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Metabolic Bone Disease

R. Grekin

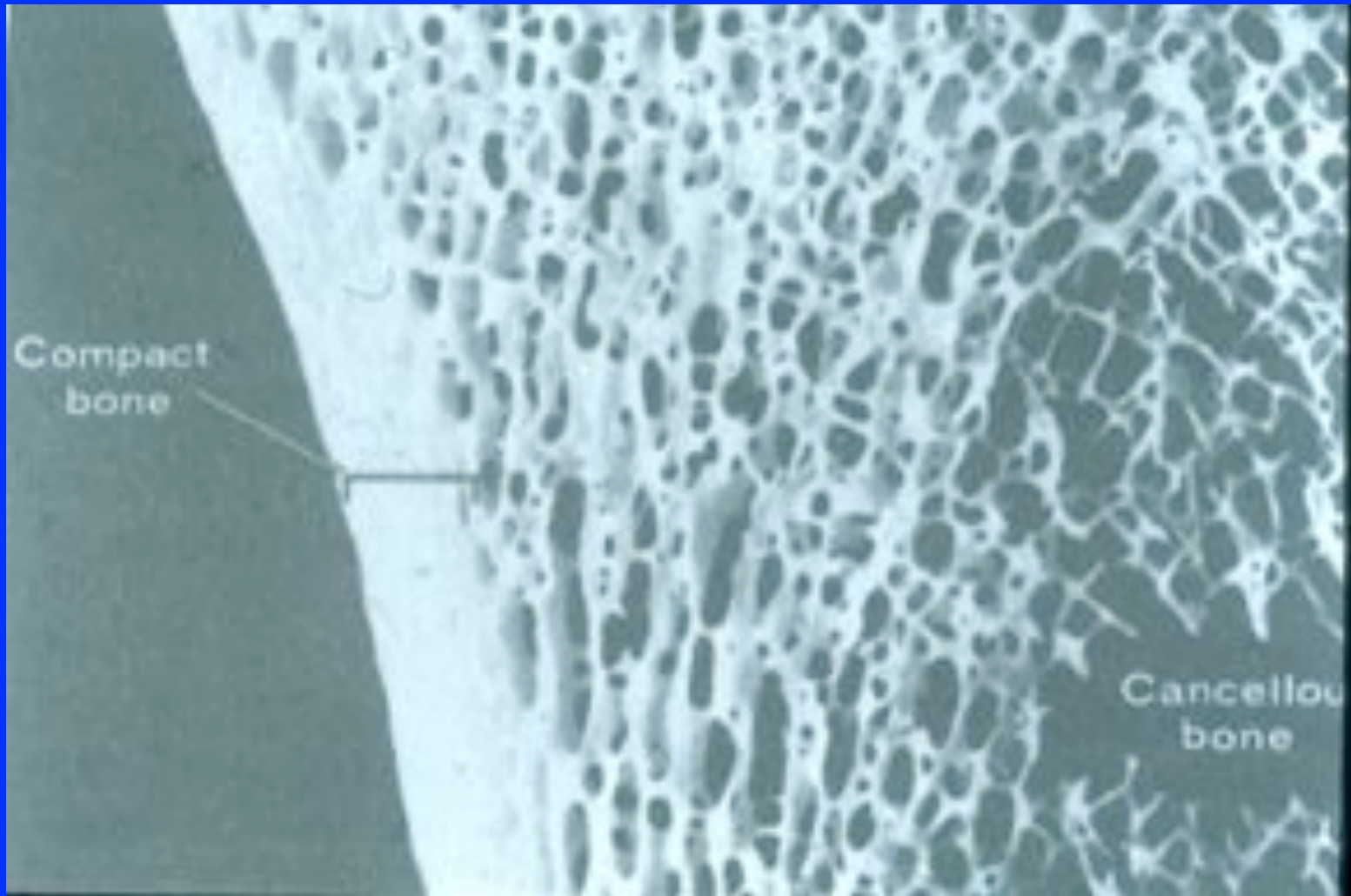
M2 Musculoskeletal

Fall 2008



BONE STRUCTURE

- **Extracellular matrix**
 - **Osteoid (type 1 collagen)**
 - **Mineral crystals**
- **Bone architecture**
 - **Cortical bone**
 - **Trabecular (cancellous) bone**

