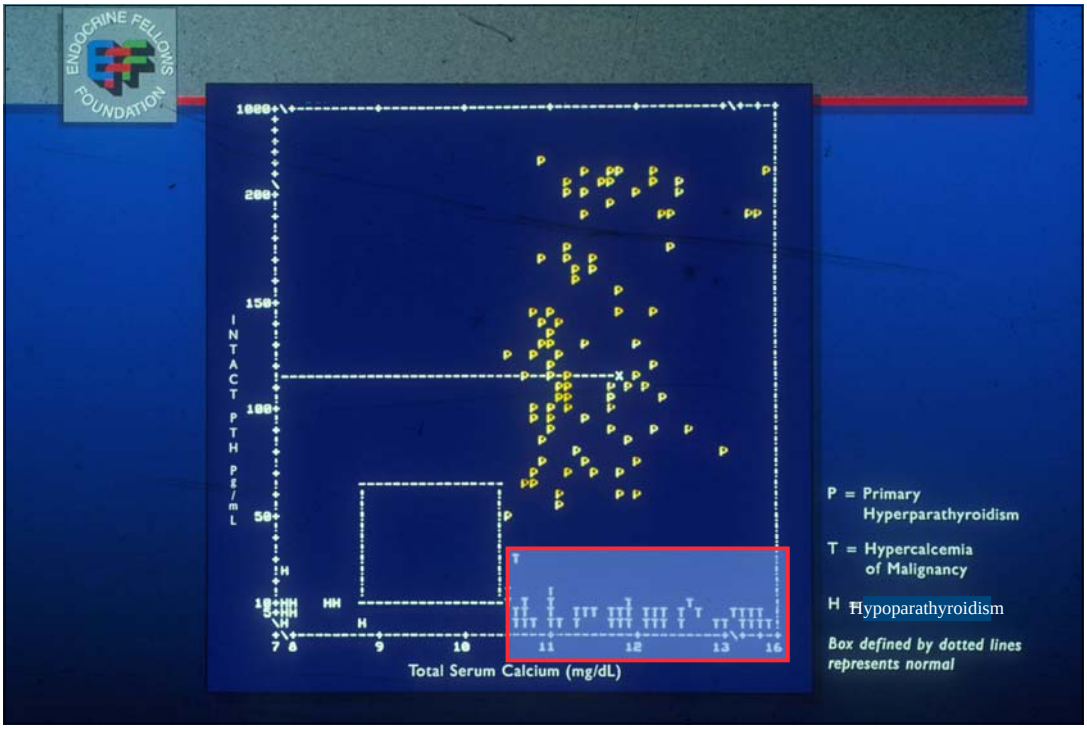
TO CUT IT OUT OR TO LEAVE IT IN…

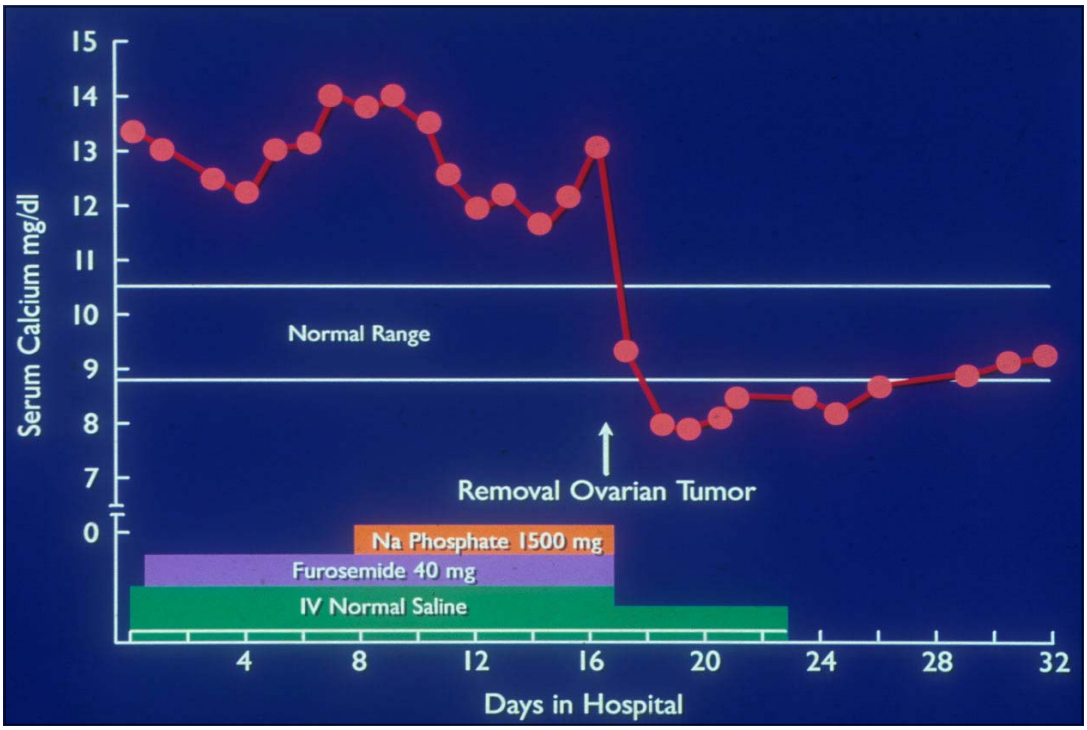
A KEY CLINICAL DILEMMA IN PRIMARY HYPERPARATHYROIDISM

Guidelines for Parathyroid Surgery (NIH Workshop, 2002)

- Hypercalcemia (> 1 mg/dl above normal)
- Stone or overt bone disease
- Marked hypercalciuria (> 400 mg/day)
- Reduced bone density (T<-2.5)
- Age (<50 years old)

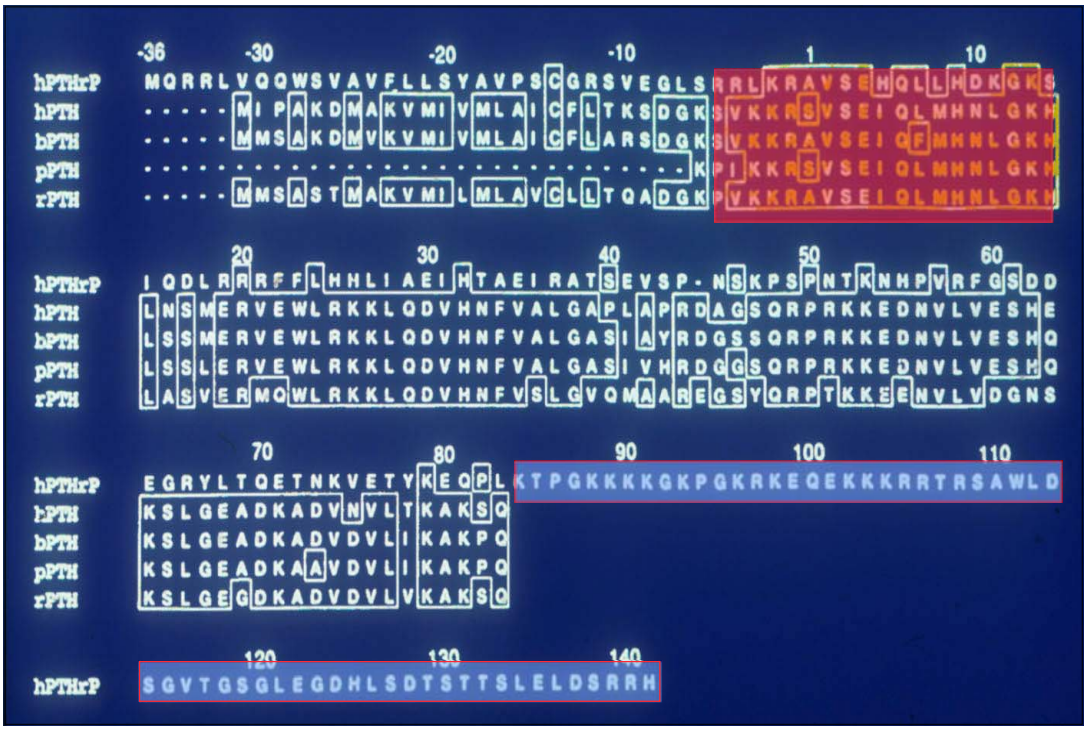
Bilezikian and Silverberg
New Eng J Med 350:1746-1751, 2004


ENDOCRINE FELLOWS FOUNDATION
INTACT PTH pg/mL
1000
200
150
100
50
H
HH
HH
H
7 8
9
10
11
12
13
16
Total Serum Calcium (mg/dL)
P = Primary Hyperparathyroidism
T = Hypercalcemia of Malignancy
H = Hypoparathyroidism
Box defined by dotted lines represents normal


Serum Calcium mg/dl
15
14
13
12
11
10
9
8
7
0
Normal Range
Removal Ovarian Tumor
Na Phosphate 1500 mg
Furosemide 40 mg
IV Normal Saline
4
8
12
16
20
24
28
32
Days in Hospital

Humoral Hypercalcemia of Malignancy

Malignant tumors synthesize and secrete humors that stimulate osteoclast-mediated bone resorption



