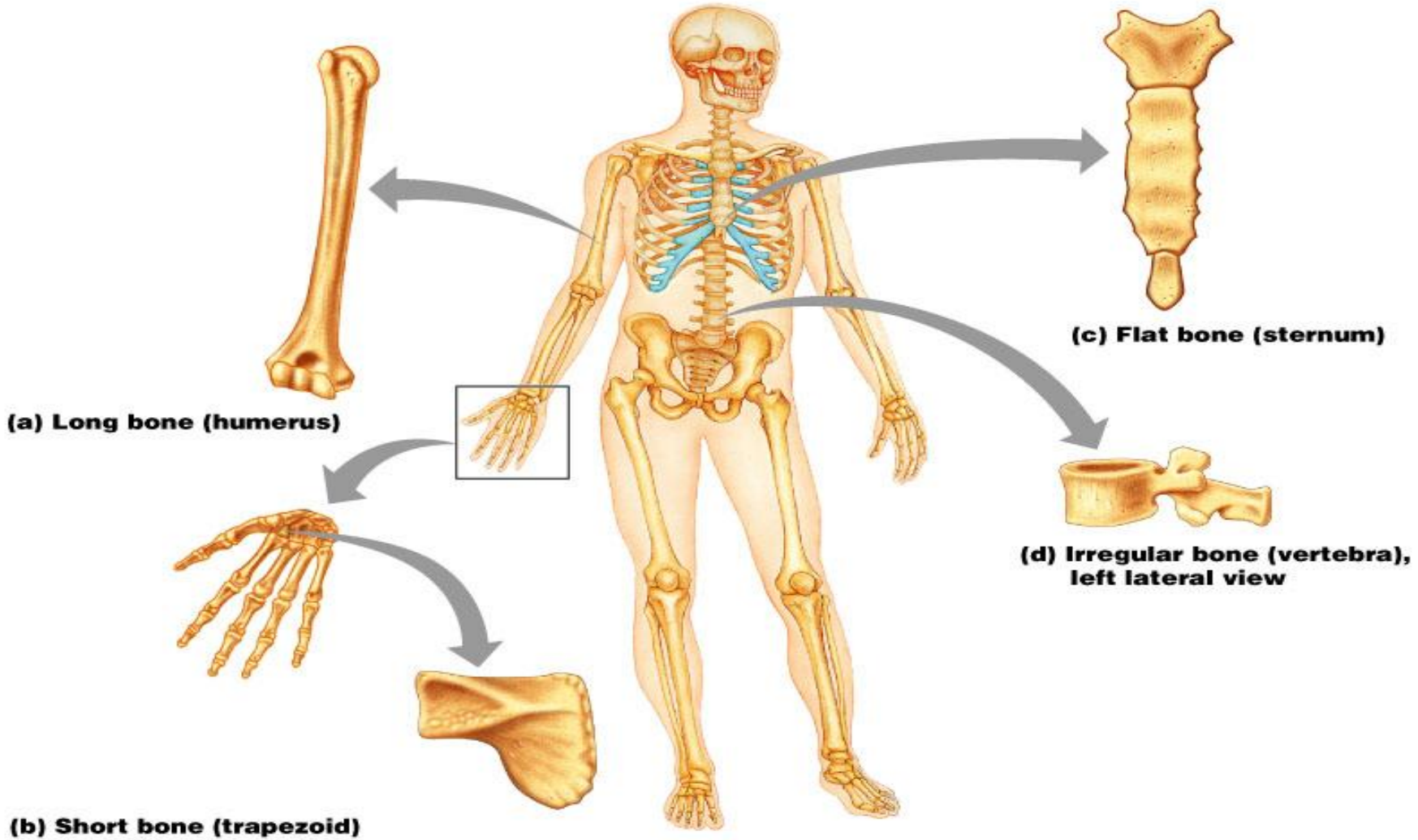
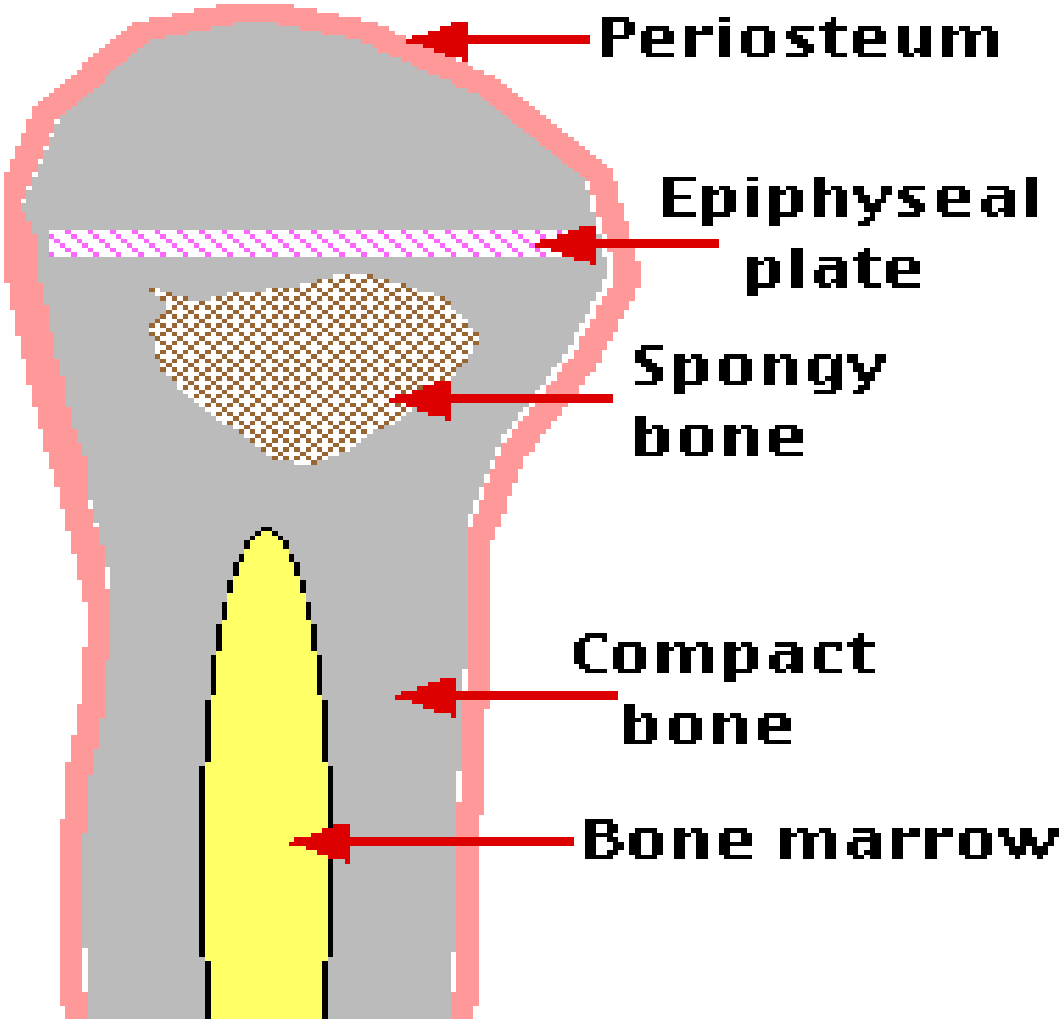
Metabolic Bone Diseases

Abdulmoein Eid Al-Agha, MBBS, DCH, FRCPCH
Professor of Pediatric Endocrinology, King Abdulaziz University Hospital, Pediatric Department
Website: http://aagha.kau.edu.sa