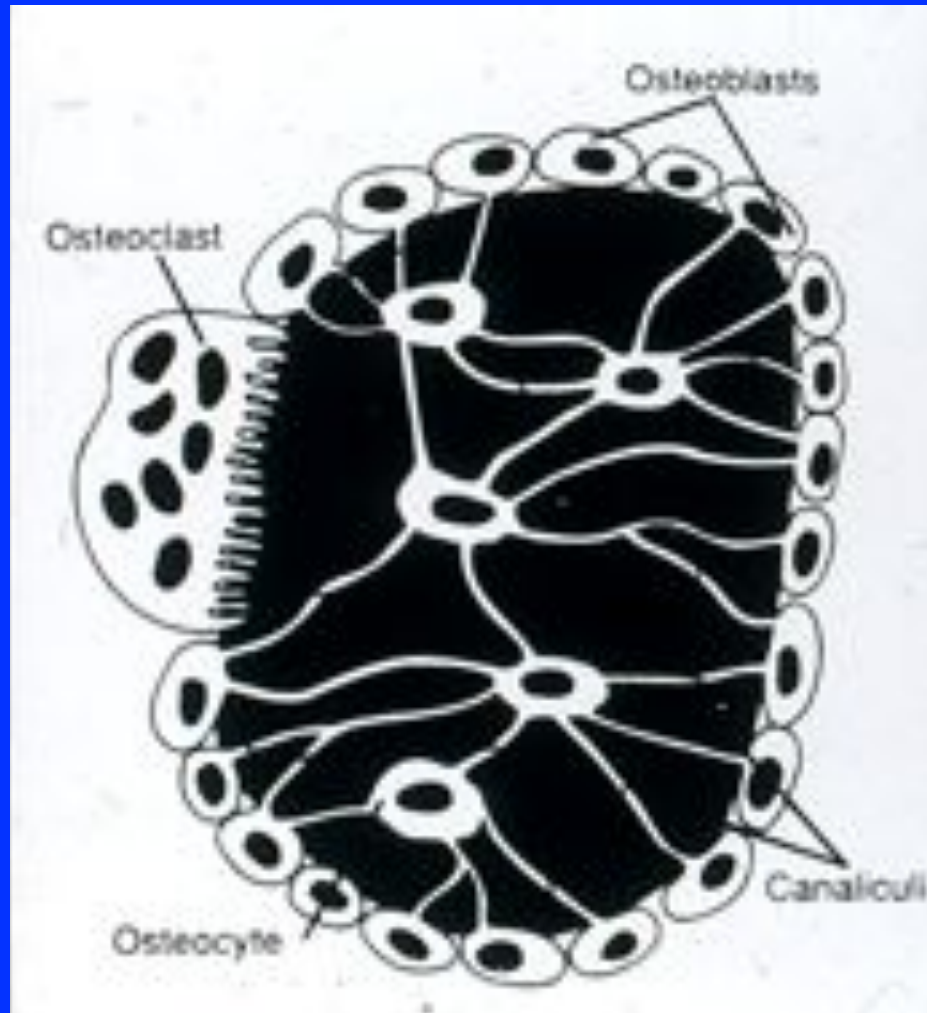


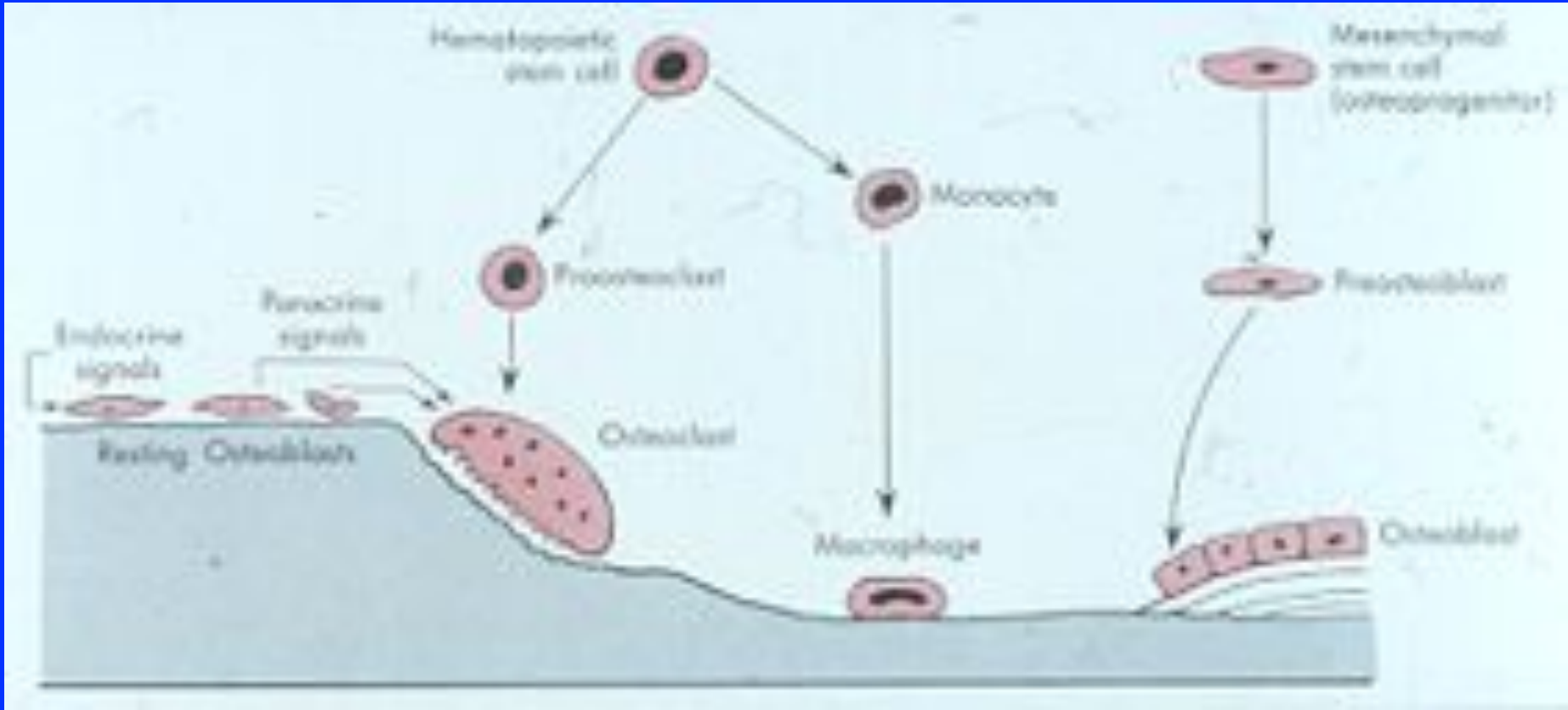
OSTEOBLASTS

- **Arise from connective tissue progenitors**
- **Produce extracellular matrix proteins: type 1 collagen and osteocalcin**
- **Responsible for mineralization: alkaline phosphatase**
- **Stimulated by growth factors: TGF- β , IGF-1**

OSTEOCLASTS

- **Multinuclear cells arising from hematopoietic precursors**
- **Contact with bone at ruffled border: acid environment and lysosomal enzymes**
- **Activity stimulated by IL-1, IL-6 and TNF**





BONE REMODELING

- **Begins with osteoclastic activity (7-10 days)**
- **Followed by osteoblastic bone reformation (3 months)**
- **Mechanical loading is an important stimulus**
- **Immobilization increases resorption and blocks formation**

