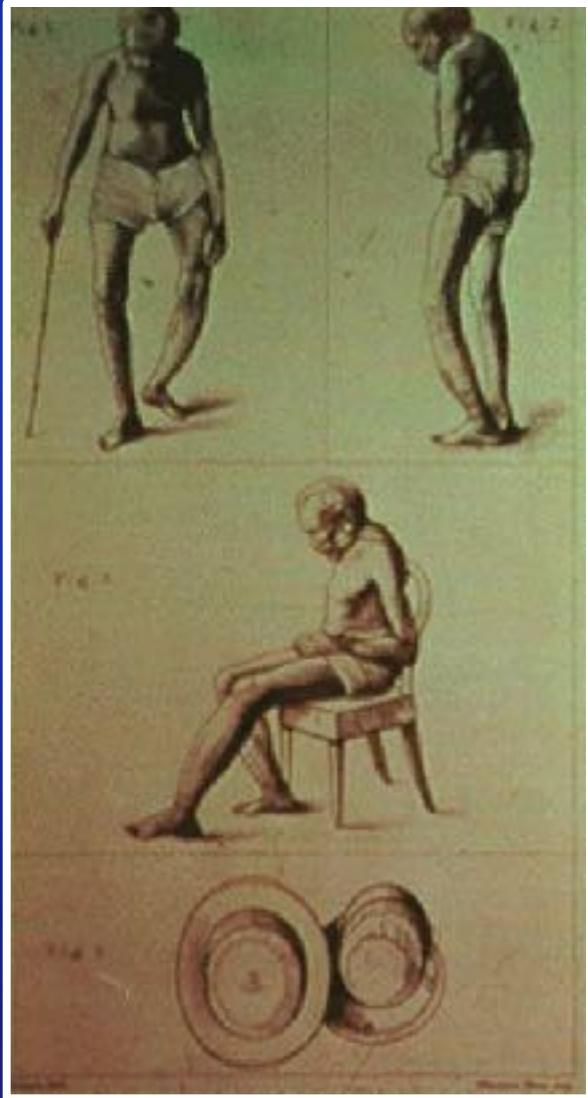


History of Paget's Disease



- Sir James Paget named disease *osteitis deformans* in 1876, suspecting basic inflammatory process^{1,2}
- Today predominantly referred to as *Paget's disease of bone*¹



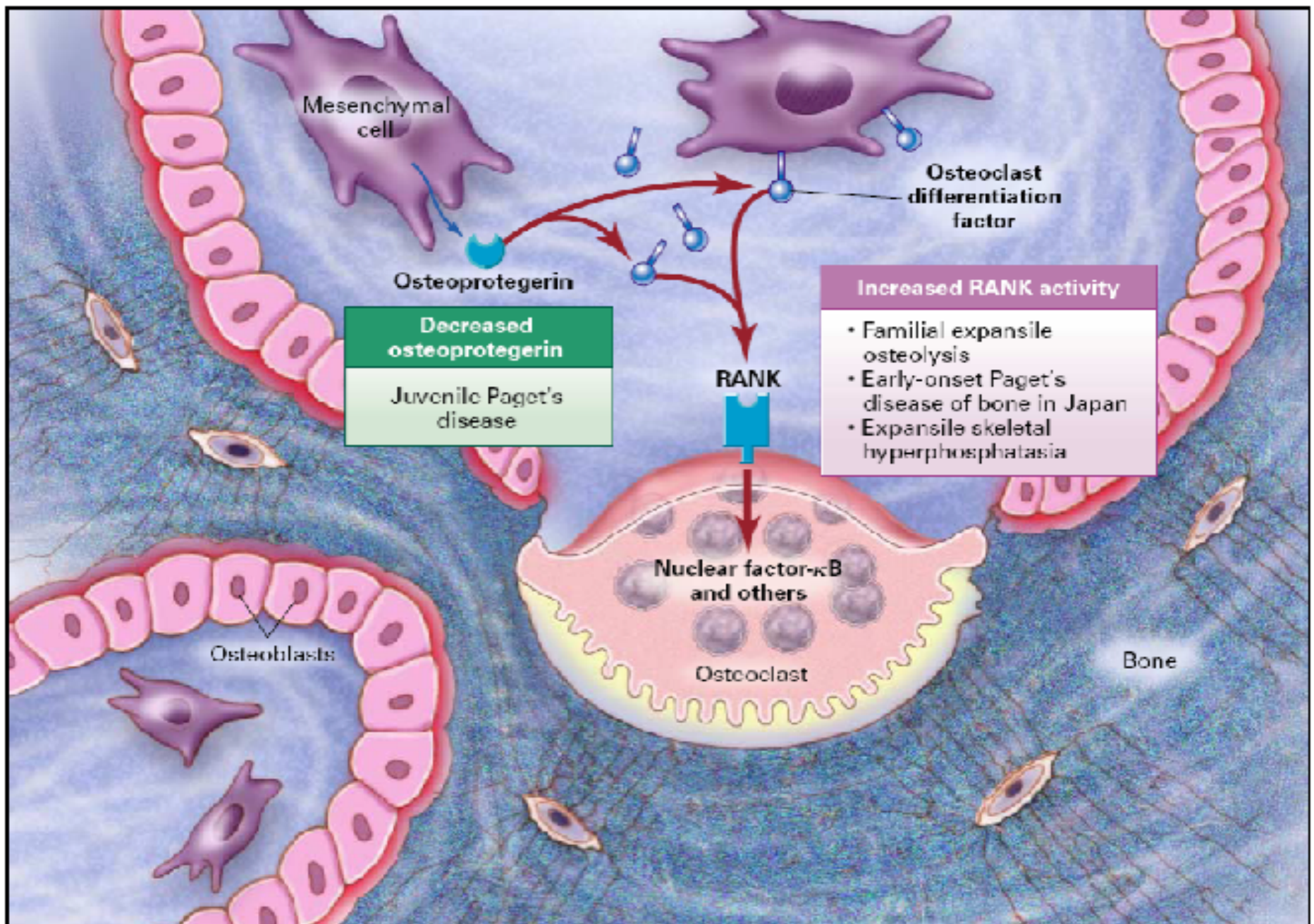
Sir James Paget

Epidemiology: Prevalence of Paget's Disease in the US

- Second most common bone disease after osteoporosis¹
- Roughly estimated at approximately 2% of the US population over age 55 years¹
 - Prevalence increases markedly with age, uncommon before age 40^{1,2}
- 15% to 30% of patients have positive family histories¹
- Most common in people of Northern European descent¹

1. Siris ES, Roodman GD. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 6th ed. Washington, DC: ASBMR; 2006:320-330.

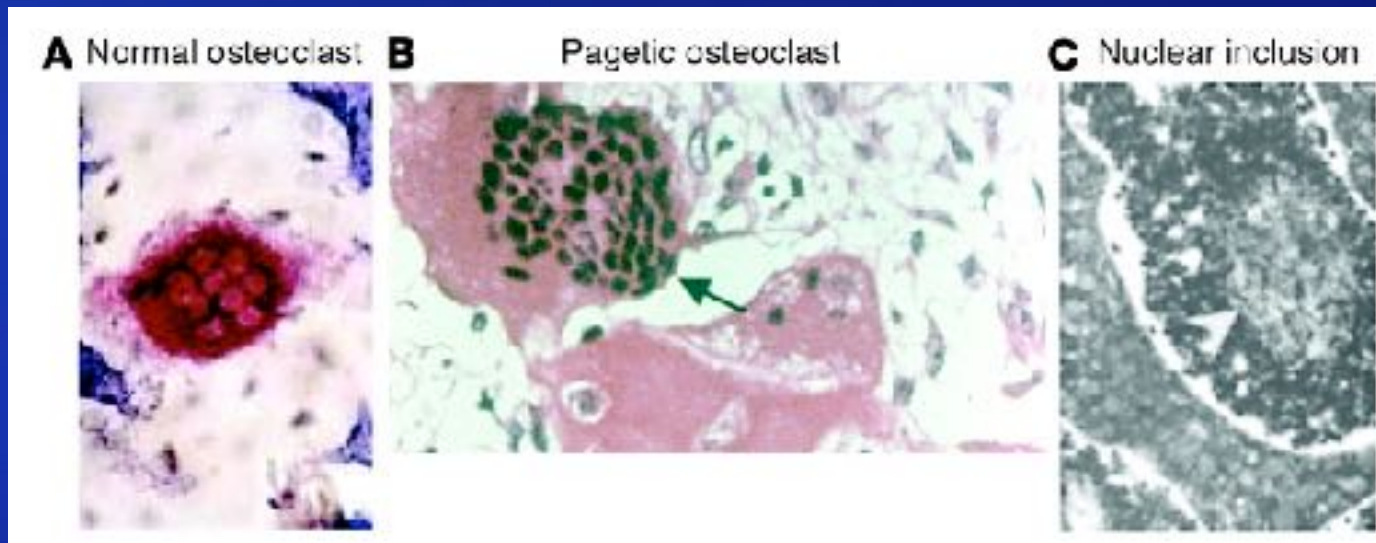
2. Altman RD, et al. *J Bone Miner Res*. 2000;15:461-465.