CLASSIFICATION OF BONE



Bone Structure



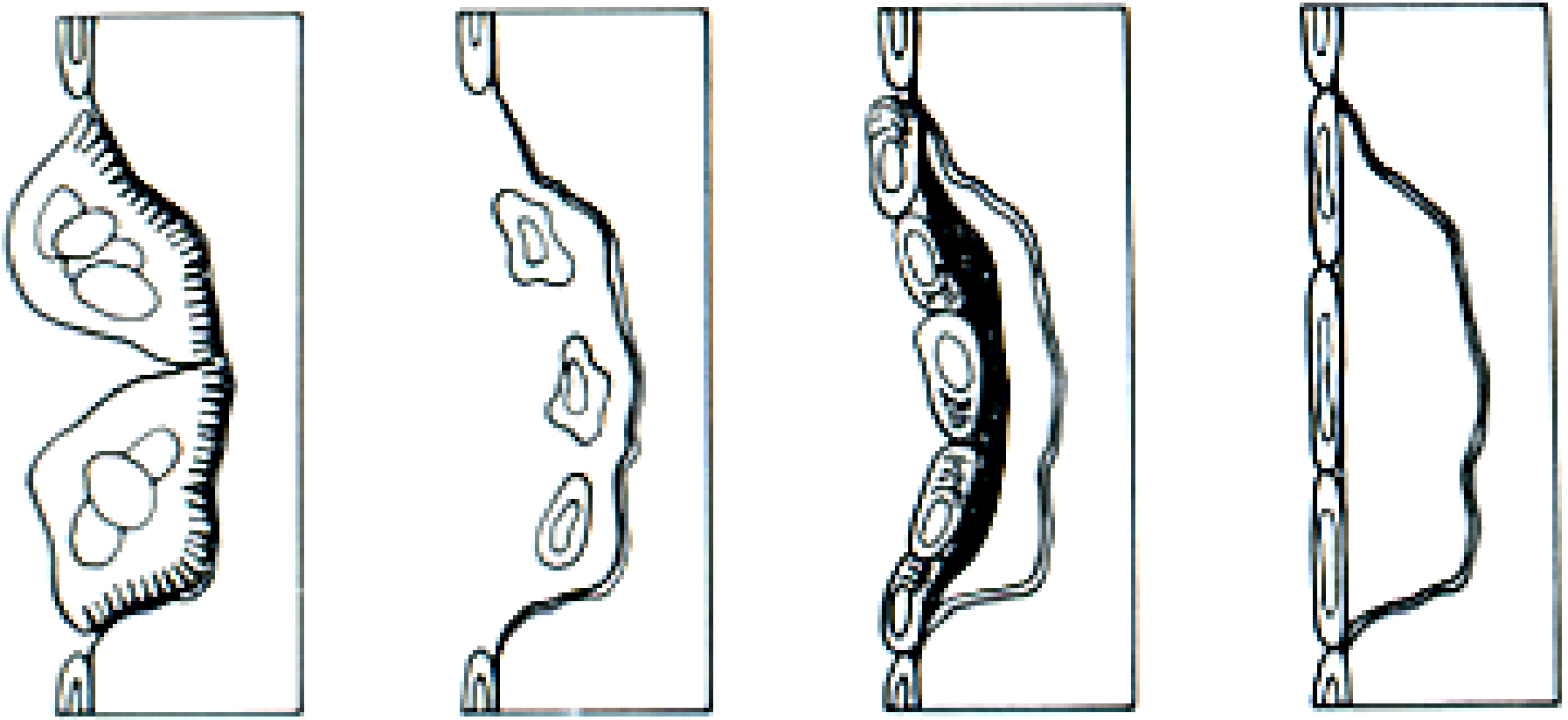
Components of bone

- Calcified matrix (90%)
  - composed of collagen fibers (type-1),
  - Glycosaaminoglycan containing spindle shaped crystals of hydroxyapatite
- Mineral Element
  - Crystals of Calcium and Phosphate are arranged either amorphously or as Hydroxyapatite Ca_{10} $(PO4)_6$ $(OH)_2$ on or within the collagen fibers.
  - Na, Zn, Mg, Cu and fluoride
- Non Collagenous Components (Proteins)
  - Osteocalcin: protein produced by the Osteoblasts
  - α2 HS- glycoprotein: produced by the liver and absorbed by the bone matrix
  - Amino Acids: about one fourth of amino acids present in collagen are proline and hydroxproline.

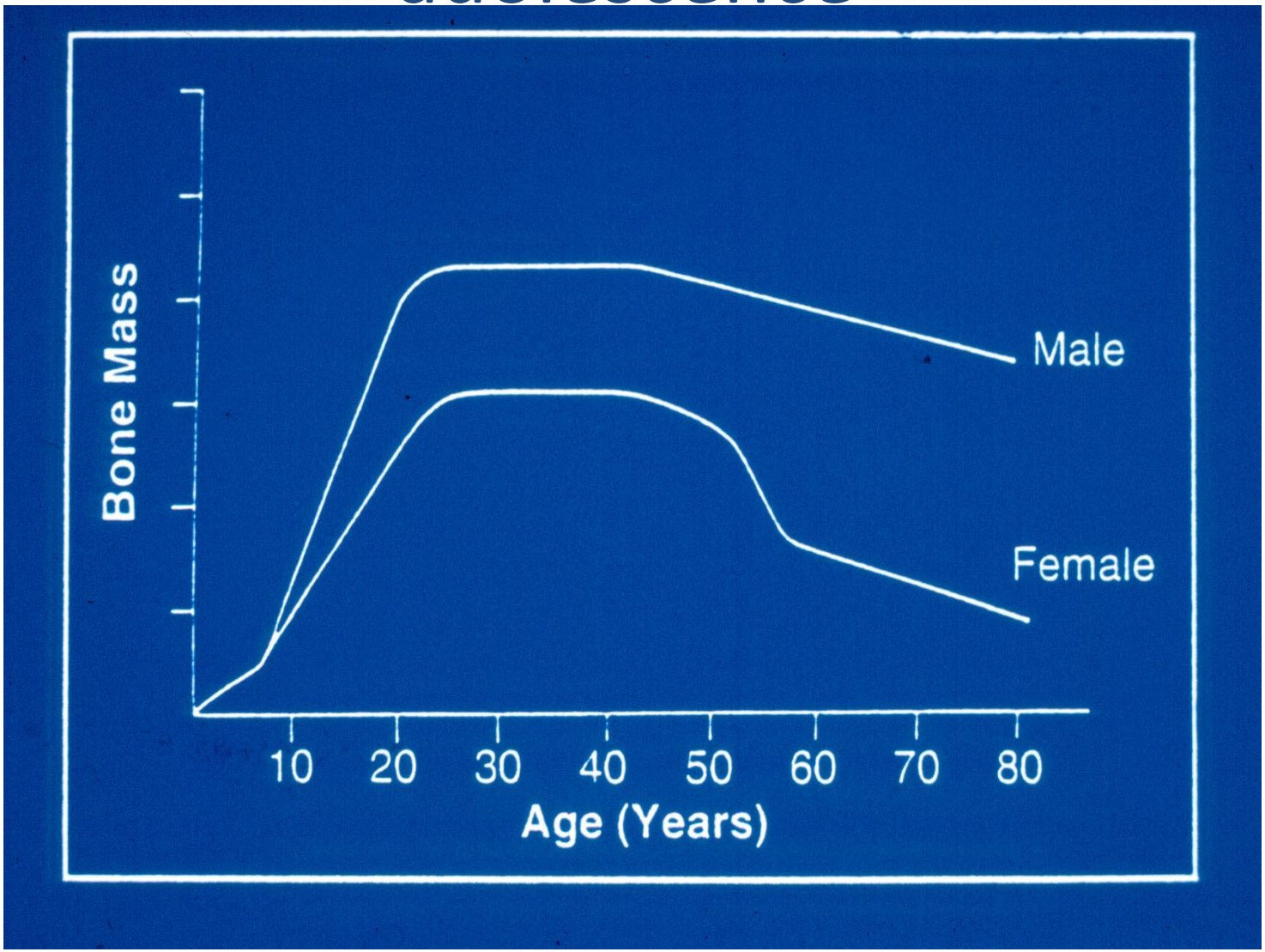
Skeleton is solid but dynamic!

- Skeleton is not static structure, but in continuous " modeling - remodeling process"
- Bone is continually remodeled throughout life because bones sustain recurring micro-trauma
- The hallmark of Rickets/ Osteomalacia is decreased bone mineralization (calcium/phosphate or both)
- The hallmark of osteoporosis is reduction in skeletal mass caused by imbalance between bone resorption & bone formation

Normal Bone Remodelling



Peak bone mass: accrued during adolescence



Determinants of Bone Mass

Extrinsic

- Diet
- Body mass/habitus
- Hormonal milieu
- Illnesses
- Exercise
- Lifestyle choices

Intrinsic

- Gender
- Family History
- Ethnicity
- Genetic factors

Calcium

- 99% of calcium in the body is stored in the bone
- 1% circulates in the blood
  - 45% circulates as free Ca ions
  - 40% bound to albumin
  - 15% bound to anions
- Corrected [Ca] = measured [Ca] + 0.02 ^{x} (40 – [albumin])
- Both total calcium & ionized calcium measurements are available in most of the biochemistry laboratory
- Ionized calcium is usually a more sensitive and specific for calcium disorders

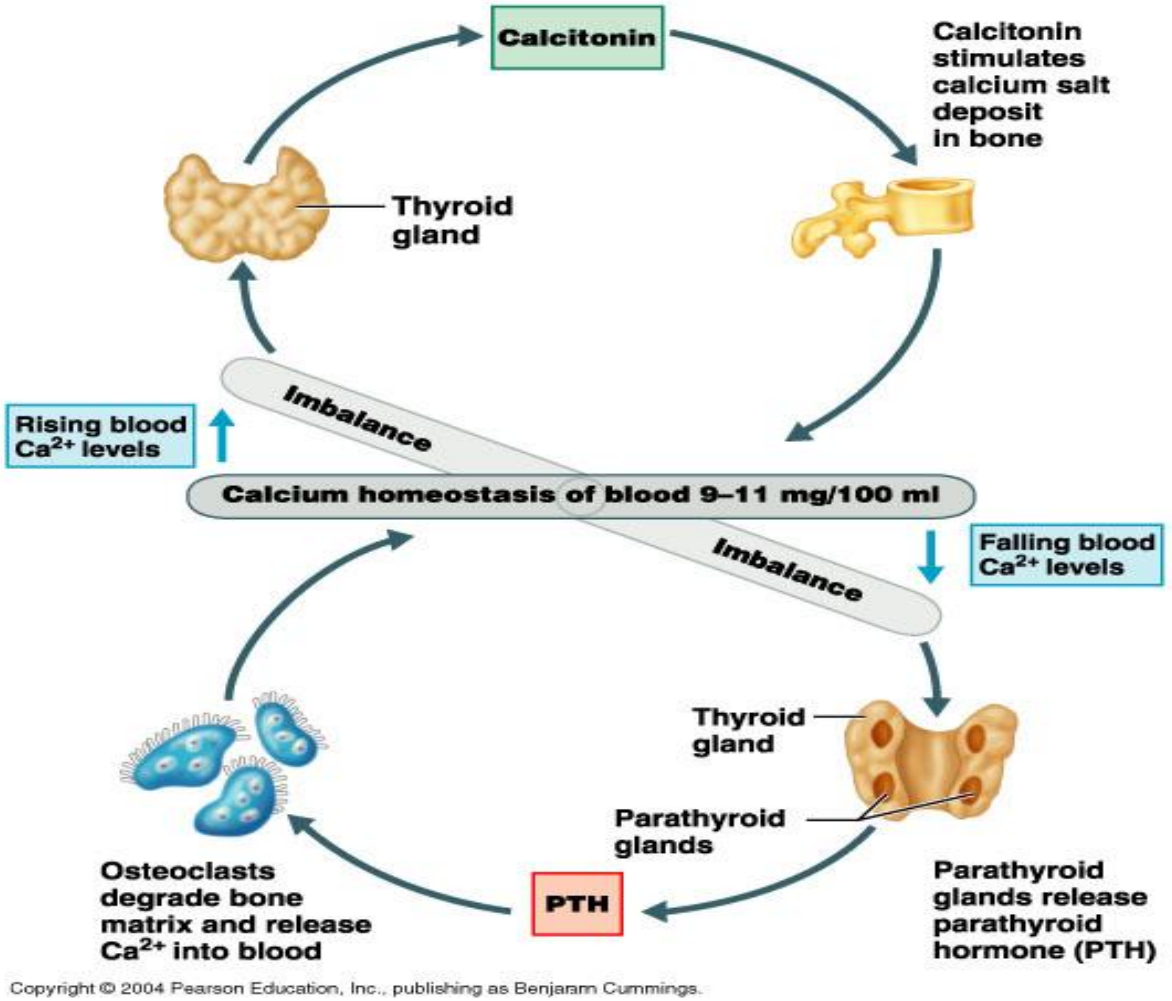
Calcium

- Active absorption in the duodenum & passive diffusion in the jejunum
- 98% reabsorption in the kidney
- Important for:
  - Bone mineralization
  - Blood coagulation
  - muscle contraction
  - Affecting enzyme activity
  - Affecting hormonal secretion