Normal Bone Remodelling



Resorption



Reversal



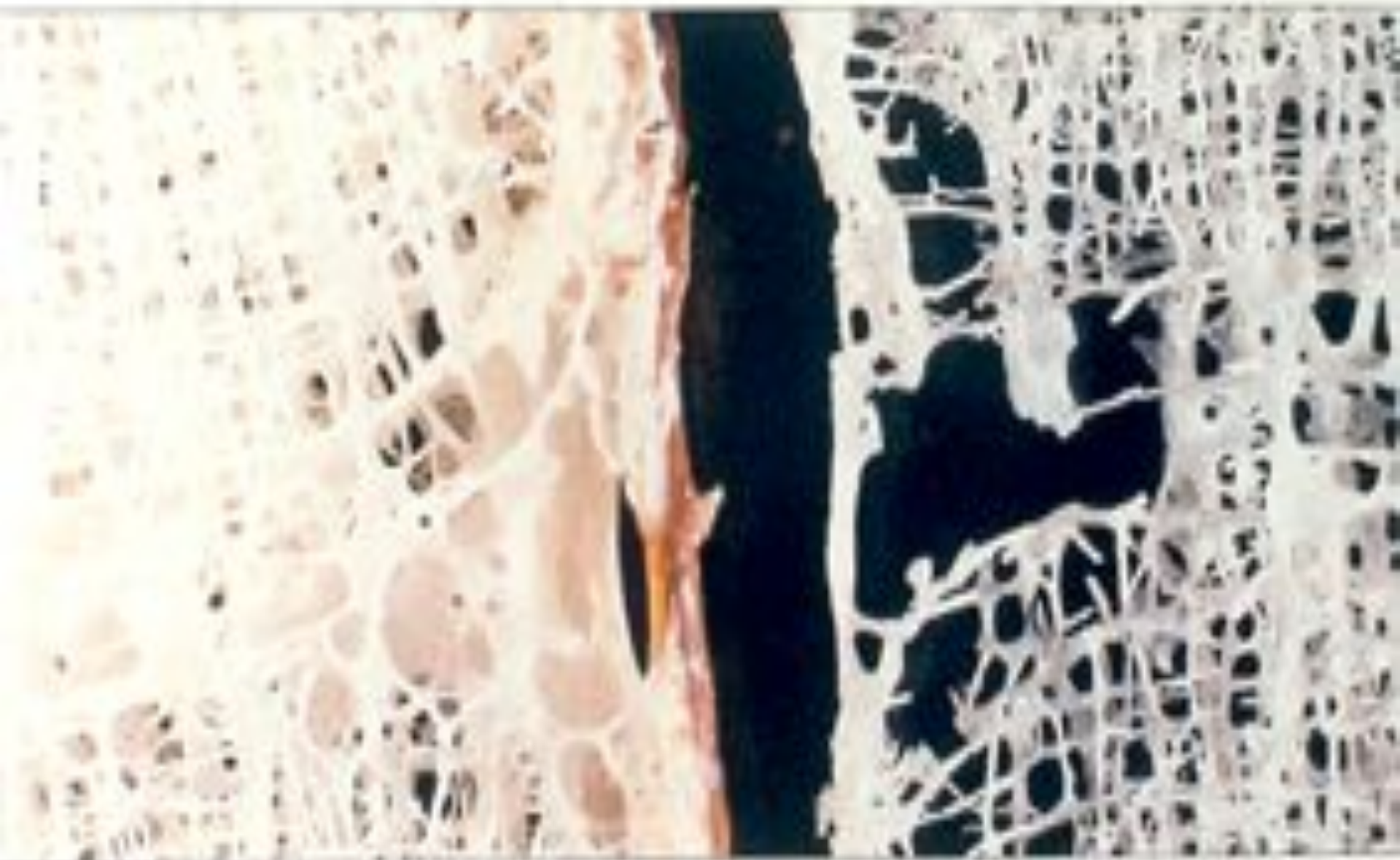
Formation



Resting

OSTEOPOROSIS

The clinical syndrome caused by a decrease in bone mass. The remaining bone is histologically normal