Parathyroid Hormone-Related Protein as an Etiology of HHM

Criteria

- Produced by the tumor
- Blood level correlates with hypercalcemia
- Mimics the clinical syndrome
- Reducing the PTHRP "burden" reverses hypercalcemia

Circulating PTHRP Levels in Hypercalcemia of Malignancy

Malignancy	% Elevated
• HTLV-1 T-cell lymphoma	99%
• Classical squamous cell carcinoma	85%
• Adenocarcinoma	58%
• Breast carcinoma	50%
• Myeloma and other hematological malignancies	21%

Budayr et al. Annals Int Med, 1989

Ikeda et al. J Clin Endo & Metlab, 1994

CAUSES OF HYPERCALCEMIA

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  - Hyperthyroidism
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    - Any other
- Lymphoma
- FHH
- Immobilization
- Acute or chronic renal disease

Symptoms, signs, and treatment of hypercalcemia

To be discussed tomorrow!

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- Useful indices of calcium metabolism
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- Hypocalcemia
- Osteoporosis

Hypocalcemia

- Hypoparathyroidism
  - Deficient secretion of parathyroid hormone
- Secondary hyperparathyroidism
  - Appropriate response to hypocalcemic stimulus
- Other causes

Hypocalcemia

Hypoparathyroidism - Deficient secretion of parathyroid hormone

- **Autoimmune hypoparathyroidism**
  - **Multiple end-organ endocrine gland insufficiency**
  - **Isolated parathyroid gland deficiency**
- Familial hypoparathyroidism
  - Defective processing of PTH gene product
  - Defective cellular trafficking of PTH gene product
  - Developmental agenesis (X-linked)
- Activating mutations of the calcium receptor
- Congenital (DeGeorge Syndrome)
- **Post-surgical hypoparathyroidism**

Hypocalcemia

Secondary Hyperparathyroidism - Appropriate response to hypocalcemic stimulus

- **Vitamin D deficiency**
  - **Nutritional**
  - **Malabsorption**
  - **Liver disease**
  - **Renal disease**
- Vitamin D resistant states
  - Vitamin D resistant rickets
  - Vitamin D dependent rickets
- Drugs
  - Foscarnet
  - Pentamidine
  - Ketaconazole
- Pseudohypoparathyroidism

Symptoms, signs, and treatment of hypocalcemia

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Progression (or Consequence) of Osteoporosis

Patient at age 50...

and 25 years later

Used with permission of the National Osteoporosis Foundation, *Osteoporosis: The Silent Disease*, National Osteoporosis Foundation, Partners in Prevention Slide Presentation, 1993.

Postmenopausal Osteoporosis

- **Osteoporosis**
  - 6 to 8 million US women age ≥ 50
- **Low bone mass**
  - 20 to 24 million
- **Fractures**
  - 40% will suffer an osteoporotic fracture in their lifetime
    - Vertebral: 15.6%
    - Hip: 17.5%
    - Forearm: 16.0%
- **1.5 million fractures annually**

Melton LJ, et al. *J Bone Miner Res* 1992;7:1005-10.
Looker AC, et al. *J Bone Miner Res* 1997;12:1761-8.
National Osteoporosis Foundation. 1998, 2002.

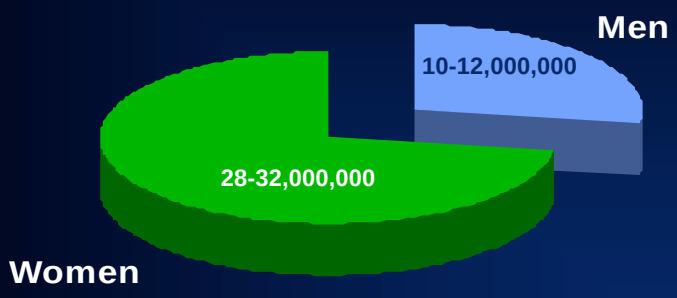
Human Costs of Osteoporosis

- Impaired function, decreased mobility
- More bone loss due to decreased activity
- Compressed abdomen, reduced appetite
- Reduced pulmonary function
- Sleep disorders
- Shortened survival
- Poor self esteem

Photo courtesy of the National Osteoporosis Foundation

Ross PD et al. *Ann Intern Med* 1991;114-23.
Silverman SL. *Bone* 1992;13 (suppl 2):S27-31.
Cooper C, et al. *Am J Epidem* 1993;137:1001-5.
Lyles et al. *Am J Med* 1993;94:595-601.
Schlaich C, et al. *Osteoporos Int* 1998;8:261-7.