Daily Calcium Requirement

- 600 mg/day in children
- 1300 mg/day in adolescents and young adults
- 1500 mg/day in pregnant women
- 2000 mg/day in lactating women
- 1500 mg/day in postmenopausal women and patients with fractures

HORMONAL CONTROL OF BLOOD CALCIUM LEVELS



Regulation of Ca metabolism

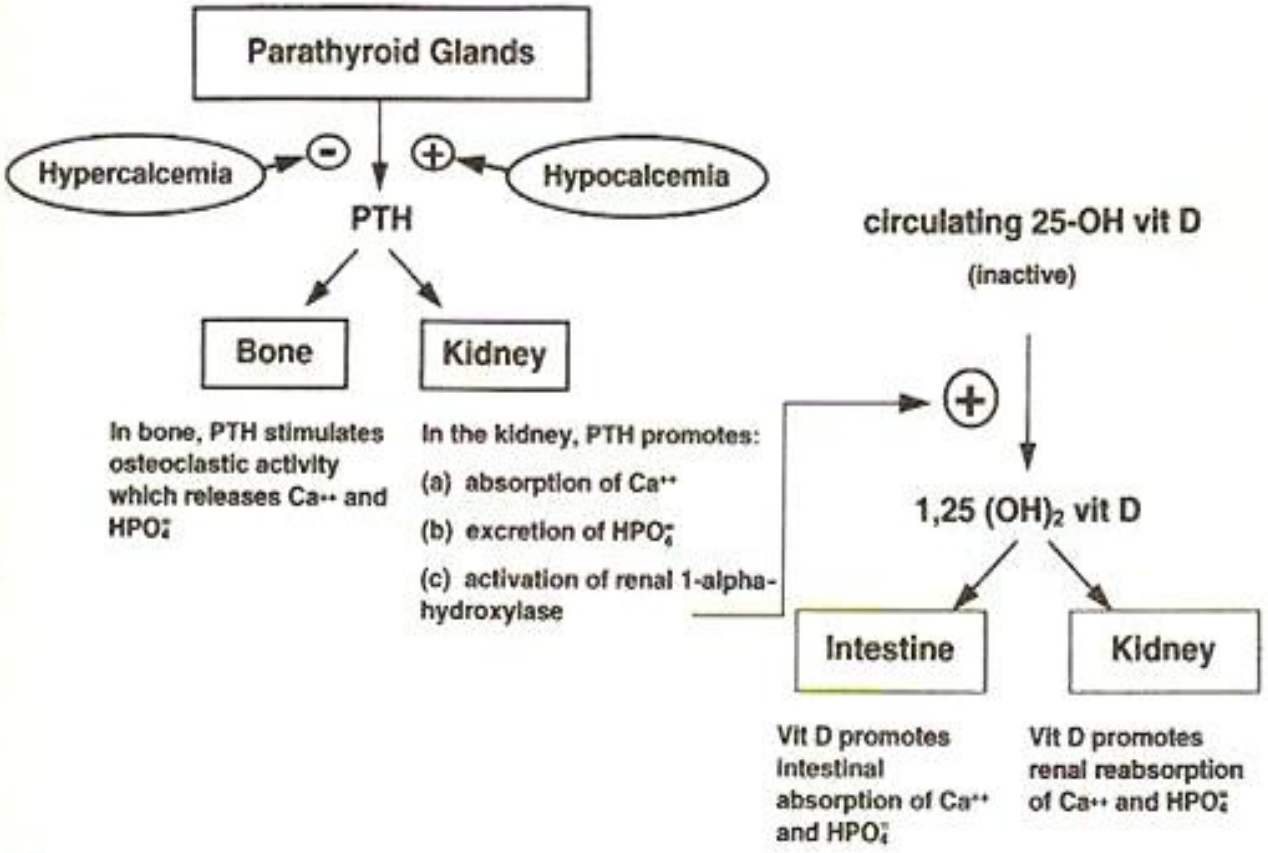


Figure 14-6. Hormonal response to hypercalcemia and hypocalcemia. PTH, parathyroid hormone; 25-OH vit D, 25 hydroxy vitamin D; $1,25(OH)_2$ vit D, dihydroxy vitamin D.

Phosphate

- High-energy phosphate bond in ATP
- Key component of bone mineral
  - 85 % of the total body phosphate is contained in bone
- Plasma Phosphate is mostly unbound
- Phosphate is critical for activity for several important enzyme including 1-alpha hydroxylation of vitamin D
- PTH lowers blood phosphate concentrations by

  Increasing renal excretion
- Vitamin D acts to increase phosphate in the blood by increasing phosphate absorption in the intestine & increase phosphate reabsorption in the kidney

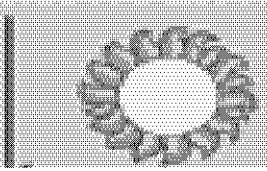
Metabolic Bone Diseases

Rickets/ Osteomalacia

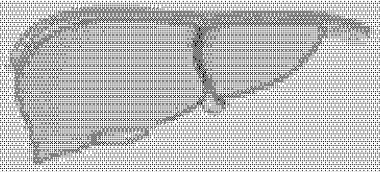
- Rickets is a disease of the growing bones in which defective mineralization occurs in both bone & cartilage of the epiphyseal growth plates
- It is associated with growth retardation & skeletal deformities
  - –Skeletal muscles have a vitamin D receptor
  - –Vitamin D deficiency causes muscle weakness
- Osteomalacia is a disorder of the mature bone in which mineralization of new osteoid bone is inadequate or delayed

Vitamin D Metabolism

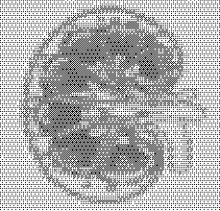
7-dehydrocholesterol



cholecalciferol (vitamin D_3)



calcidiol (25[OH] D_3)



calcitriol
($1\alpha,25[OH]_2D_3$ and $24R,25[OH]_2D_3$)

Effects of Calcitriol

Intestines
- Increased calcium absorption
- Increased phosphorus absorption
- Decreased magnesium absorption

Parathyroid gland
- Increased mineralization indirectly via increased calcium absorption in intestinal lumen
- At high doses, increased osteoclastic bone

Kidneys
- Autoregulation of calcitriol production

Years of research have led to an in-depth understanding of the metabolism of vitamin D. But the moniker of "vitamin" is not correct in the classic sense. In reality, vitamin D is a prohormone that has many effects.

Sources of Vitamin D

- Sun light
  - Synthesis in body from precursor sterol
- All Milk products (fortified)
- Cod liver oil
- Egg yolk
- Dried Fig

Types

- Hypocalcaemic Rickets (commonest type)
- Hypophosphatemic Rickets (not common)
- Combined Rickets (combination of hypocalcaemia and hypophosphetemia)

Hypocalcaemic rickets (with secondarily elevated parathyroid hormone levels)

- Lack of vitamin D due to:
  - Decreased sun exposure
  - Dietary-deficient intake
  - Malabsorption diseases that affects absorption of vitamin D (e.g. celiac disease, CF, chronic diarrhea…etc)
- Chronic liver diseases (affects conversion of cholecalciferol to calcidiol)
- Anticonvulsant drugs (phenytoin, phenobarbitone due to increased metabolism of vitamin D by inducing cytochrome P450 activity)

Nutritional Rickets

Lack of vitamin D

- Commonest cause in Saudi Arabia and in developing countries
- Lack of exposure to U/ V sun light
  - Dark skin
  - Covered body
  - Kept in-door
- Exclusive breast feeding
  - Limited intake of vitamin –D fortified milk and diary products
- During rapid growth
  - Infancy
  - puberty

- Celiac disease
- Pancreatic insufficiency
  - Cystic fibrosis
- Hepato-biliary disease
  - Biliary Artesia
  - Cirrhosis
  - neonatal hepatitis
- Drugs
  - Anti-convulsants
    - Phenobartbitone
    - Phenytoin
- Diet
  - Excess of phytate in diet with impaired calcium absorption (chapati flour)

Renal Tubular Acidosis (RTA)

- Metabolic acidosis from proximal or distal tubular disease
- Renal wasting of calcium (hypercalciuria)
- Accompanied with other urinary loss:
  - Phosphate
  - Glucose
  - Protein
- Isolated or generalized forms
- Fanconi (generalized form of RTA)
  - Associated with cystinosis, tyrosinemia, Wilson's disease