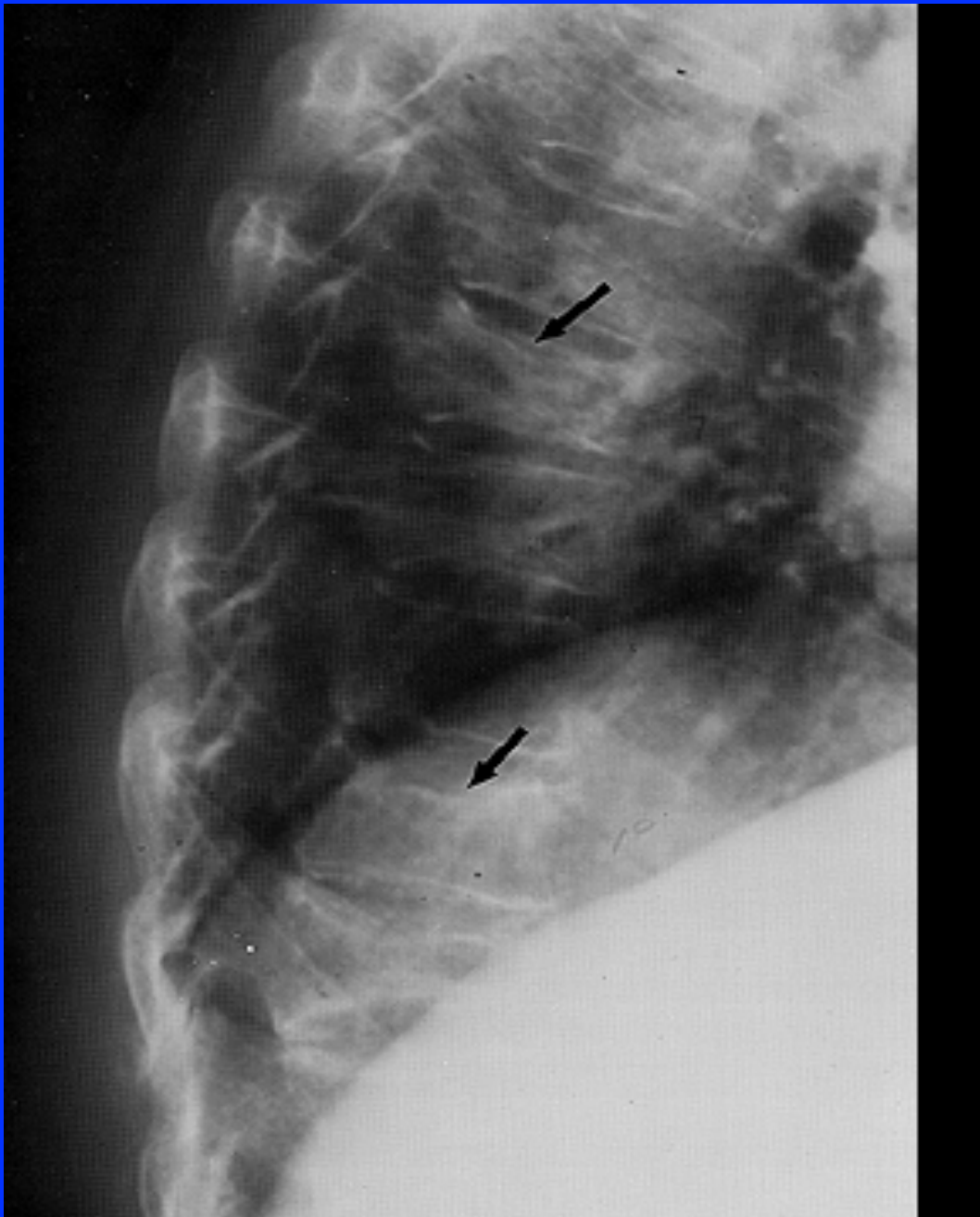
OSTEOPOROSIS: ETIOLOGY

- **Positive family history, thin body habitus, poor nutrition, Caucasian and Asian race, fair skin and cigarette smoking all predict increased risk**
- **Glucocorticoids decrease bone formation and induce hypogonadism**

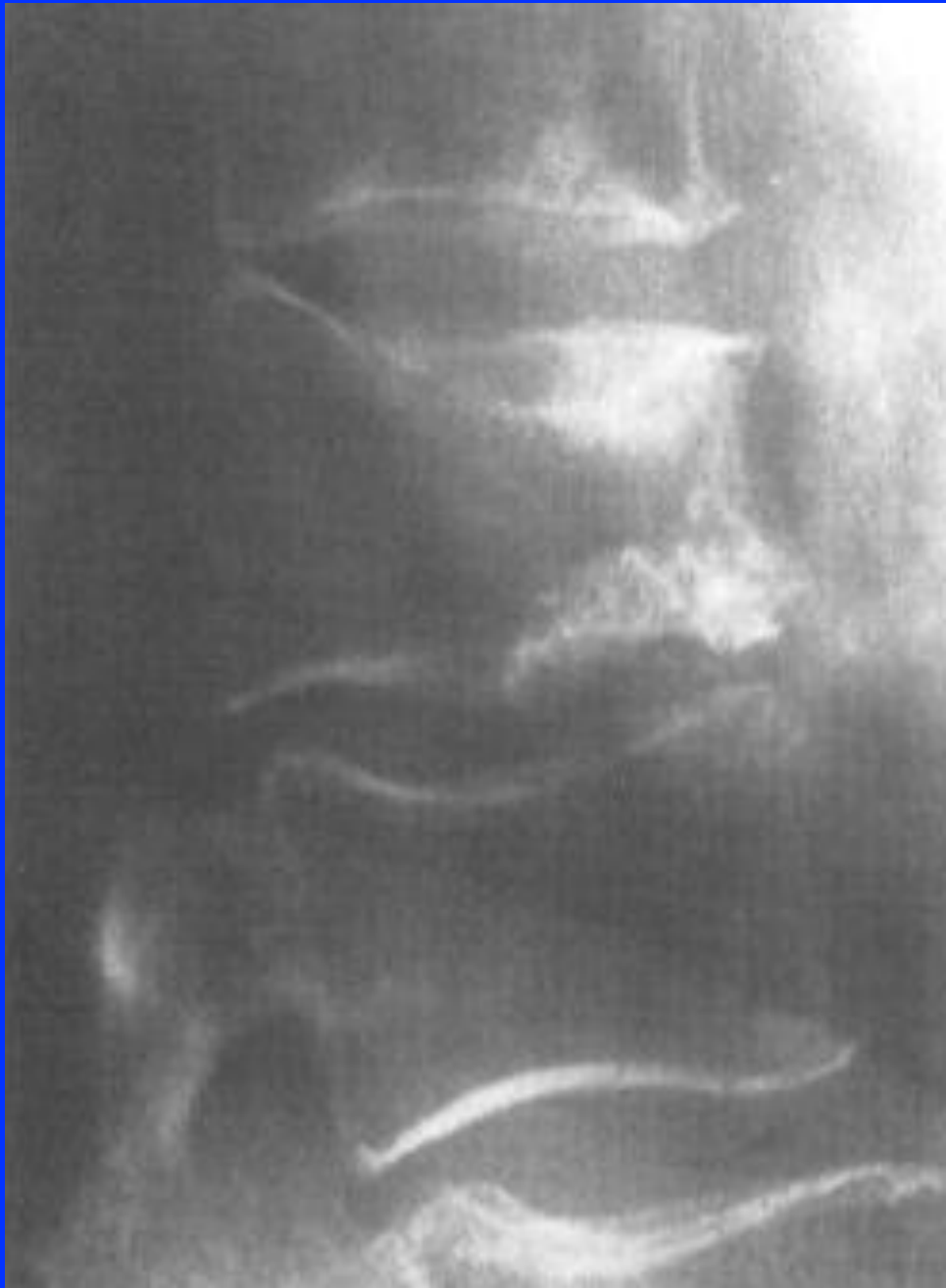
OSTEOPOROSIS: CLINICAL MANIFESTATIONS

- **Early osteoporosis is asymptomatic**
- **As skeletal integrity declines, fractures occur, often with minimal trauma**
- **Vertebral compression fractures are most common, hip and wrist fractures also are major problems**
- **End stage disease associated with marked dorsal kyphosis**