Paget's Disease: Description

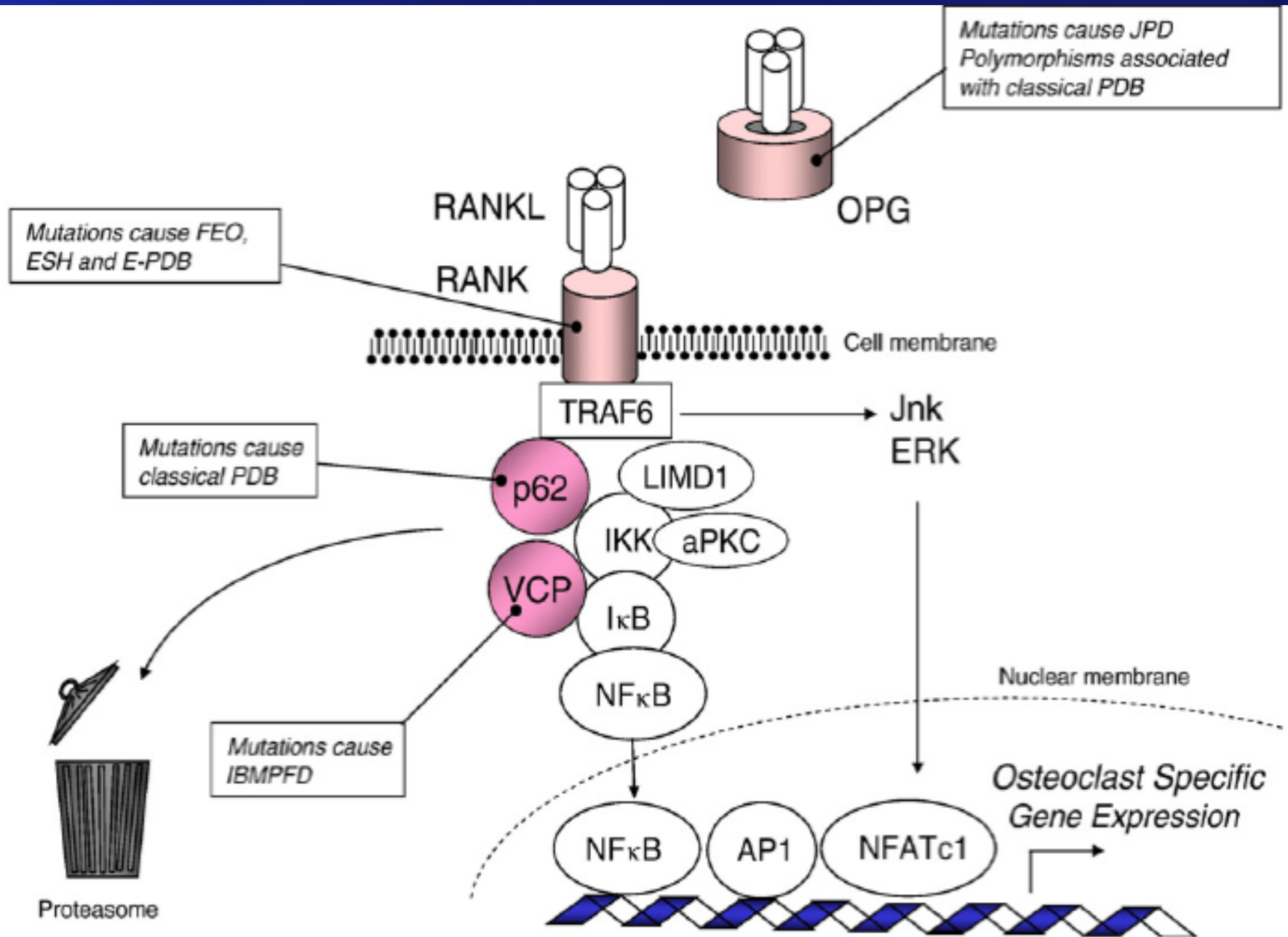
- Chronic, progressive skeletal disorder
- Increased size and number of osteoclasts
- Localized areas of excessive bone resorption and formation
 - May have only one affected bone or have pagetic lesions in multiple bones
 - New lesions rarely develop in previously unaffected bone after diagnosis

Osteoclasts in normal bone and in Paget's disease



Roodman, G. D. et al. *J. Clin. Invest.* 2005;115:200-208

ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ



ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ

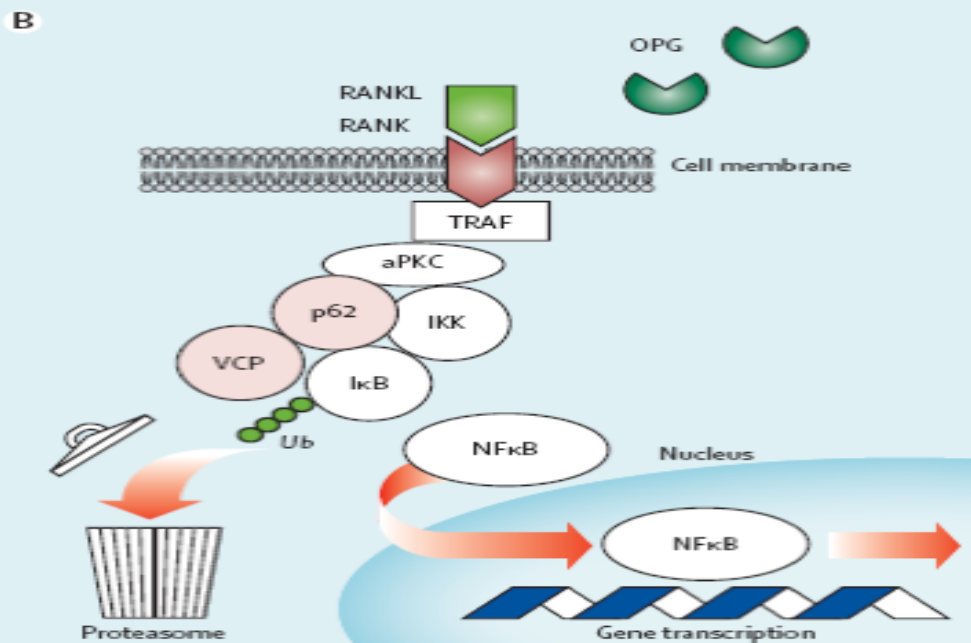
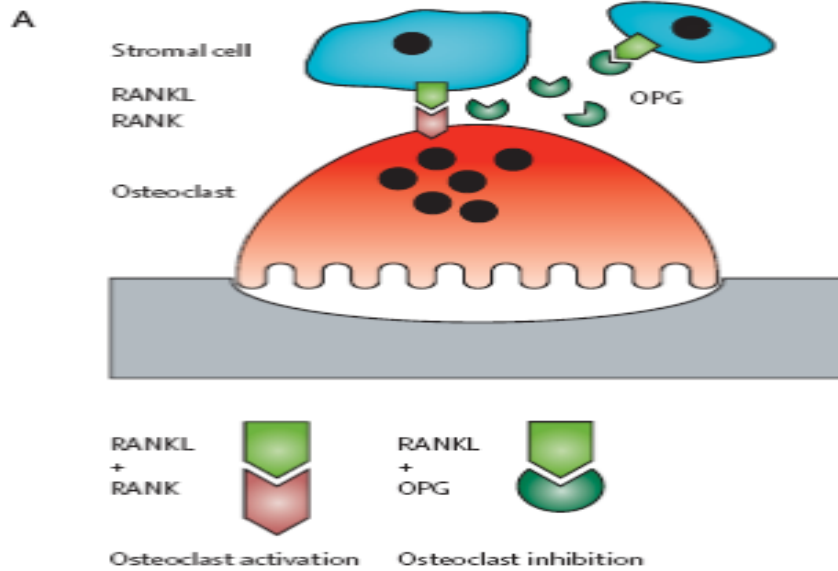
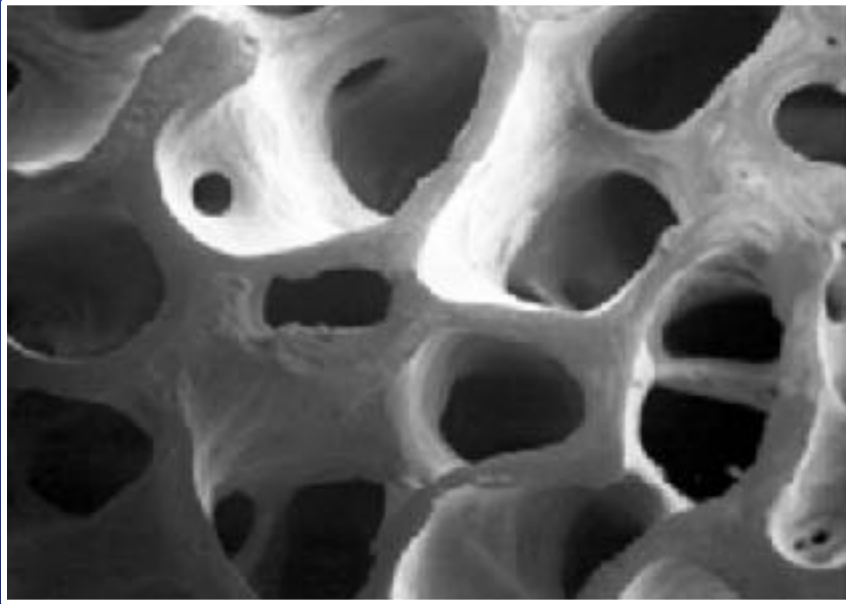