- Chronic renal failure (Renal Osteodystrophy)
  - progressive renal disease is associated with a decline in serum calcium resulting from several factors
  - RTA (Renal Tubular Acidosis)
  - Hereditary Rickets
  - Type 1 vitamin D-dependent rickets occurs because of a defect in one-alpha hydroxylase enzyme which is responsible for the conversion of 25-OH vitamin D into the active metabolite
  - Type 2 vitamin D-dependent rickets occurs because of End-organ resistance to calcitriol is very rare autosomal recessive disorder which is usually caused by mutations in the gene encoding for vitamin D receptors

Hereditary Rickets

- Hypophosphatemic rickets (Vit D resistant)
- Vitamin D dependent rickets

Vitamin D dependent rickets

Type 1

- Rare, autosomal recessive
- Lack of 1 α hydroxylase enzyme
- Clinically and Biochemically similar to nutritional rickets except it appears early at 3-4 months

Type 2

- Rare autosomal recessive disorder
- 1 α hydroxylase enzyme is present
- Lack of Calcitriol receptors
- Common in Arabs
- Baldness
- Severely affected individuals
- Unresponsive to treatment

Hypophosphatemic rickets (without secondarily elevated parathyroid hormone level)

- Nutritional phosphate deficiency
- Prematurity
- Decreased intestinal absorption of phosphate
  - Ingestion of phosphate binders (aluminum hydroxide)
- Renal phosphate wasting
  - RTA (proximal type)
  - Vitamin D resistant rickets
- Tumor induced Osteomalacia (oncogenic osteomalacia)
- Hereditary Hypophosphatemic rickets

Hereditary Hypophosphatemic Rickets

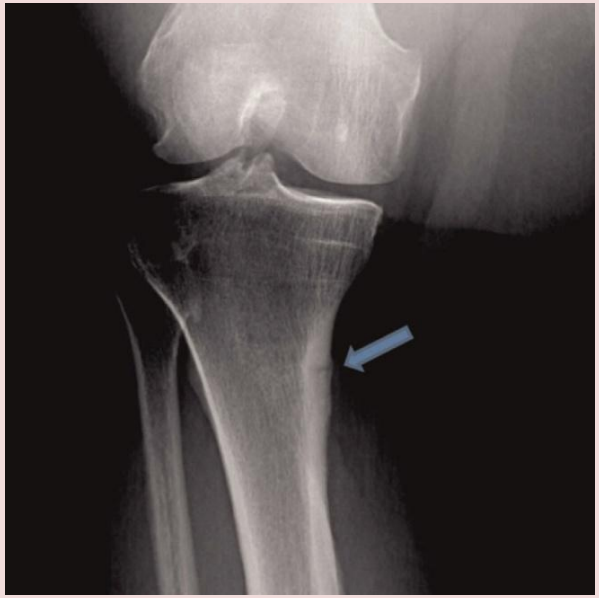
- X-linked dominant / Autosomal dominant
- Males affected more than females
- Commonest inherited form of rickets
- Prevalence 1: 25000
- Phosphate wasting by renal tubules leads to:
  - Low serum phosphate
  - Normal calcium
- In-appropriate low or normal 1,25-di hydroxy vitamin D
  - phosphate is the major stimulus for 1α hydroxylase
- Severe rickets and short stature by 1-2 years

XLH

- XLH is a type of rickets characterized by excessive loss of phosphate unrelated to calcium levels
  - Caused by a mutation in the phosphate-regulating gene (PHEX)
  - Leads to impaired renal tubular reabsorption of phosphate

Clinical Manifestations:

- Growth retardation (short stature)
- Bowed legs
- Lower extremity insufficiency fractures
- Arthritis and Osteomalacia (adults)
- Low blood phosphate and vitamin D
- Raised urine phosphate
- Raised serum ALP in children
- Normal serum calcium



XLH is treated with Vitamin D metabolites (calcitriol) and phosphate

Congenital rickets

- Onset of this type happens in the first six months of life
- It is quite rare in industrialized countries
- It is common in developing countries, including Saudi Arabia
- It occurs when there is maternal vitamin D deficiency during pregnancy
- Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies
- Newborns may have symptomatic hypocalcaemia (e.g. seizure, tetany..etc)
- Use of prenatal vitamins containing vitamin D prevents this entity as well prophylactic vitamin D supplementation from birth dose of 500 to 1000 unit/day will prevent this entity

Skeletal manifestations

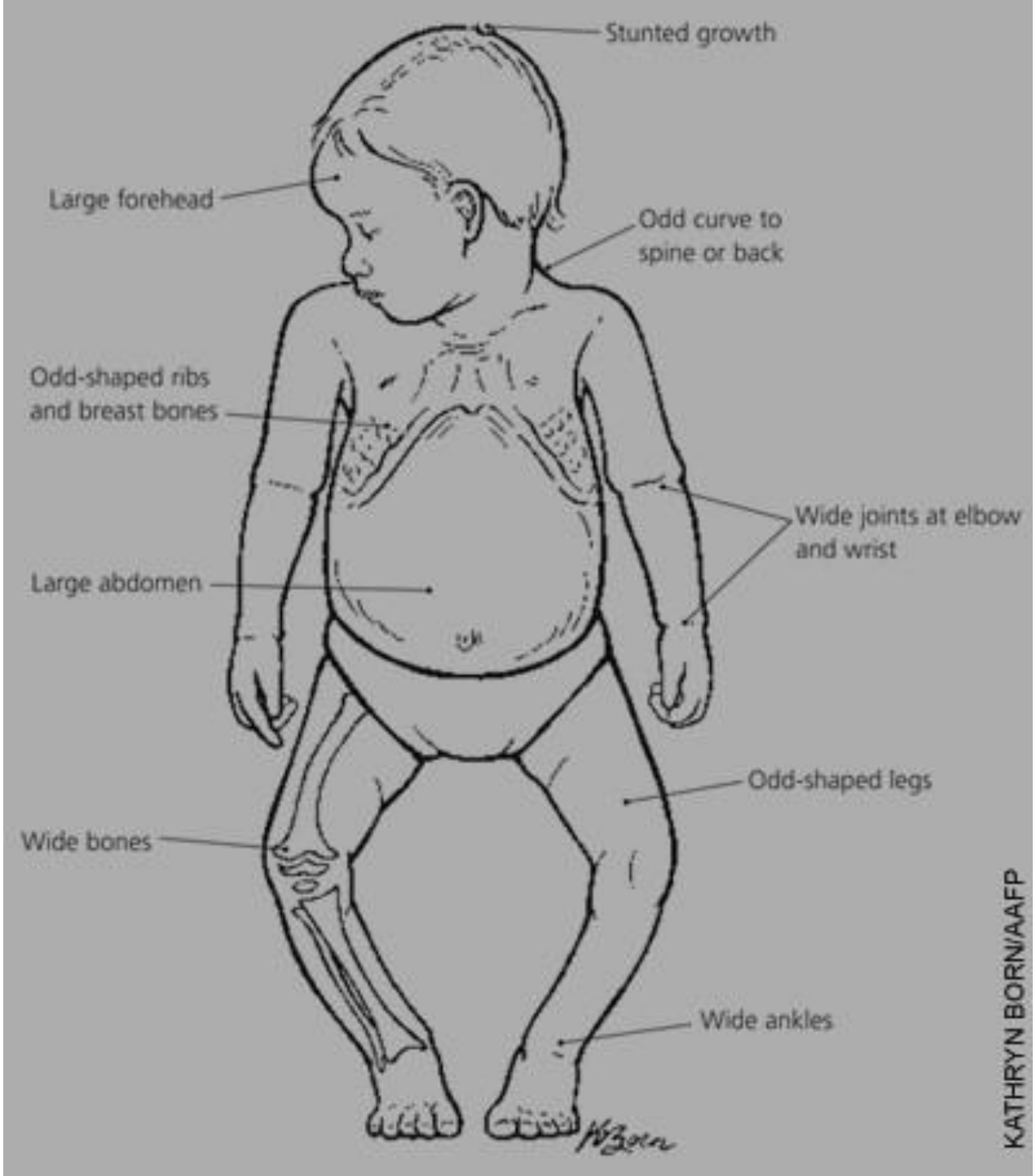
Craniofacial

- Craniotabes
- Delayed closure of anterior fontanel
- Frontal and parietal bossing
- Delayed eruption of primary teeth
- Enamel defects and caries teeth

Skeletal manifestations

Extremities

- Enlargement of long bones around wrists and ankles
- Bow legs, knock knees, anterior curving of legs
- Coxa vara and green stick fractures
- Deformities of spine, pelvis and leg – rachitic dwarfism
- Lower extremities deformities are extensively involved in familial hypophosphatemic rickets
- Upper limb more involved than lower limbs in Hypocalcemic rickets


Stunted growth
Large forehead
Odd curve to spine or back
Odd-shaped ribs and breast bones
Wide joints at elbow and wrist
Large abdomen
Odd-shaped legs
Wide bones
Wide ankles
KATHRYN BORN/AAFP

Extra skeletal manifestations

- **SEIZURES AND TETANY**

– Secondary to hypocalcaemia in Vitamin D deficiency rickets and VDDR type 1

- **HYPOTONIA AND DELAYED MOTOR DEVELOPMENT**
  - In rickets developing during infancy