**Osteoporosis: A Significant Public Health Problem
Onset and Advanced Osteoporotic Patients**







OSTEOPOROSIS: INCIDENCE

- **40% of 50 year old Caucasian and Asian women will have an osteoporotic fracture during their lifetime**
- **13% of men and Black women will have such a fracture**
- **1/3 of these fractures will be hip fractures, a condition associated with 5-20% mortality**

OSTEOPOROSIS: DIAGNOSIS

- **Plain films provide very poor assessment of bone density**
- **Density best measured with bone densitometry (DEXA) measurements**
- **Criteria for diagnosis is bone density more than 2.5 standard deviations below the mean for young normals**

BONE MARKERS

- **Osteoblast:** Alkaline phosphatase and osteocalcin
- **Osteoclast:** Pyridinoline crosslinks and N-telopeptide

CAUSES OF OSTEOPENIA

- **Hypogonadism, both in men and women**
- **Cushing's syndrome**
- **Hyperparathyroidism**
- **Hyperthyroidism**
- **Osteomalacia**
- **Multiple myeloma**

OSTEOPOROSIS: PREVENTION

- **Adequate calcium intake in susceptible individuals**
- **Avoid hypogonadism**
- **Weight bearing exercise**

OSTEOPOROSIS: TREATMENT

- **Fall prevention**
- **Calcium supplementation**
- **Vitamin D**

OSTEOPOROSIS: TREATMENT

- **Gonadal steroid replacement**
 - **Major, well established effects to decrease osteoclastic activity**
 - **Long term therapy increases bone mass and decreases fracture risk**

OSTEOPOROSIS: TREATMENT

- **Raloxifene**
 - **Selective estrogen receptor modulator**
 - **Increases bone density and decreases fracture risk**
 - **Probably not as potent as estrogen**

OSTEOPOROSIS: TREATMENT

- **Raloxifene**
 - **No trophic effect on breast or uterus**
 - **May cause or worsen hot flashes**
 - **Increased risk of thromboembolic disease**

OSTEOPOROSIS: TREATMENT

- **Bisphosphonates: Alendronate, Risedronate, Ibandronate and Zoledronic Acid**
 - **Potent inhibitors of osteoclast activity**
 - **Promote significant increase in bone density and decrease fracture risk by about 50%**
 - **Rare instances of erosive esophagitis and gastritis**
 - **Osteonecrosis of the mandible**

OSTEOPOROSIS: TREATMENT

- **Calcitonin**
 - Available as a nasal spray
 - Slows bone loss, usually does not restore bone
 - May provide pain control for acute fracture
 - occasional nausea, vomiting, flushing

OSTEOPOROSIS: TREATMENT

- **Parathyroid hormone (Teriparatide)**
 - **Potent stimulator of osteoblast activity**
 - **Increases bone mass up to 13%**
 - **Reduces fracture risk by about 50%**
 - **Given as a single daily injection**
 - **Low incidence of side effects, hypercalcemia, nausea**

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- **Adequate calcium and vitamin D**
- **Gonadal steroid replacement**
- **Bisphosphonates**

OSTEOMALACIA and RICKETS

**Clinical syndromes that result from
inadequate bone mineralization**

OSTEOMALACIA: ETIOLOGY

- **Vitamin D deficiency or resistance**
 - **Inadequate intake and sunlight**
 - **Malabsorption**
 - **Severe liver disease**
 - **Renal failure**
 - **Hereditary syndromes**

OSTEOMALACIA: ETIOLOGY

- **Phosphate deficiency**
 - **Renal tubular disorders**
 - **Tumor associated osteomalacia**
 - **X-linked hypophosphatemia**
 - **Phosphate binders**

OSTEOMALACIA: ETIOLOGY

- **Inhibitors of mineralization**
 - **Aluminum**
 - **Fluoride**

VITAMIN D DEFICIENCY

- **Vitamin D deficiency leads to decreased absorption of calcium by the GI tract.**
- **As serum calcium starts to fall, secondary hyperparathyroidism occurs.**

VITAMIN D DEFICIENCY

- **Elevated Pth levels may maintain serum calcium in the normal range, but at the cost of phosphaturia, hypophosphatemia and increased bone reabsorption**
- **Low serum phosphate results in inadequate bone mineralization and osteopenia.**

VITAMIN D DEFICIENCY

- In severe cases, secondary hyperparathyroidism is not adequate to maintain serum calcium levels, and hypocalcemia occurs.