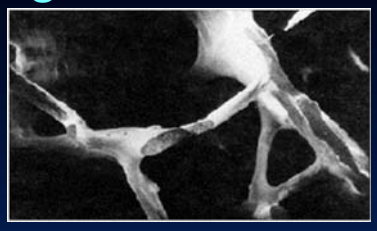
Incidence of Osteoporosis and Osteopenia



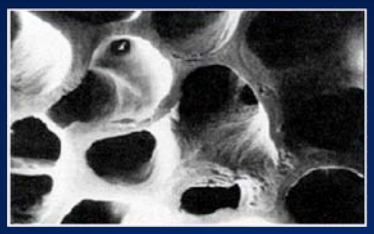
National Osteoporosis Foundation, 2002.

Osteoporosis: defining the Problem

"A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture."



Osteoporotic bone



Healthy bone

NIH Consensus Development Conference on Osteoporosis, 2000.

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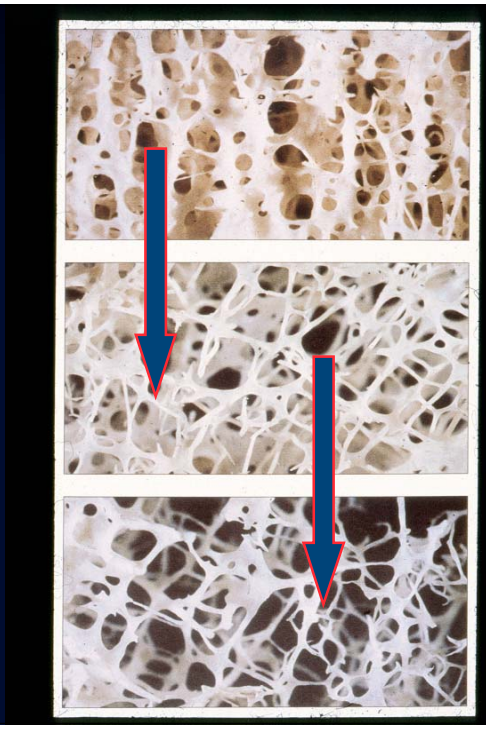
Independent Risks for Hip Fracture in Older Women

Major Risk Factors

- Age
- Any fracture after age 50
- The menopause
- Maternal history of hip fracture
- Glucocorticoids
- Smoking
- Alcohol abuse
- High bone turnover
- Low body weight (<127 lbs)

Cummings SR, et al. *N Engl J Med* 1995;23:332:767-73.
Garnero P, et al. *J Bone Miner Res* 1996;11:1531-8.



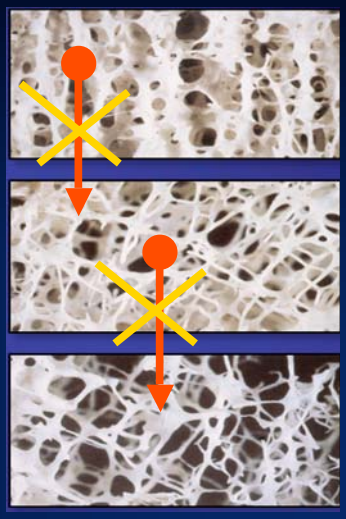
Therapeutic Goals

↓ Bone Remodeling

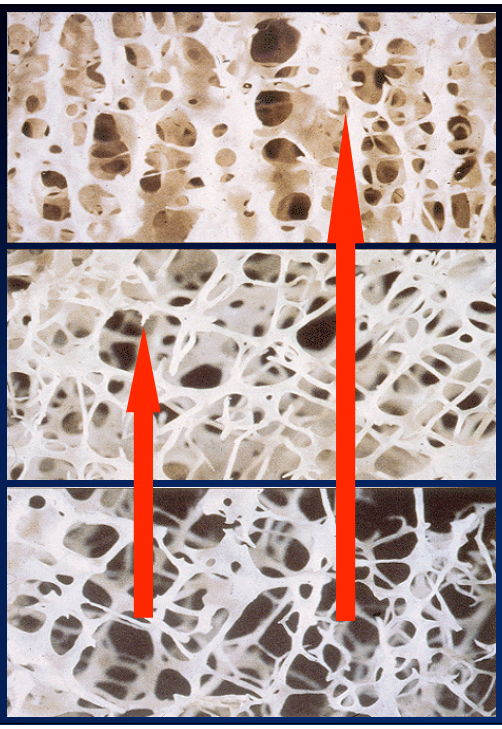
Stabilize or increase BMD

Maintain trabecular architecture

Increase mineralization density of bone matrix



Therapeutic Goals



THERAPEUTIC CONSIDERATIONS

- **HOW TO PREVENT?**
- **HOW TO TREAT?**

Diagnosis, evaluation and treatment of osteoporosis

To be discussed tomorrow!