- **PROTUBERANT ABDOMEN, BONE PAIN, WADDLING GAIT AND FATIGUE**

– In older children presenting with rickets

Extra – Skeletal manifestations

- **Features of** primary problems
- **Features of** hepatic disease

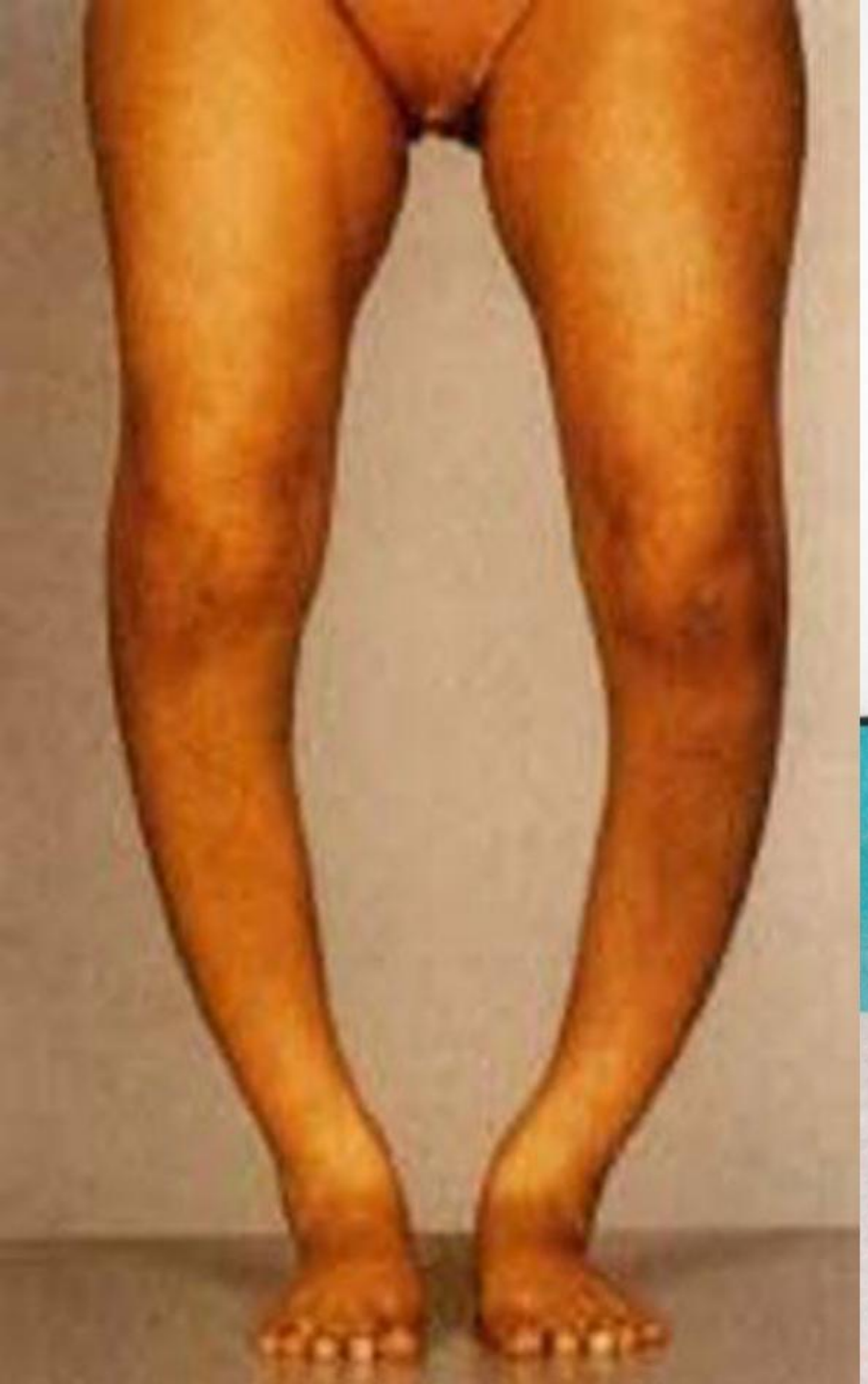
renal failure

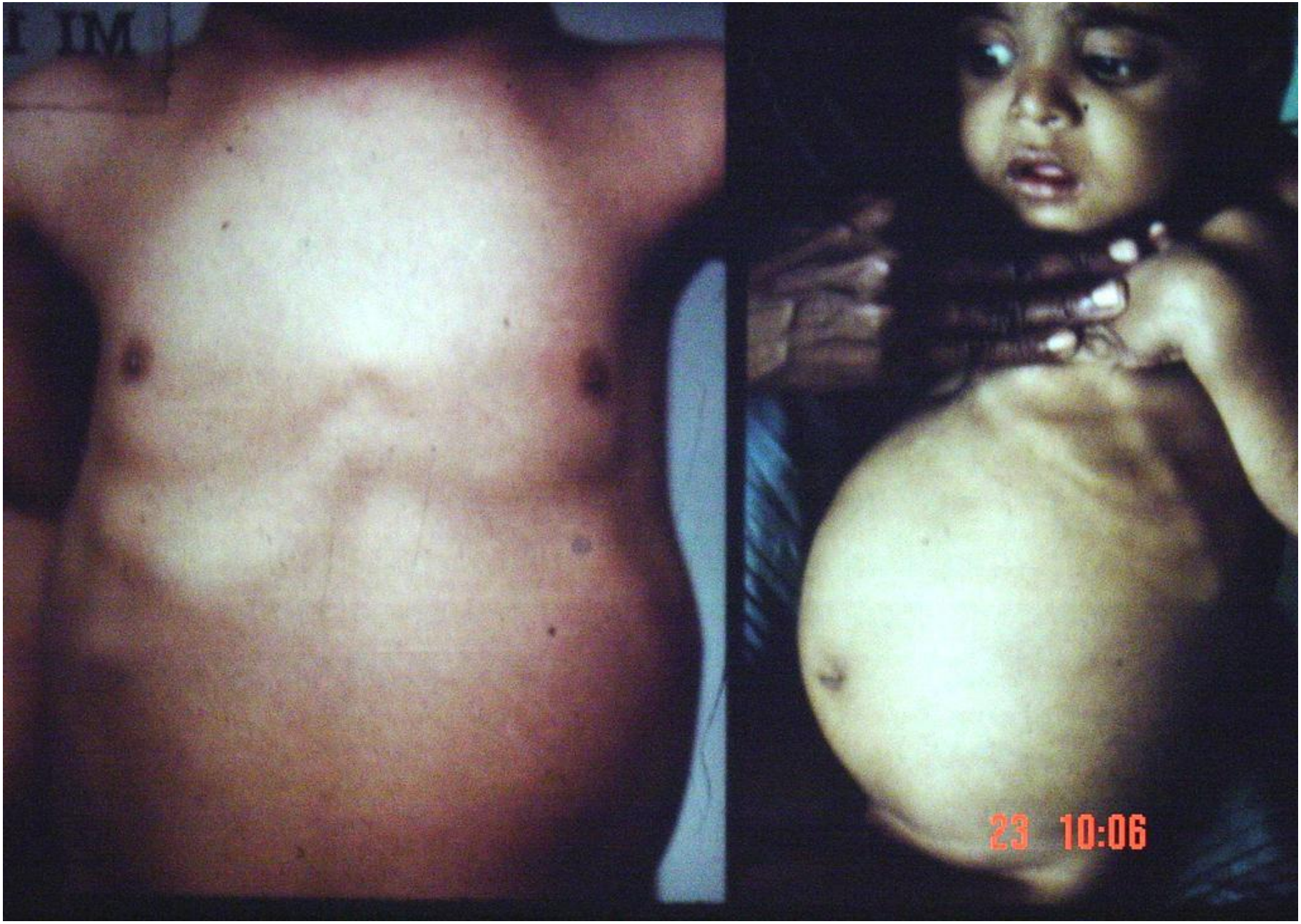
recurrent vomiting.

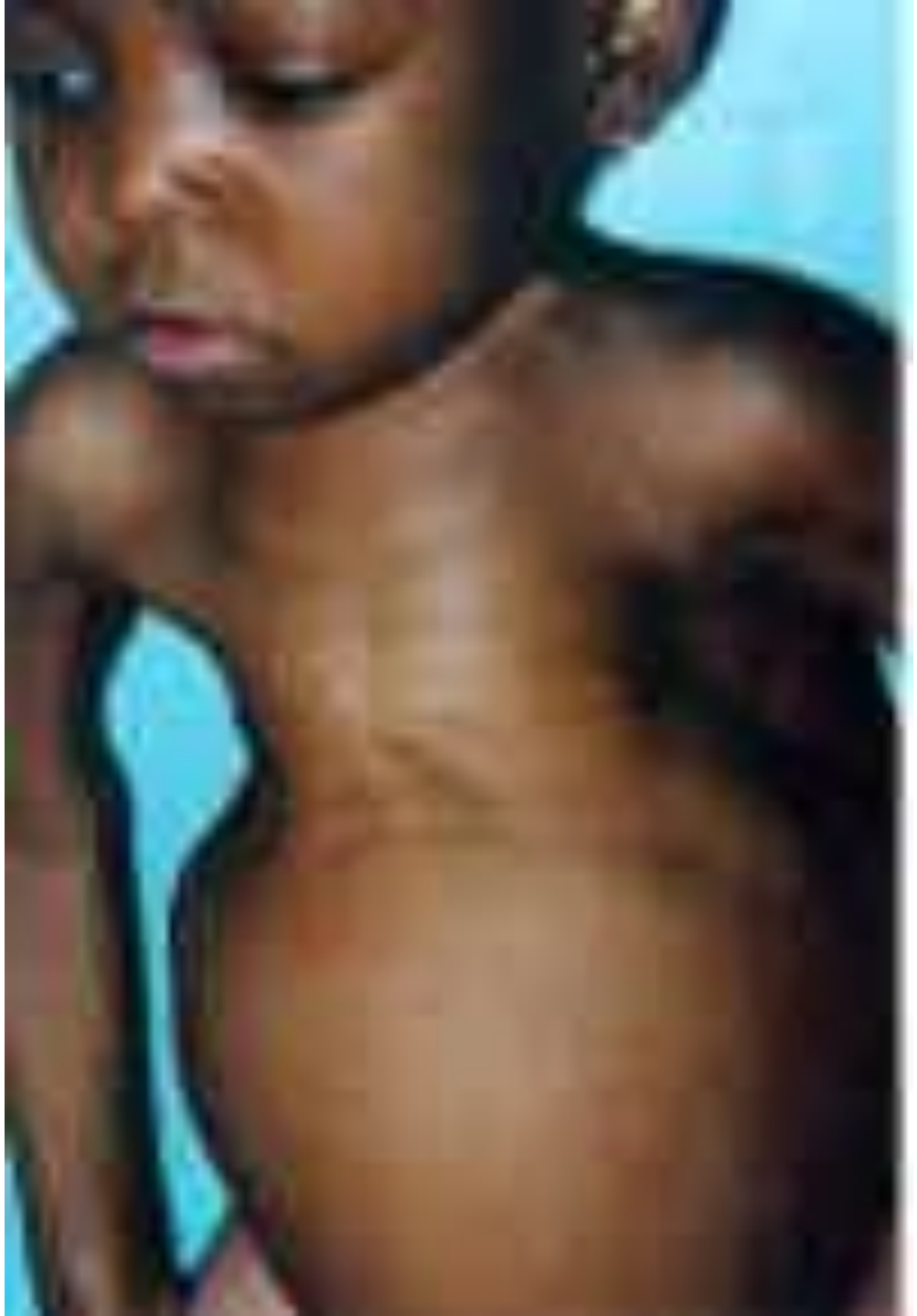
acidotic breathing or failure to thrive.