OSTEOMALACIA: CLINICAL MANIFESTATIONS

- **Bone pain and pathologic fractures**
- **Decreased bone density**
- **Hypophosphatemia, increased alkaline phosphatase, and increased PTH**

OSTEOMALACIA: CLINICAL MANIFESTATIONS

- **Late hypocalcemia**
- **Pseudofractures**
- **In children, bowing of the legs and rachitic rosary, short stature**

OSTEOMALACIA: DIAGNOSIS

- **Low levels of 25-hydroxyvitamin D**
- **Elevated parathyroid hormone and alkaline phosphatase**
- **Bone biopsy**

OSTEOMALACIA: EVALUATION

- **Careful diet and sunlight history**
- **Renal function**
- **Fecal fat determination**
- **Anti IgA tissue transglutaminase antibodies. Small bowel biopsy**



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PAGET' S DISEASE OF BONE

- **Common disorder of increased bone turnover**
- **Etiology unknown**
- **Increased bone resorption with compensatory increased bone formation leads to thick, abnormal bones**

PAGET' S DISEASE: CLINICAL MANIFESTATIONS

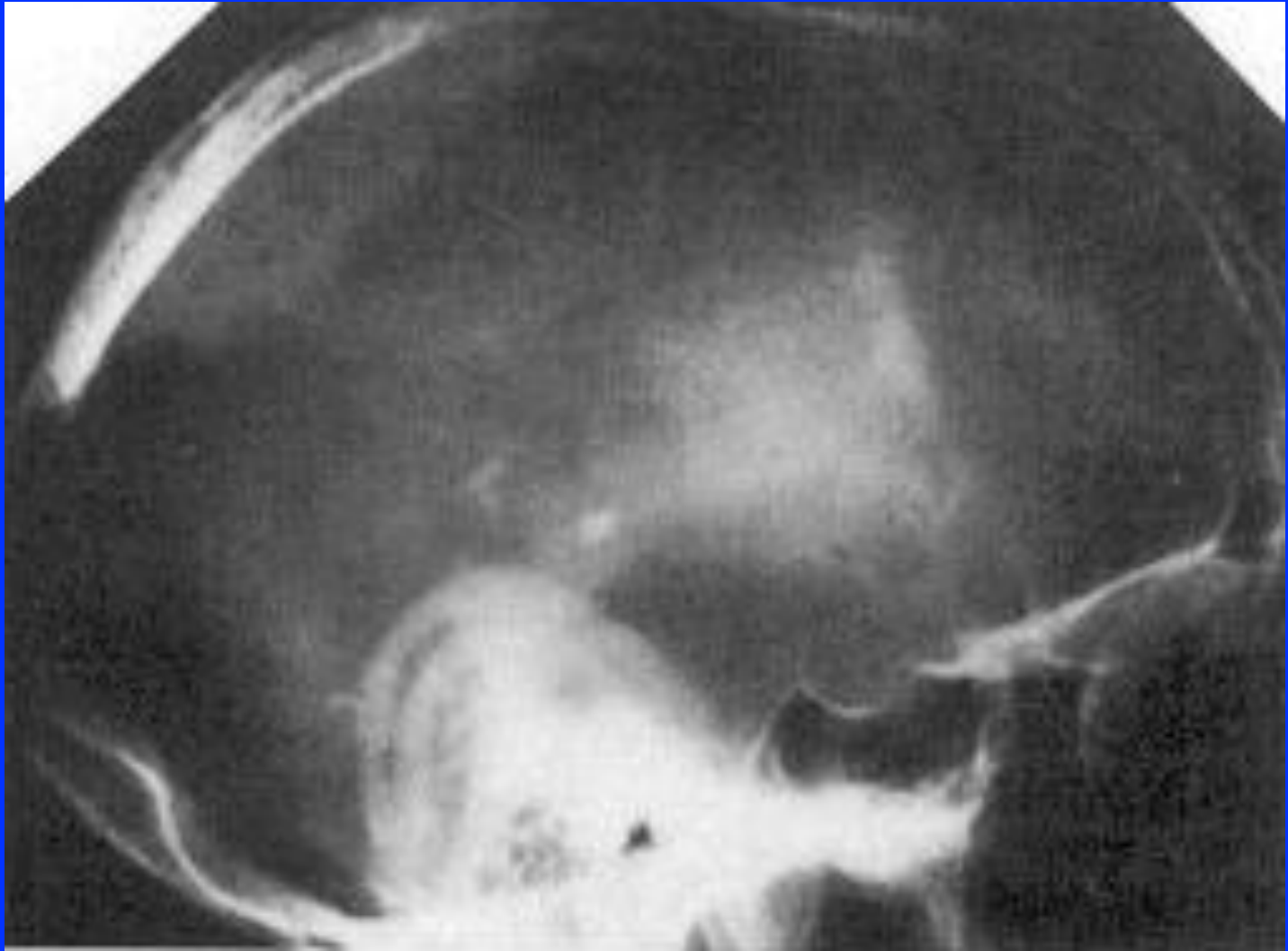
- **Many patients asymptomatic**
- **Bone pain and deformity**
- **Fractures**
- **Arthritis**
- **Nerve compression**
- **Osteogenic sarcoma**