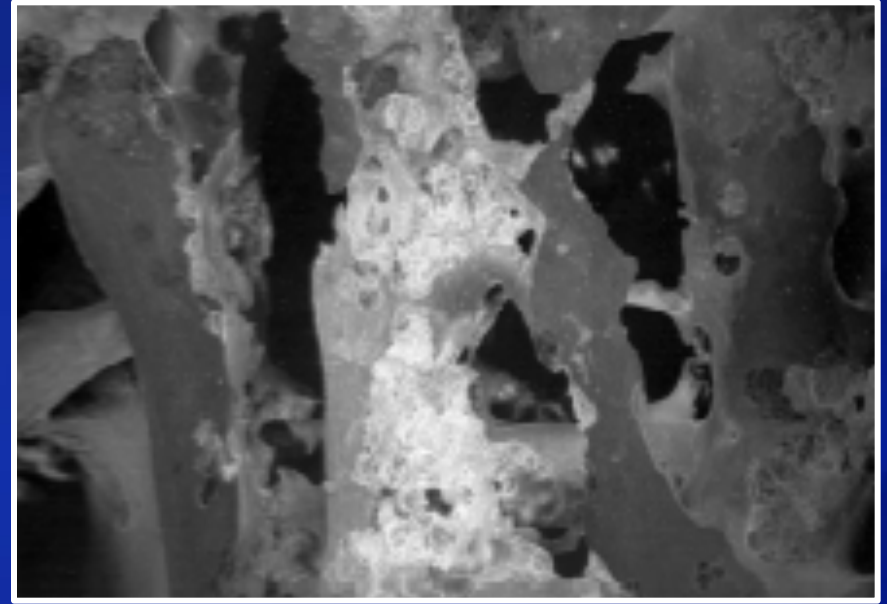
Figure 1: Regulation of osteoclast activity by the RANK-NFκB signalling pathway

Pagetic Bone and Normal Bone

Normal



Pagetic



Siris ES, Roodman GD. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 6th ed. Washington, DC: ASBMR; 2006:320-330.

Paget's Disease: Clinical Presentation

- Usually mild or asymptomatic¹
- Diagnosis is often based on incidental findings¹
 - Elevated total or bone specific serum alkaline phosphatase
 - Radiological findings
- Patients may present with symptoms that are nonspecific or suggestive of other conditions¹
 - Pain
 - Fracture
 - Deformity
 - Osteoarthritis
 - Hearing loss

Paget's Disease: Common Sites of Involvement

- Paget's disease can occur in any bone, but most commonly:
 - Skull
 - Vertebrae
 - Pelvis
 - Femur
 - Tibia

Diagnosing Paget's Disease: Tests

- Laboratory tests^{1,2}
 - Alkaline phosphatase, a marker of bone formation
 - Any level above normal, especially in the absence of elevated liver enzymes
 - Bone-specific alkaline phosphatase may be more reliable. Elevated markers of bone resorption (serum β C-telopeptide of type 1 collagen [CTX], urine N-telopeptide of type I collagen [NTX])
- Radiographs^{1,2}
 - Characteristic appearance usually confirms diagnosis
- Bone scan to assess extent of disease¹

1. Lyles KW, et al. *J Bone Miner Res.* 2001;16:1379-1387.

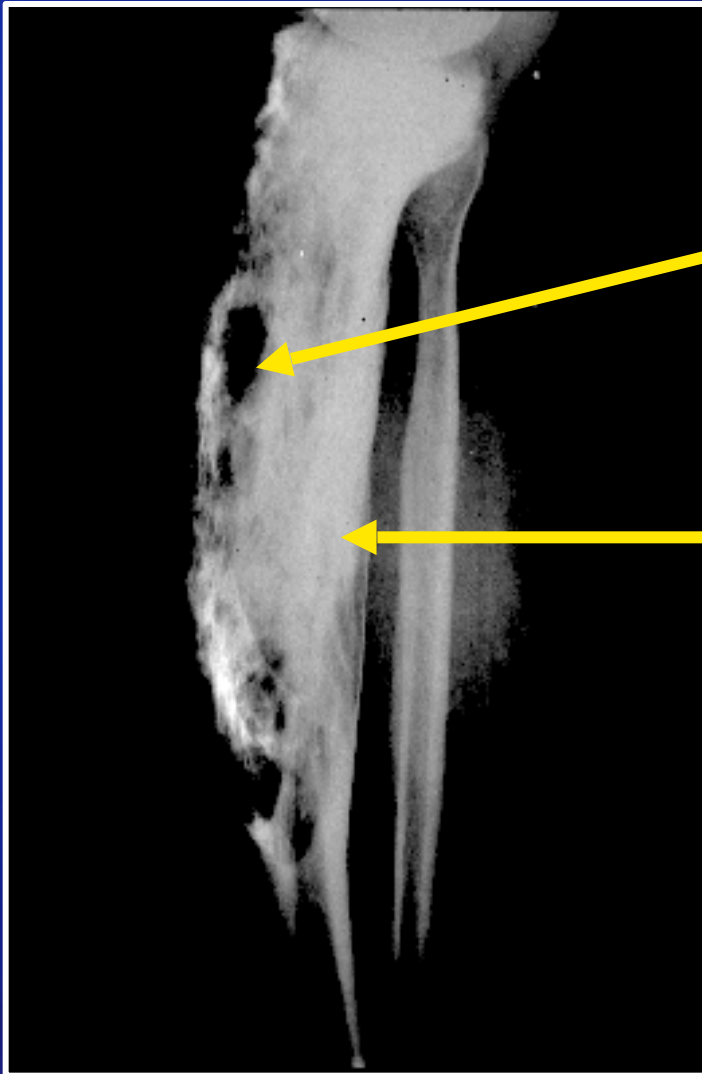
2. Selby PL, et al. *Bone.* 2002;31:366-373.

Early-Stage (Lytic) Paget's Disease: Tibia



V-shaped "blade of grass" lesion characteristic of lytic phase of Paget's disease

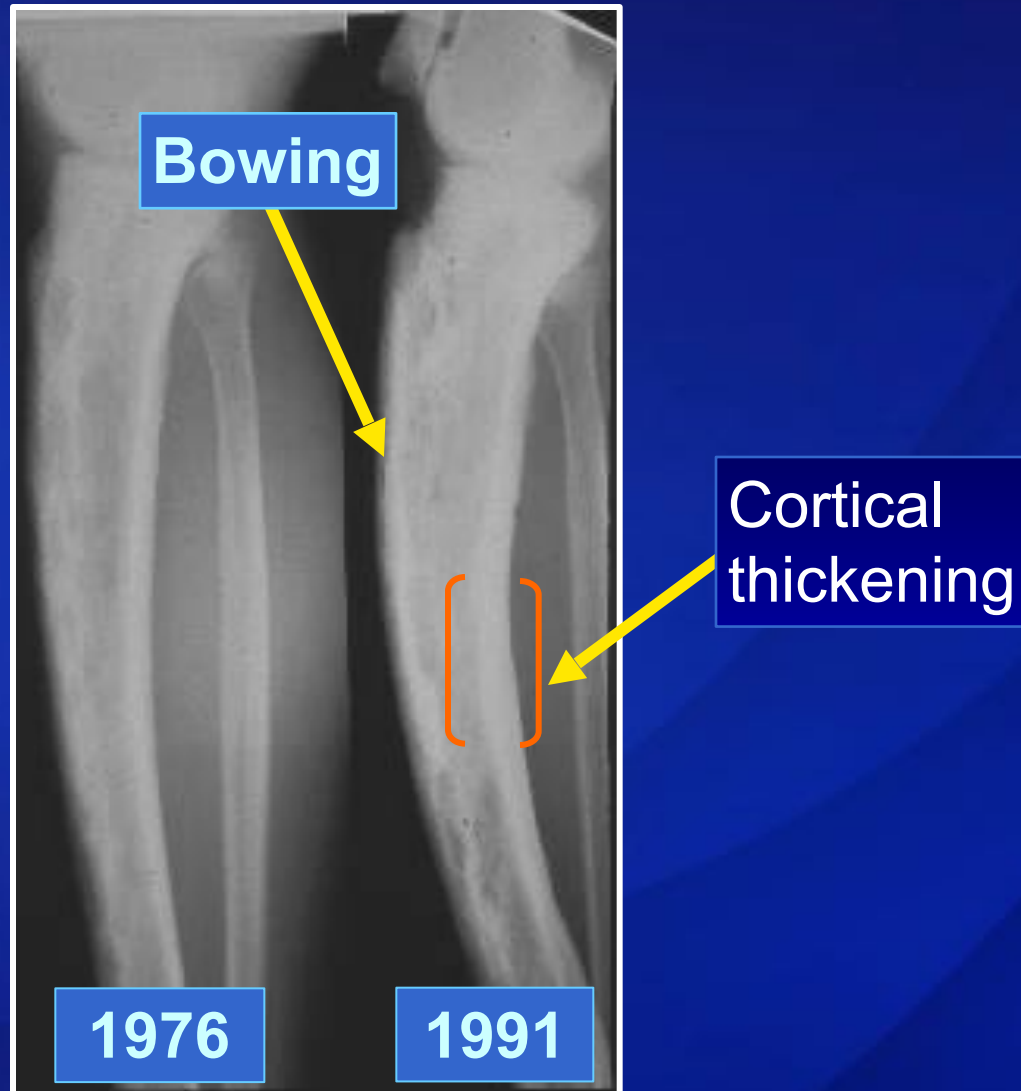
Advanced Paget's Disease in the Tibia: Sclerotic and Lytic Lesions