- **ASYMPTOMATIC**

- Recent studies documenting the high prevalence of vitamin D deficiency and the need to increase dietary vitamin D intake
- Epidemiological studies and new information on the role of vitamin D in preventing autoimmune diseases, cardiovascular disease, and cancer
- Prospective and retrospective epidemiologic studies all indicate that levels of 25-hydroxyvitamin D below 20 ng / milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers.




23 10:06



Biochemical findings of rickets

- Vitamin D deficiency rickets
  - Low- normal serum calcium level
  - Normal – low phosphate level
  - Increased secretion of PTH (secondary hyperparathyroidism) to compensate for low calcium
  - Hyperparathyroidism will increase renal excretion of phosphate, leads to low serum phosphate level
  - Elevated alkaline phosphatase enzyme
  - Reduced urinary calcium level
  - Low level of both 25 hydroxy vitamin D
  - Elevated parathyroid hormone level

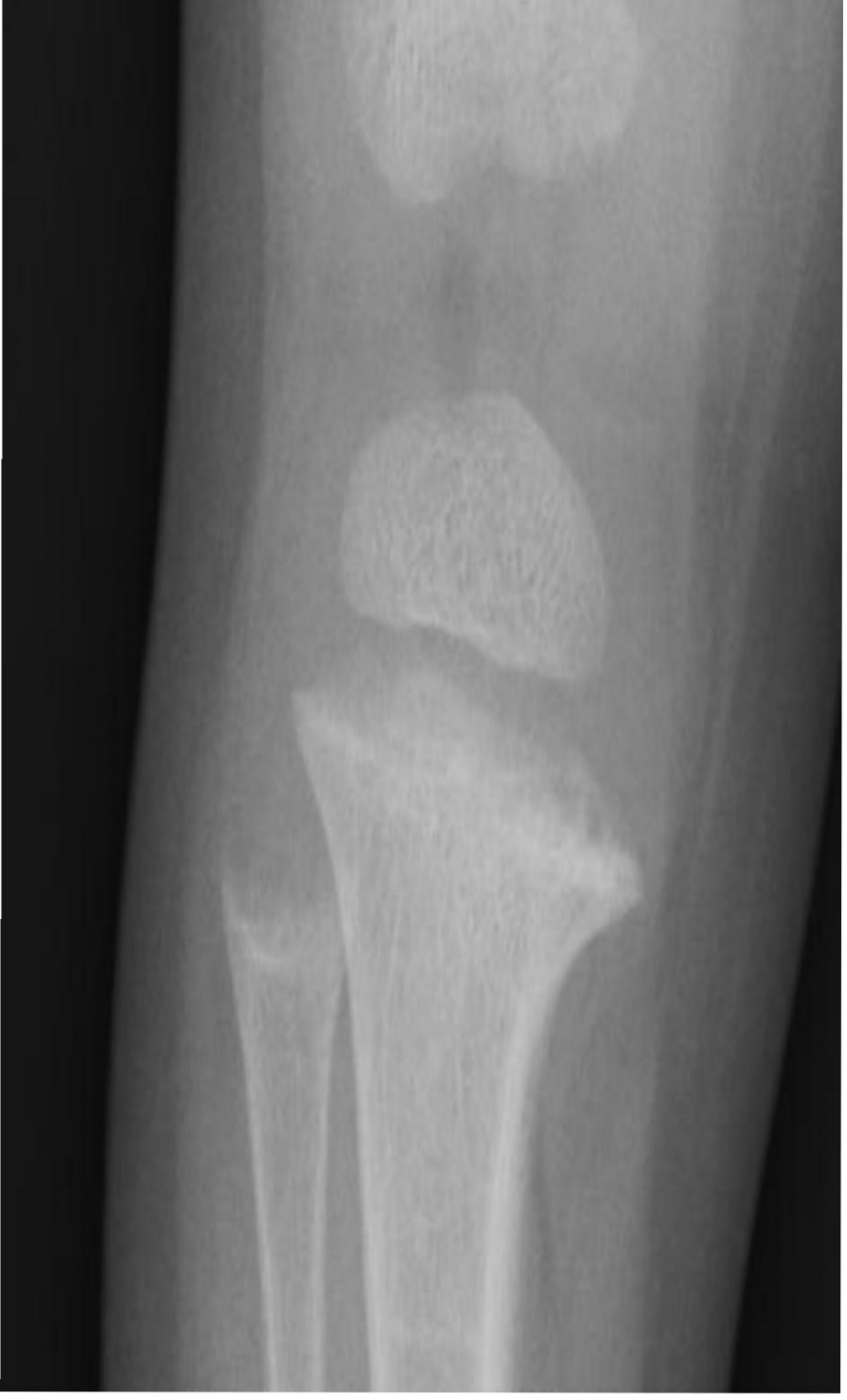
Biochemical findings of rickets

Hypophosphatemic rickets

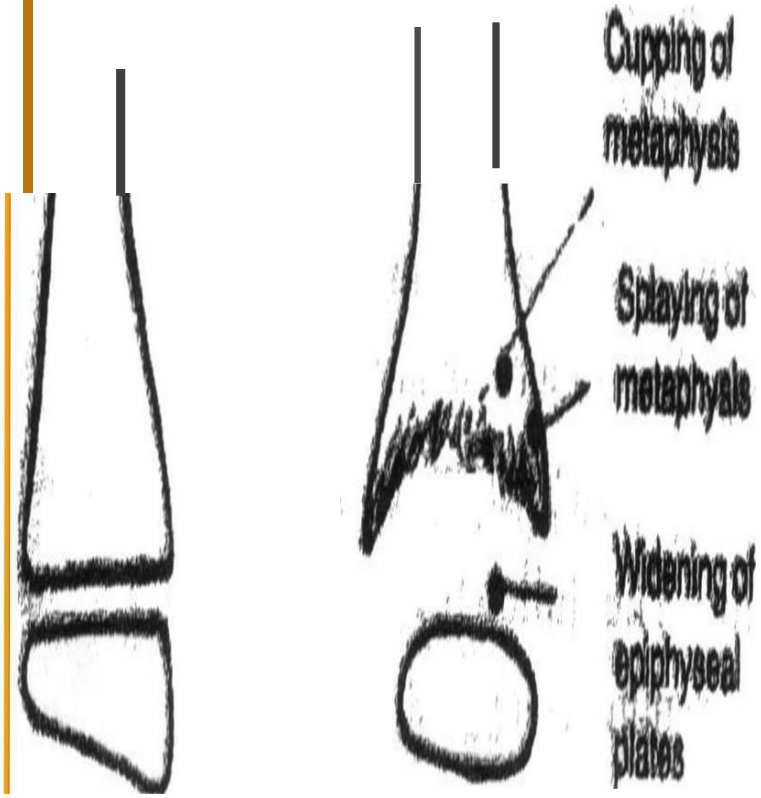
- Low serum phosphate level
- Normal calcium level
- Normal parathyroid hormone level
- High alkaline phosphatase level
- Low or normal 1,25-di hydroxy vitamin D
  - phosphate is the major stimulus for 1α hydroxylase