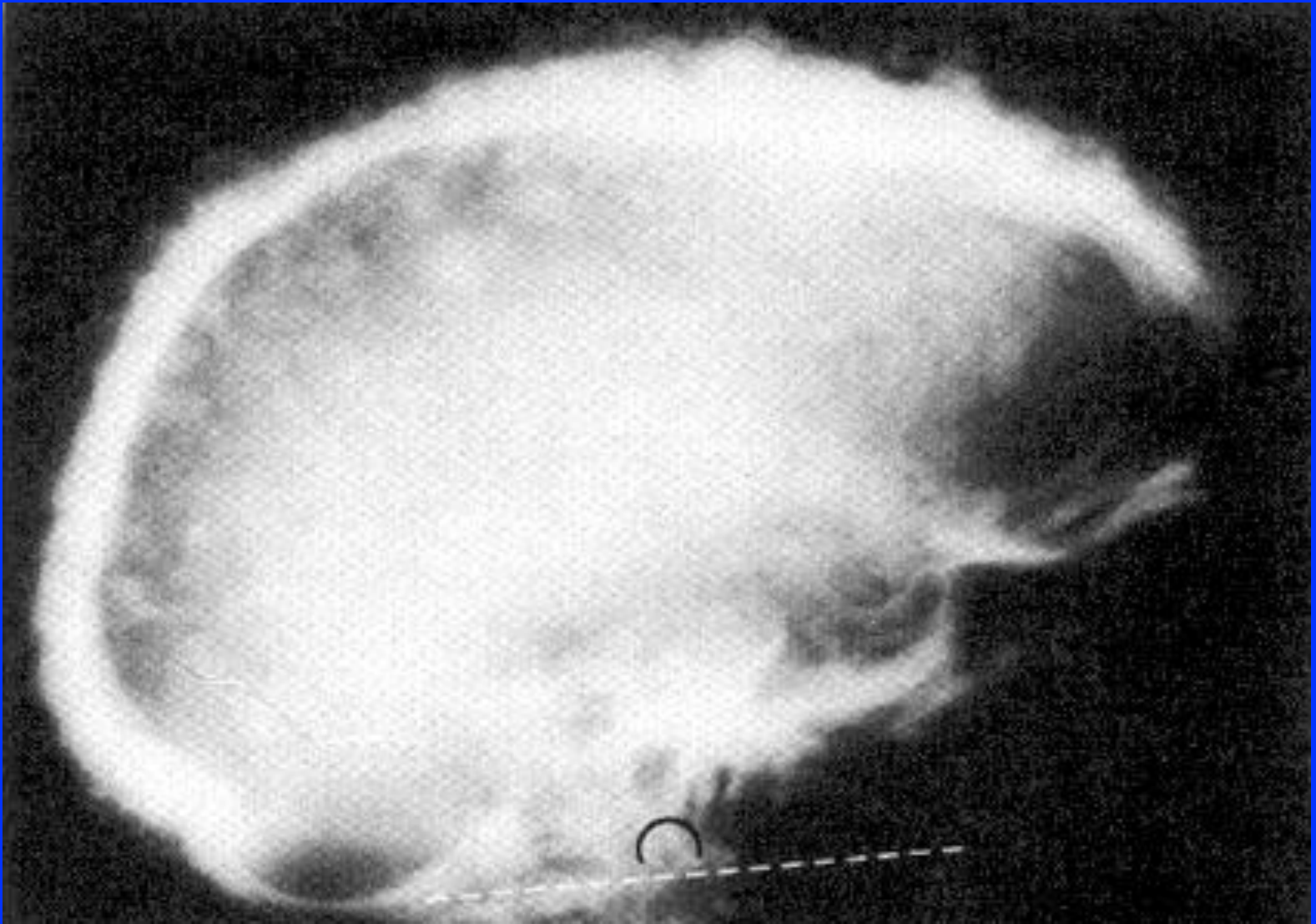
PAGET' S DISEASE: DIAGNOSIS

- **Increased alkaline phosphatase**
- **Characteristic radiographic appearance**
- **Bone scan to determine extent of disease**

PAGET' S DISEASE: TREATMENT

- **Only indicated for symptoms or high fracture risk**
- **Bisphosphonates are often helpful**
- **Calcitonin is also of value, but not as effective as bisphosphonates**





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