Secondary osteolytic front

Primarily sclerotic changes, with enlargement and thickening of long bones

Paget's Disease: Progression Over 15 Years in Untreated Patient



1976

1991

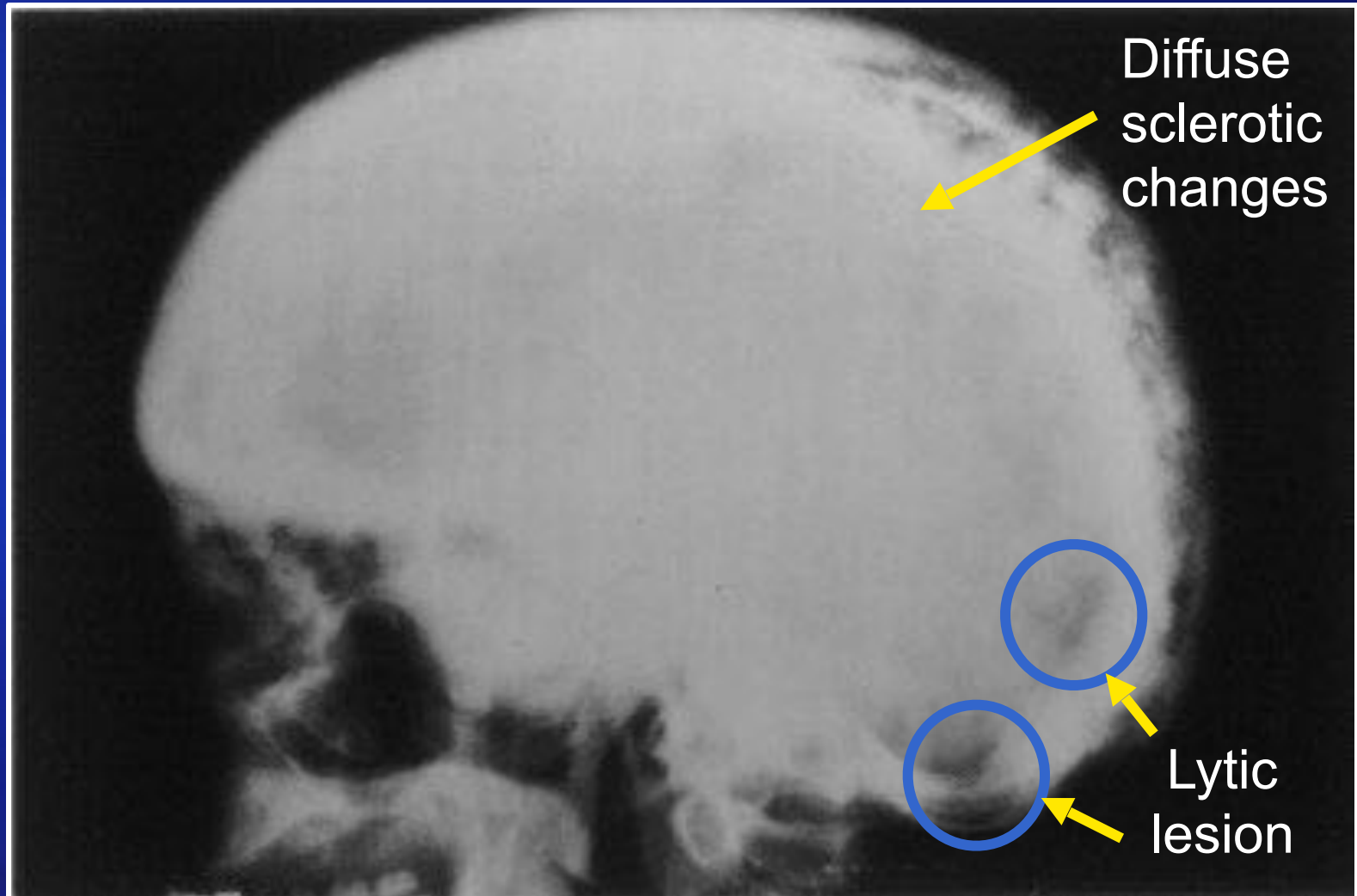
Early-Stage (Lytic) Paget's Disease in the Skull: Known as "Osteoporosis Circumscripta"



Lytic
border

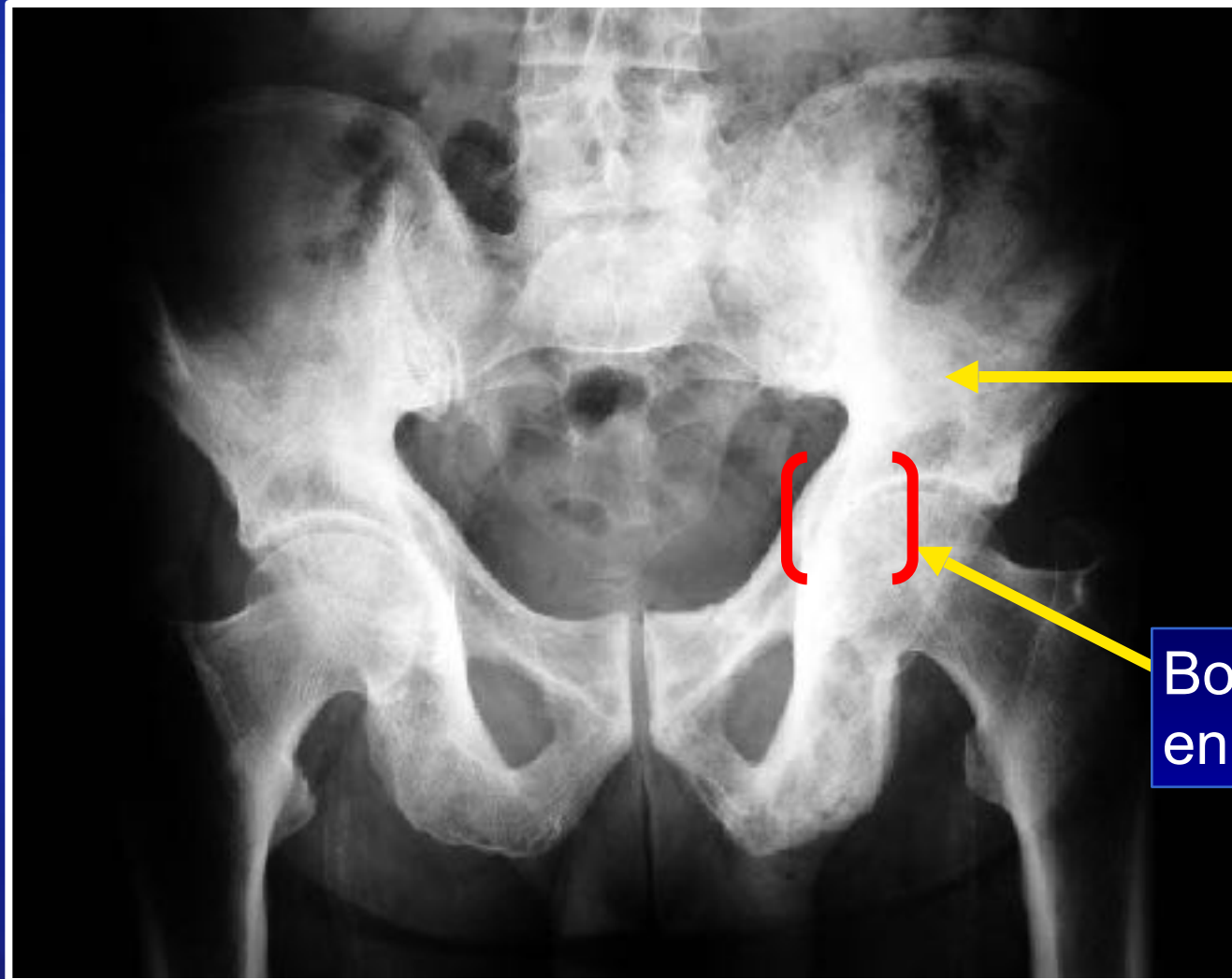
Courtesy of Pierre Delmas, MD.

Advanced (Sclerotic) Paget's Disease: "Cotton Wool" Skull



Courtesy of Pierre Delmas, MD.