Radiological findings of rickets

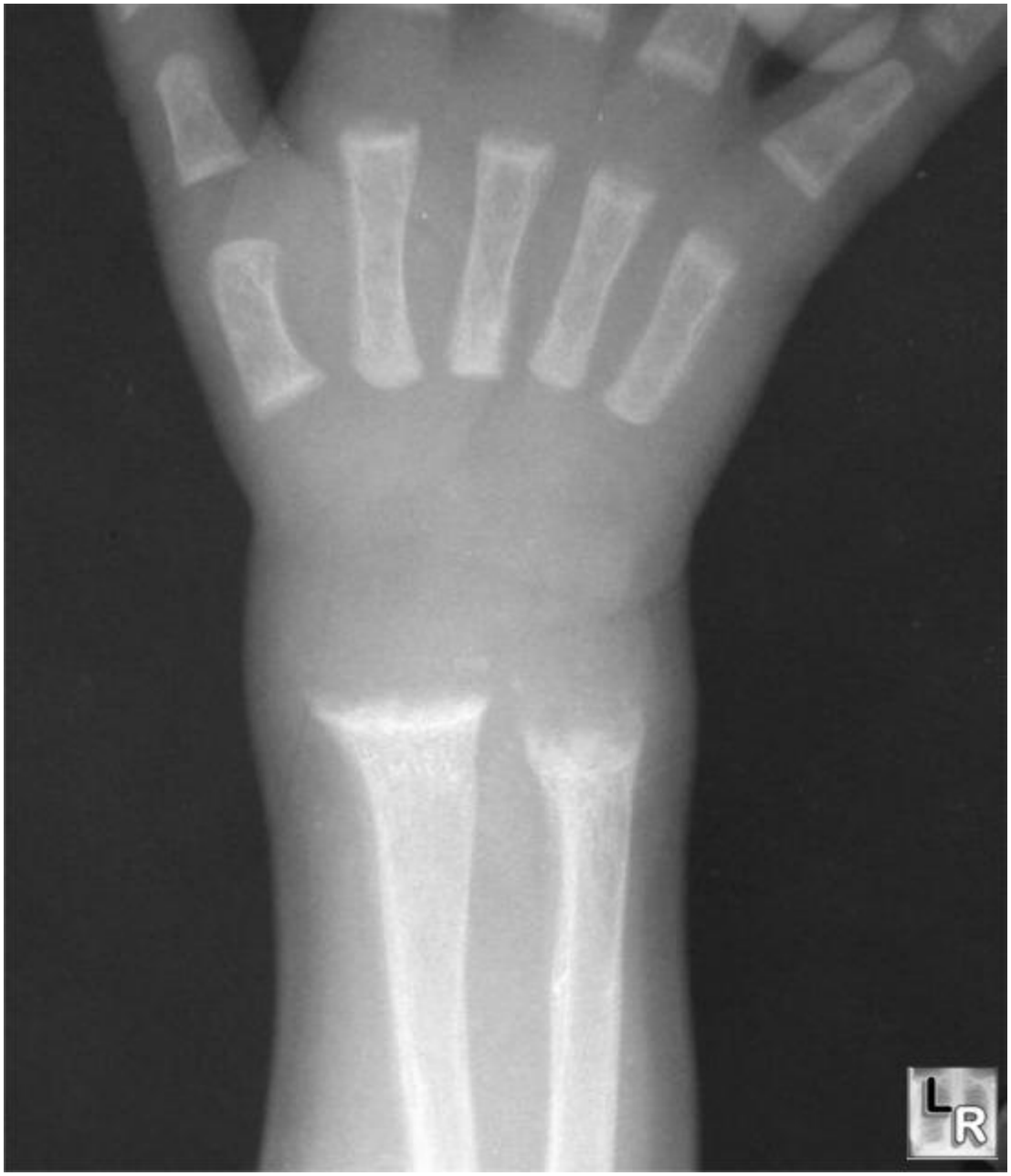
- Generalized Osteopenia
- Widening of the unmineralised epiphyseal growth plates
- Fraying of metaphysis of long bones
- Bowing of legs
- Pseudo-fractures (also called loozer zone)
  - Transverse radio lucent band, usually perpendicular to bone surface
- Complete fractures
- Features of long standing secondary hyperparathyroidism
- (Osteitis fibrosa cystica)
  - Sub-periosteal resorption of phalanges
  - Presence of bony cyst (brown Tumor)