Advanced Paget's Disease in the Pelvis



Diffuse
sclerotic
changes

Bony
enlargement

Paget's Disease of Femur



X-Ray

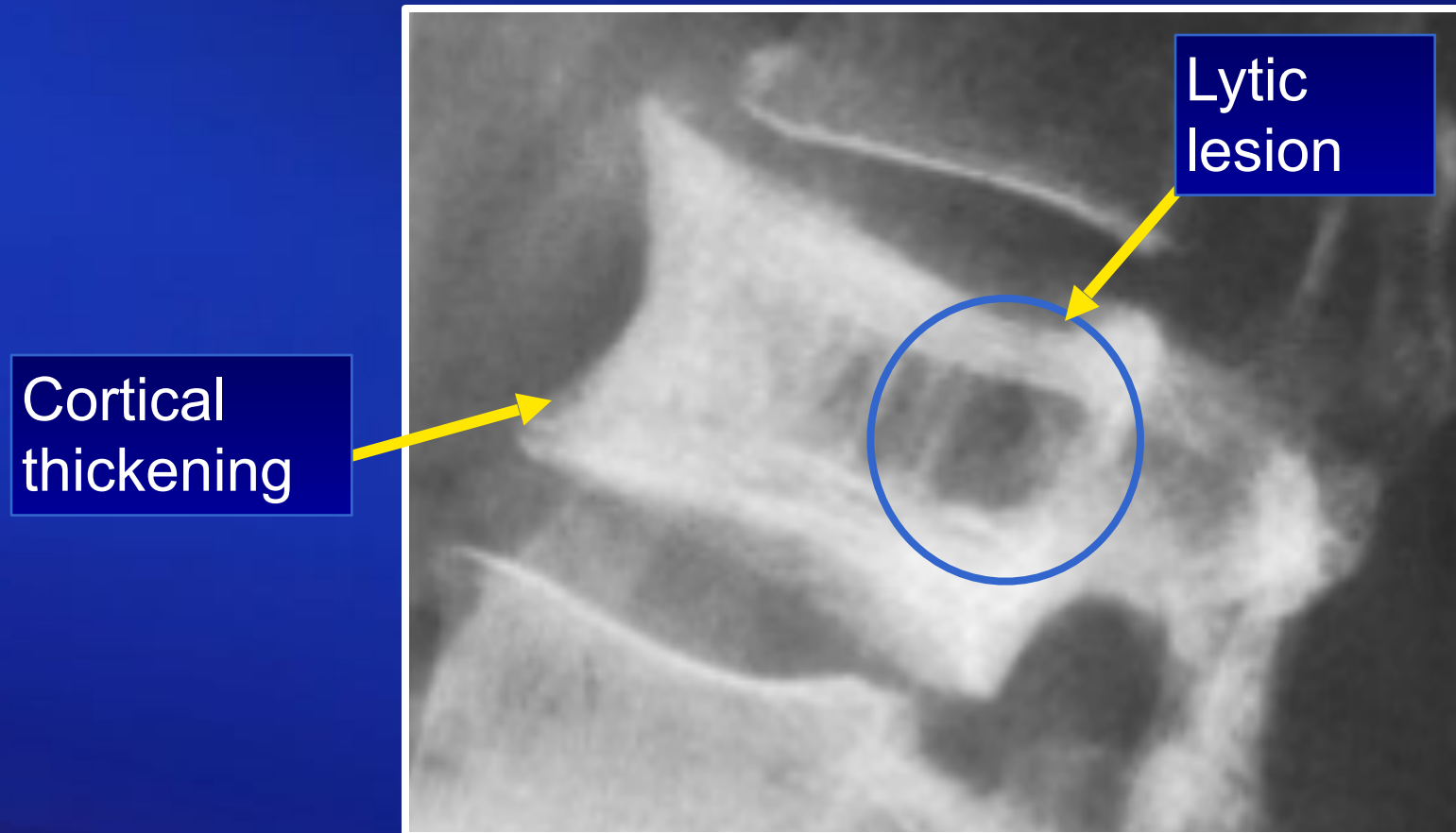


Bone Scan

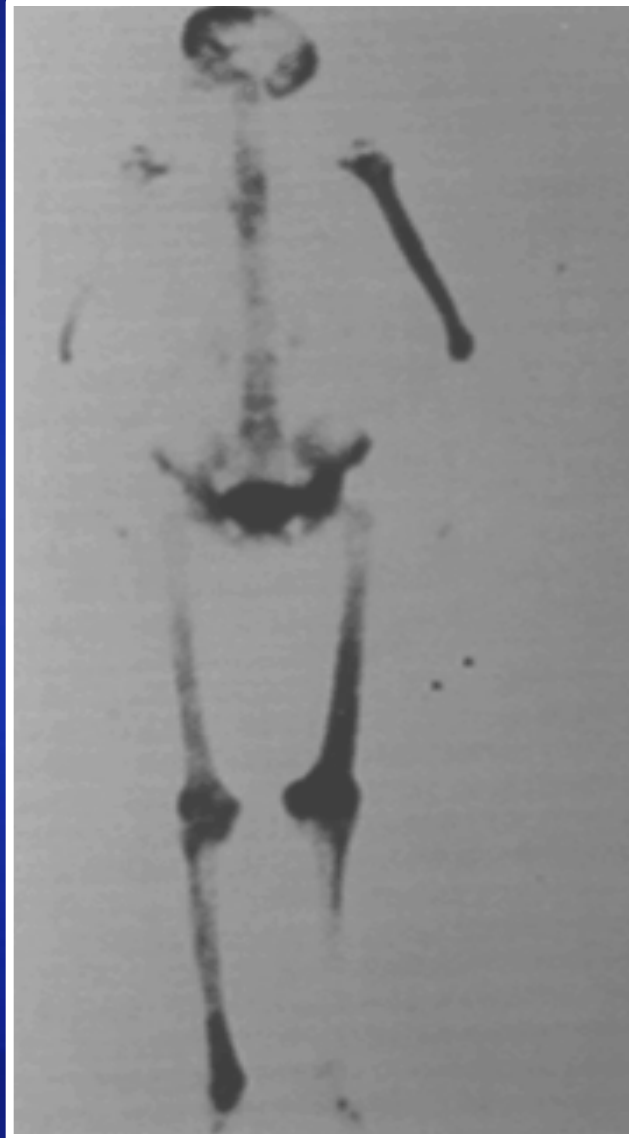


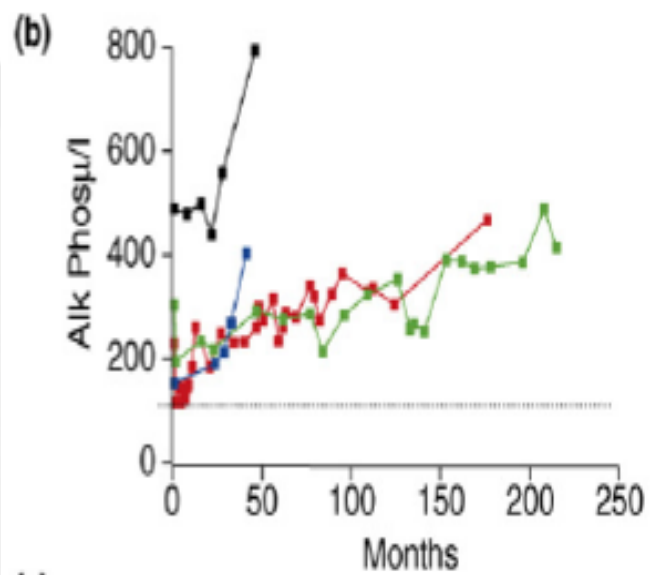
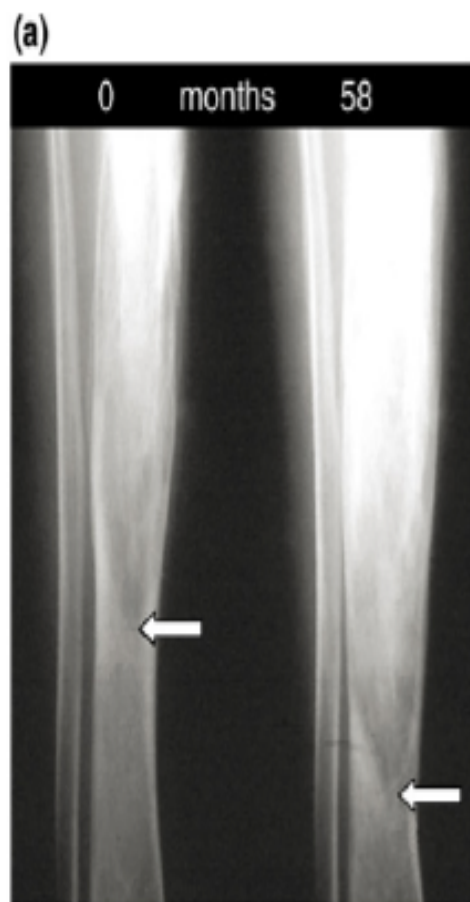
Pathology

Paget's Disease: "Picture Frame" Vertebral Body

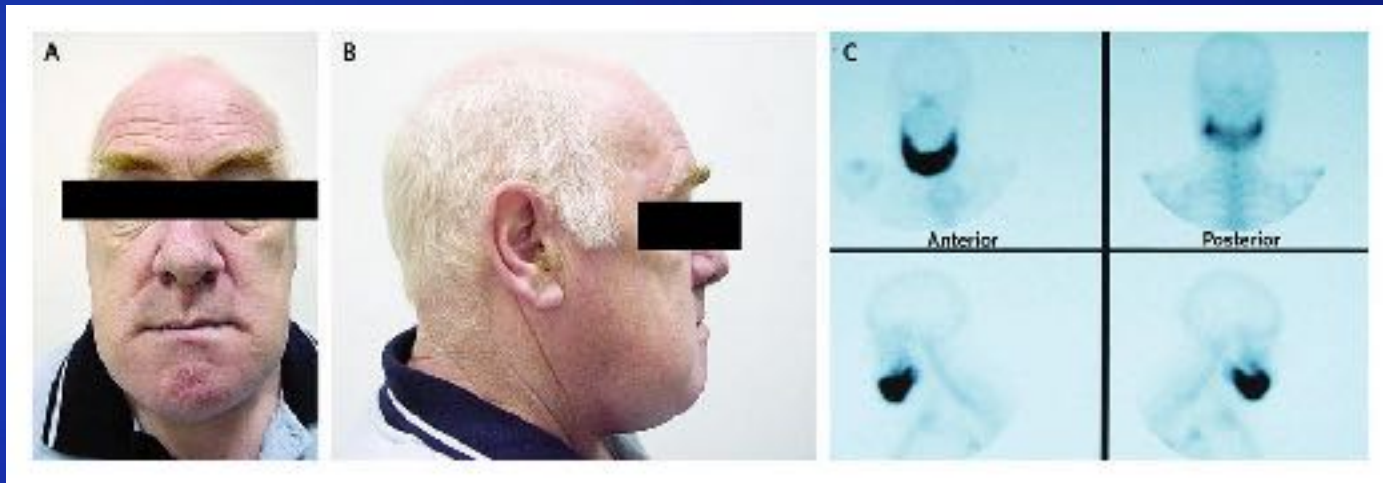


A Bone Scan Showing Polyostotic Disease





A 55-year-old man presented with a 2-year history of painful jaw enlargement and progressively ill-fitting dentures



Patel M and Bhalla A. N Engl J Med 2008;358:625



Panel: Complications of Paget's disease of bone

Common

- Bone pain
- Bone deformity
- Pathological fracture
- Osteoarthritis
- Deafness

Less common

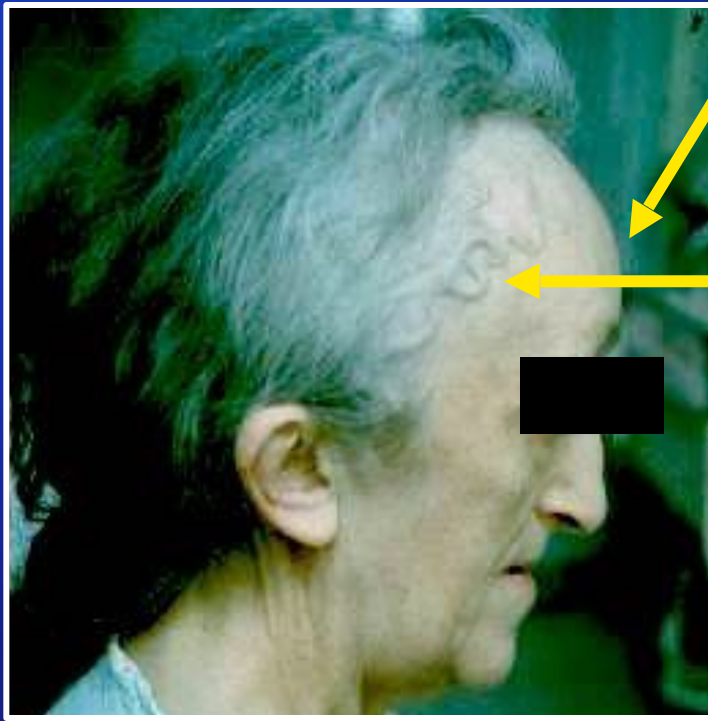
- Spinal stenosis
- Nerve compression syndromes

Rare

- Hypercalcaemia (with immobilisation)
- Hydrocephalus
- Paraplegia
- Cardiac failure
- Osteosarcoma

Paget's Disease in the Skull

**Skull
enlargement**



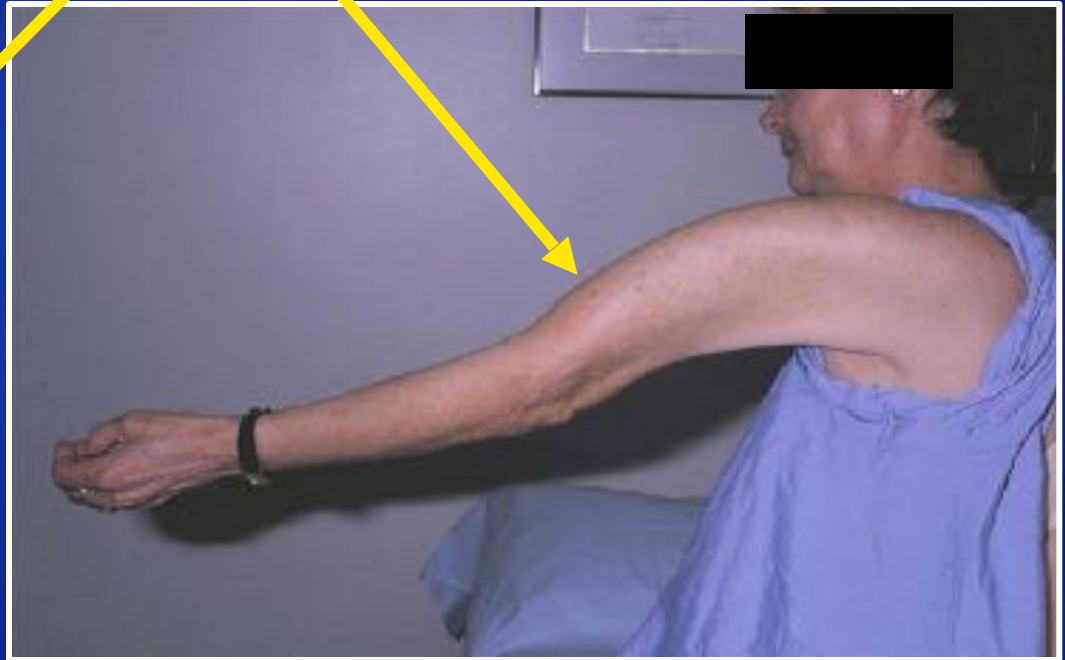
**Dilated
scalp
veins**



Skeletal Deformities: Bowling of Long Bones



**Bowing of
humerus**



Skeletal Deformities: Bowling of Lower Limbs

**Bowed
femurs**



**Bowed
tibias**

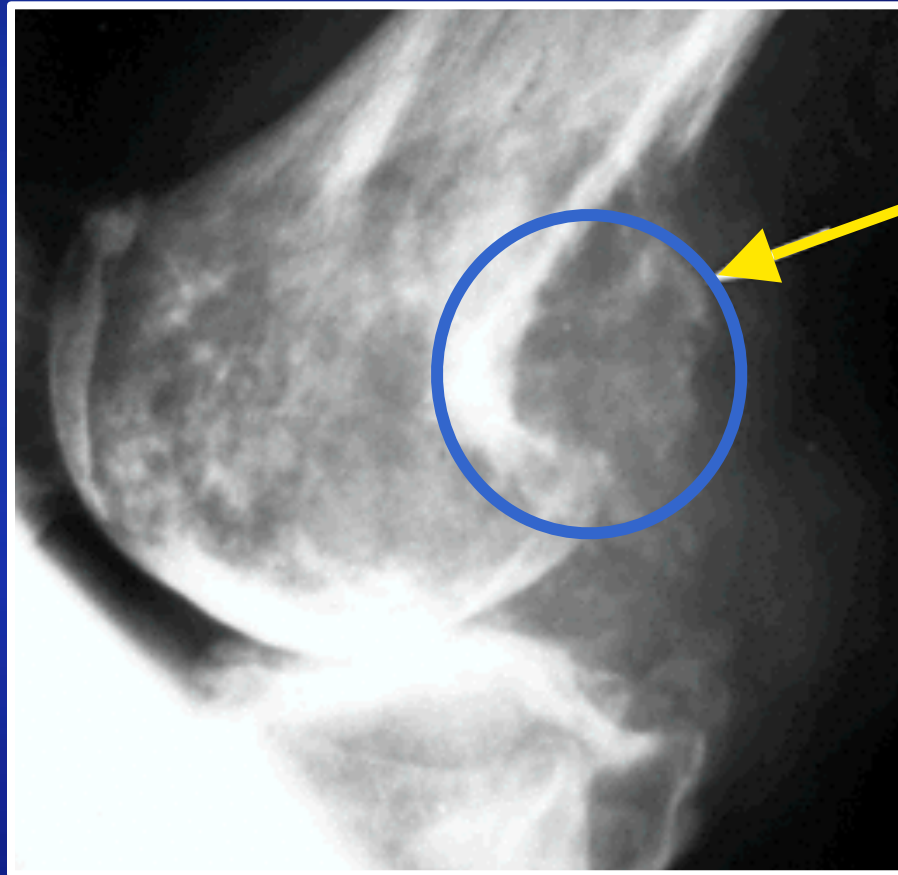


Complications of Paget's Disease: Complete (Chalk-Stick) Fracture in a Femur



Courtesy of Pierre Delmas, MD.

Complications of Paget's Disease: Osteosarcoma in Pagetic Femur



**Sarcomatous
degeneration**

Reproduced with permission from: N. Kelepouris. Clinical manifestations and diagnosis of Paget's disease of bone. In: Rose, BD (Ed), UpToDate (version 13.3), Waltham, MA 2006. Copyright © 2006 UpToDate, Inc.

Complications of Paget's Disease: Giant Cell Tumor of Scapula



Courtesy of F. Singer, MD

Managing Paget's Disease: Bisphosphonates and Other Treatment Strategies

- Bisphosphonates (gold standard of antipagetic therapy)¹⁻³
- Subcutaneous calcitonin (rarely used)^{1,2}
- Pain management
 - NSAIDs, COX-2 inhibitors, analgesics, opioids^{1,2}
- Surgery^{1,2}
 - Fractures, bone deformities, osteoarthritis

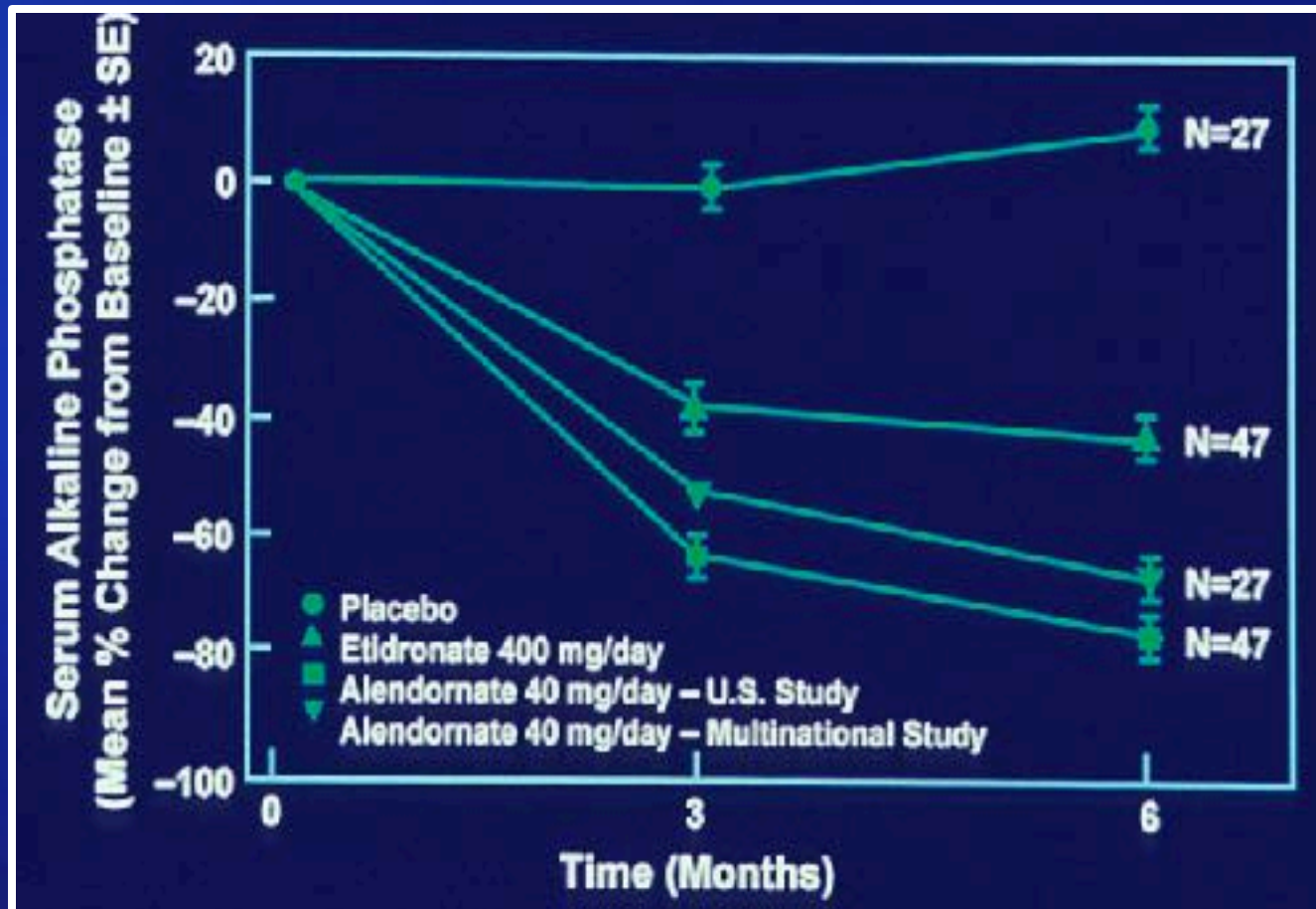
Indications for Treatment of Paget's Disease

- Bone pain
- Preparation for orthopedic surgery
- Fracture of pagetic bone
- Hypercalcemia and/or hypercalciuria
- Neurologic deficit associated with cranial or vertebral disease
- Presence of high-output congestive heart failure
- Prevention of future complications

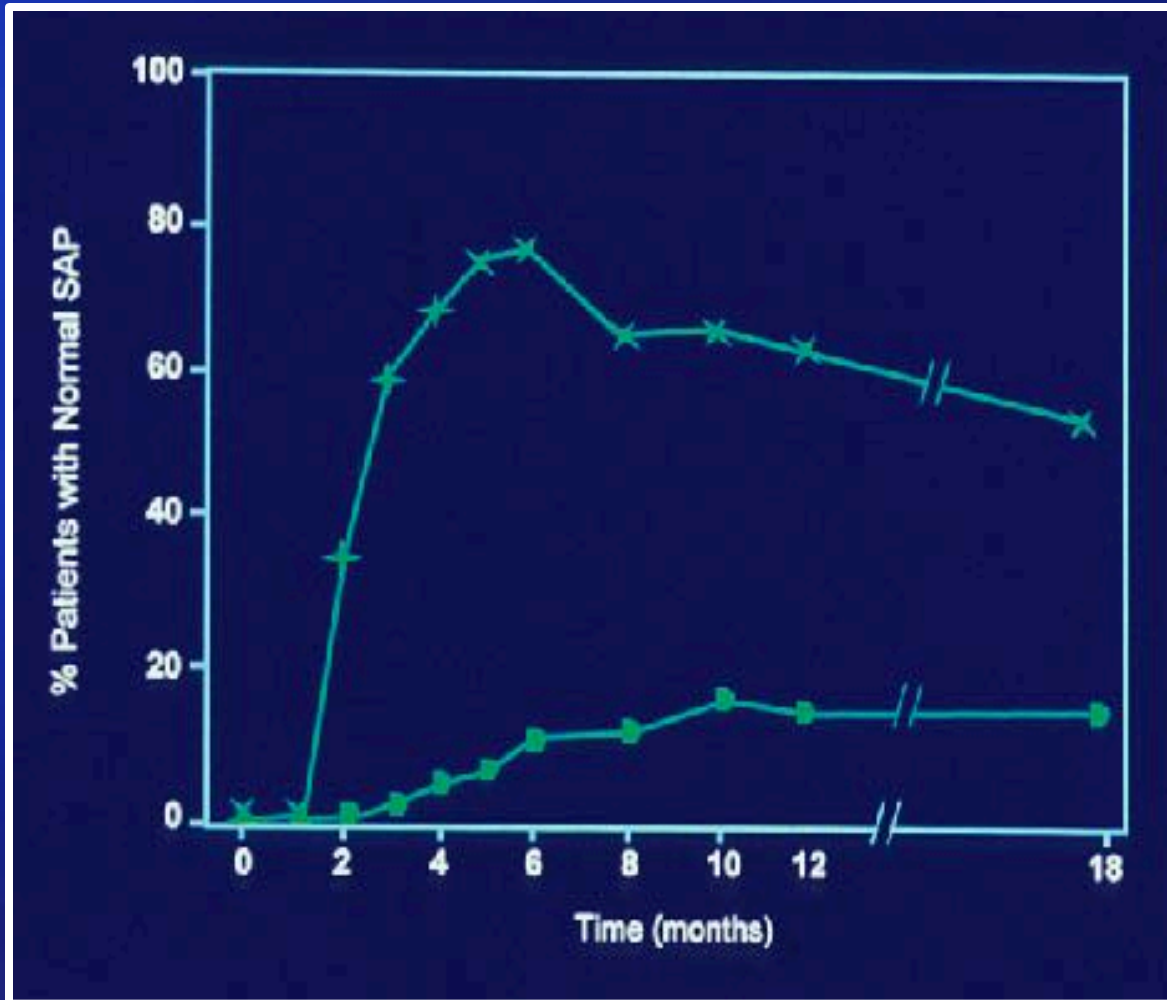
FDA-Approved Therapies and Dosing Regimens for Paget's Disease*

Agent	Dose	Duration of Therapy
Oral agents		
Didronel® (etidronate)	5 -10 mg/kg/d or 11-20 mg/kg/d	6 mo 3 mo
Skelid® (tiludronate)	400 mg/d	3 mo
Fosamax® (alendronate)	40 mg/d	6 mo
Actonel® (risedronate)	30 mg/d	2 mo
IV agents		
Aredia® (pamidronate)	30 mg/d	4 h on 3 cons. days
Reclast® (zoledronic acid)	5 mg	Single, 15 min. infusion

Effect on Serum Alkaline Phosphatase of Alendronate 40 mg/day Vs. Placebo or Etidronate 400mg/day



Biochemical Remission Induced by Risedronate Treatment



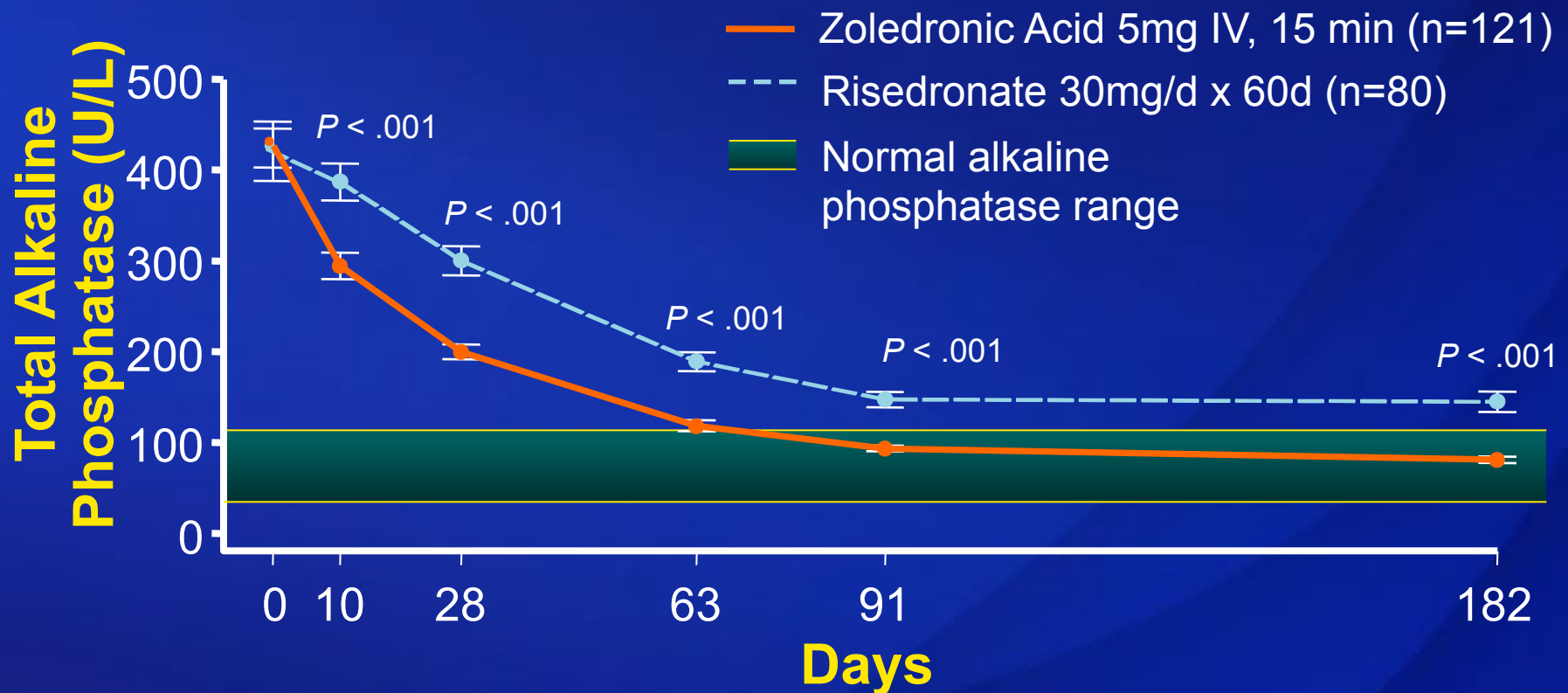
Risedronate 30 mg/day x 2 mos.



Etidronate 400 mg/day x 6 mos.

Zoledronic Acid Lowers Alkaline Phosphatase Levels More Than Risedronate

Mean (\pm SE) Total Alkaline Phosphatase by Visit

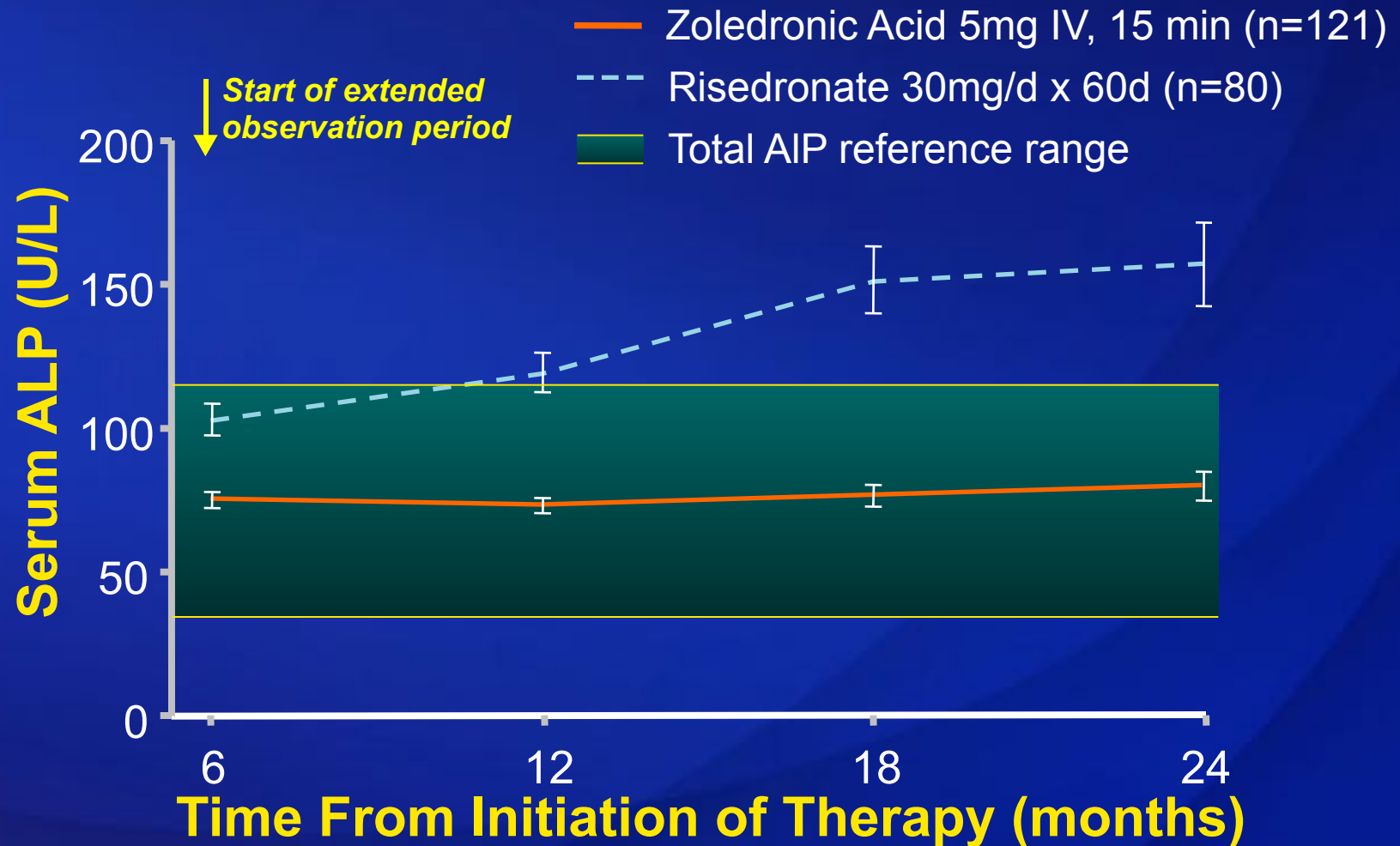


Reid IR, et al. *N Engl J Med*. 2005;353:898-908.

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Adapted with permission, 2007.

During Study Extension, Zoledronic Acid Maintained Mean Serum ALP Better Than Risedronate



Mean (\pm SE) of the absolute value and reference ranges are presented.
Adapted from Hosking D, et al. *J Bone Miner Res.* 2007;22:142-148.
With permission of the American Society for Bone and Mineral Research.

Adverse Events With Zoledronic Acid Comparable to Risedronate After Day 3

	Zoledronic Acid (n = 177)	Risedronate (n = 172)	
Adverse Eventst†	Patients, n (%)		P Value
Total with any AE	117 (66.1)	126 (73.3)	.16
Pain in arm or leg	13 (7.3)	12 (7.0)	.99
Arthralgia	9 (5.1)	19 (11.0)	.05
Dizziness	9 (5.1)	5 (2.9)	.41
Nasopharyngitis	9 (5.1)	14 (8.1)	.29
Diarrhea	8 (4.5)	9 (5.2)	.81
Headache	7 (4.0)	10 (5.8)	.46
Back pain	4 (2.3)	12 (7.0)	.04

Bisphosphonates

- Adverse effects
 - UGI intolerance, diarrhea (oral)
 - Acute phase reaction
 - Musculoskeletal/bone pain
 - Hypocalcemia
 - Renal failure reported with high dose intravenous bisphosphonates (obtain serum creatinine level before each dose of intravenous bisphosphonate)
 - Ocular inflammation (rare)
 - Osteonecrosis of jaw (ONJ) -rare
- Contraindications
 - Hypocalcemia
 - Vitamin D deficiency
 - Hypoparathyroidism
 - Severe renal insufficiency

Bisphosphonates, Vitamin D and Calcium

- Correct vitamin D deficiency before administering a bisphosphonate
- Instruct patients to take 1500 mg of calcium and 800 units of vitamin D (preferably vitamin D₃) daily during the 10 days after an infusion of zoledronic acid

Patient Follow-Up

Untreated Patients

- Annual serum total or bone specific alkaline phosphatase measurement
- Periodic x-rays of osteolytic lesions

Treated Patients

- Serum total or bone specific alkaline phosphatase measurement every 3-6 months
- Bone resorption markers are optional
- Periodic x-rays of osteolytic lesions

ΕΥΧΑΡΙΣΤΩ