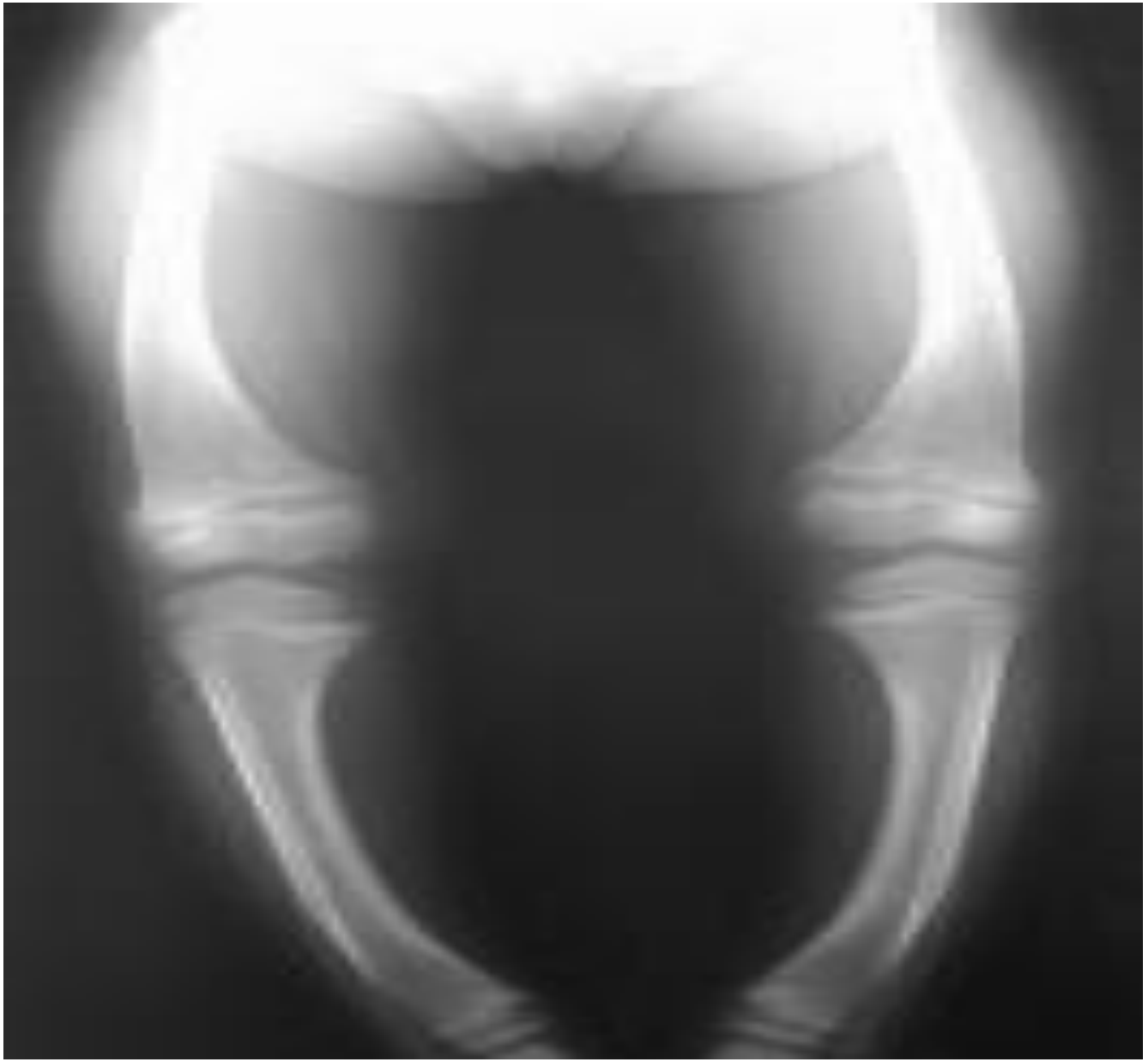


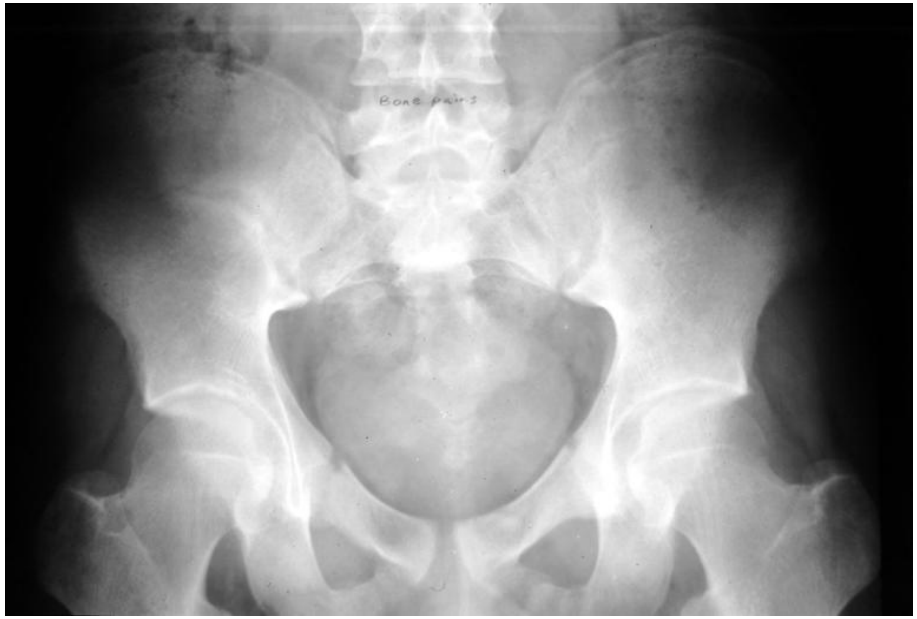
bW

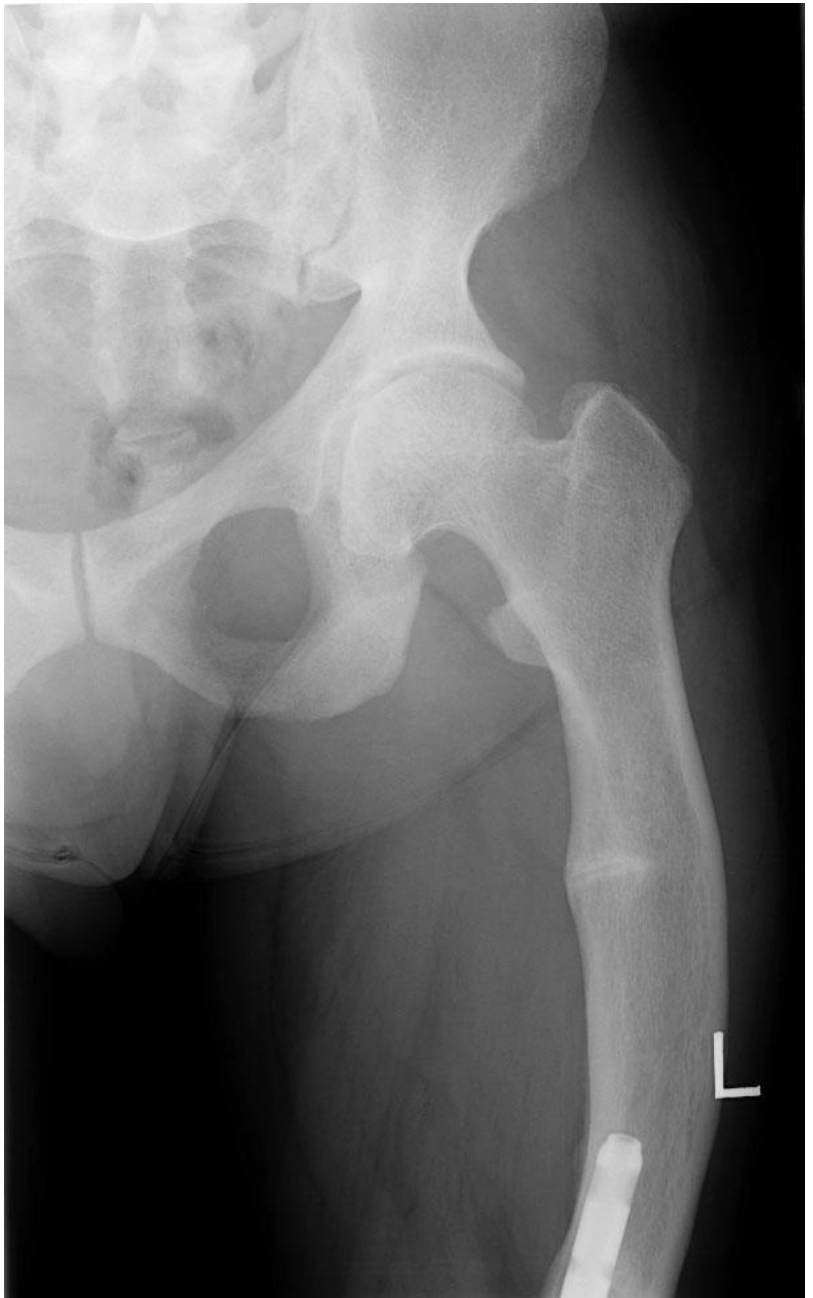


Radiological features of rickets.


L
R




Bone pair


L

Prevention

- Pay much attention to the health care of pregnant and lactating women, instruct them to take adequate amount of vitamin D
- Adequate sensible sun exposure is an excellent source of vitamin D and should be recommended to all patients for both the treatment and prevention of vitamin D deficiency
- Usually, exposure of the arms and legs (with sun protection on the face) for about 15 to 30 minutes (depends on degree of skin pigmentation, time of day, season, latitude, dust, and age of patient) between 10 a.m. and 3 pm at least twice a week is sufficient to stimulate cutaneous vitamin D production
- Advocate breast feeding, give supplementary food on time
- Vitamin D supplementation:
  - In premature, twins and weak babies, give Vitamin D 800IU per day
  - For term babies and infants the demand of Vitamin D is 400IU per day
  - For those babies who can't maintain a daily supplementation, inject muscularly Vitamin D3 10000-200000 IU

Therapy

- Administration of vitamin D preparation
  - Vit D2 or vitamin D3 in nutritional rickets
  - 1α hydroxy vitamin D = one alpha in renal rickets, Hypophosphatemic rickets
  - 1, 25 Di hydroxy Vitamin D = Calcitriol in hepatic rickets
- Calcium supplement initially in severe disease
  - To avoid hungry bone hypocalcaemia
- Phosphate supplements in Hypophosphatemic rickets
- Intravenous calcium and phosphate in vitamin D receptor resistance

Therapy

- Vitamin D 2000-4000IU/day for 6-12 weeks, then change to preventive dosage (400IU)
- A single large dose:
  - For severe case, or Rickets with complication, or those who can’t bear oral therapy.
  - Vitamin D3 200000-300000IU, intramuscular dosage will be used after 2-3 months

Osteoporosis in children

- Skeleton is not static structure, but in continuous “ modeling - remodeling process”
- Bone is continually remodeled throughout life because bones sustain recurring micro-trauma
- The hallmark of osteoporosis is reduction in skeletal mass caused by imbalance between bone resorption & bone formation

- Bone tissue in skeleton increases until mid 20s
- Factors that influence bone accretion during childhood & determine the peak bone mass are:
  - Heredity “genetic potentials”
  - Ethnic origin
  - Gender
  - Diet such as calcium & vitamin D intake
  - Physical activity
  - Endocrine status
  - Sporadic risk factors such as cigarette smoking

- Gender

– Bone density is generally higher in males than in females
– Before puberty, boys & girls develop bone mass at similar rates
– After puberty, boys tend to acquire greater bone mass than girls

- Race

– for reasons still not well understood, BMD varies from various racial groups
– African American girls tend to achieve higher peak bone mass than Caucasian girls
– More research is needed to understand the differences in bone density between various racial & ethnic groups

Gene	Protein	Chromosome
AHSG	α2 HS-glycoprotein	3q27
VDR	VDR	12q12–q14
ESR1	ER 1 (α)	6q25.1
ESR2	ER 2 (ß)	14q23
COL1A1	Collagen, type 1,α 1	17q21.3–q22.1
COL1A2	Collagen, type 1,α 2	7q22.1
CALCR	Calcitonin receptor	7q21.3
TNFRGF5	TNF receptor	1p36.3– p36.2

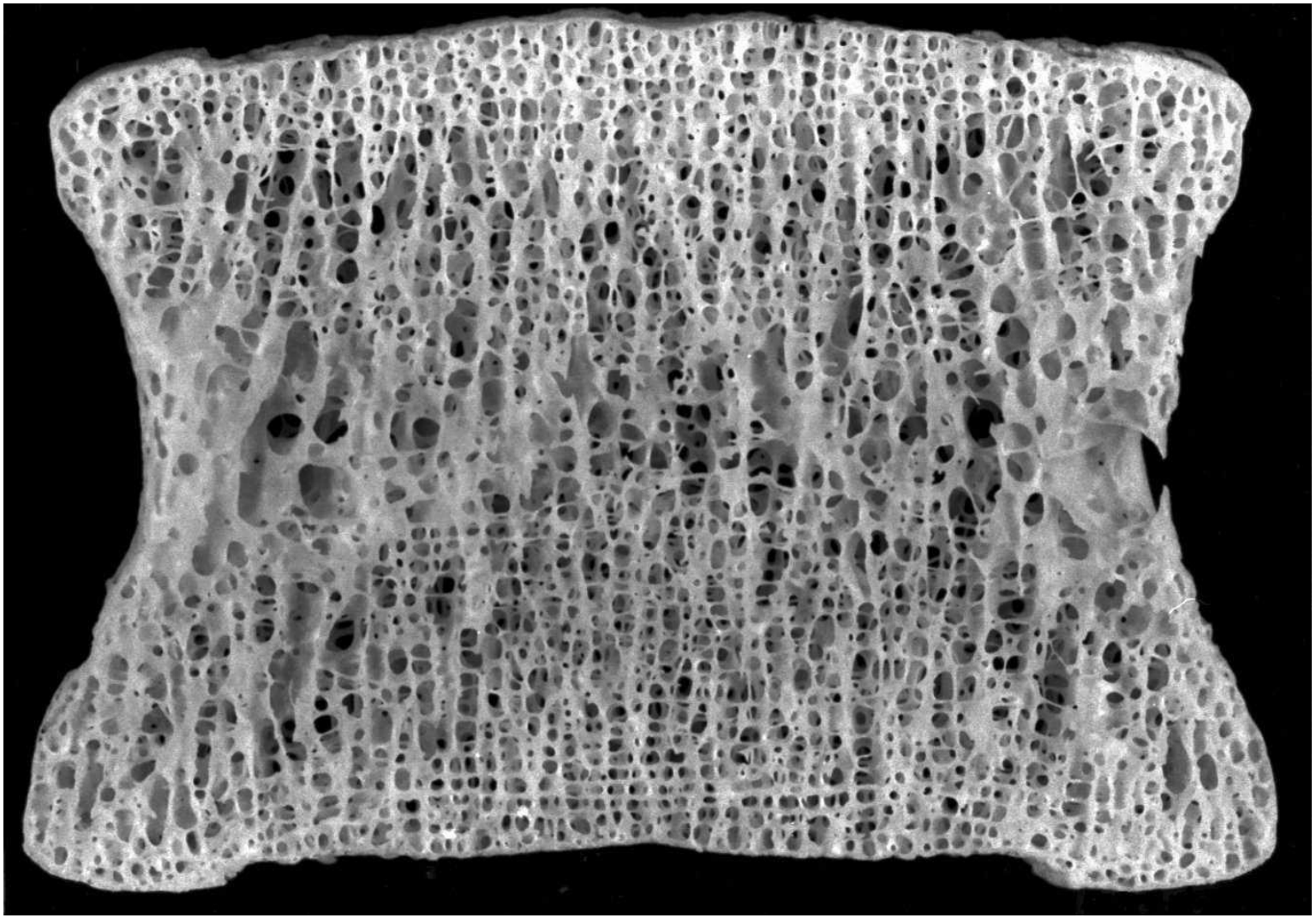
- Nutritional status
  - Calcium is essential nutrient for bone health
  - A well-balanced diet including adequate amounts of vitamins & minerals such as magnesium, zinc & vitamin D are important for bone health
- Physical activity
  - is important for building- up healthy bones
  - benefits of activity are most pronounced in weight - bearing areas
    - hips during walking and running
    - arms during gymnastics
    - upper-body in weight-lifting

Definition of “osteoporosis” in children

- No WHO definitions in children and teens
- Concern for low bone mass
  - BMD Z-score by DXA $\leq$ -2.0 SD
  - Slightly low if Z-score between -1.0 and -2.0
- “Diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of BMD alone.”

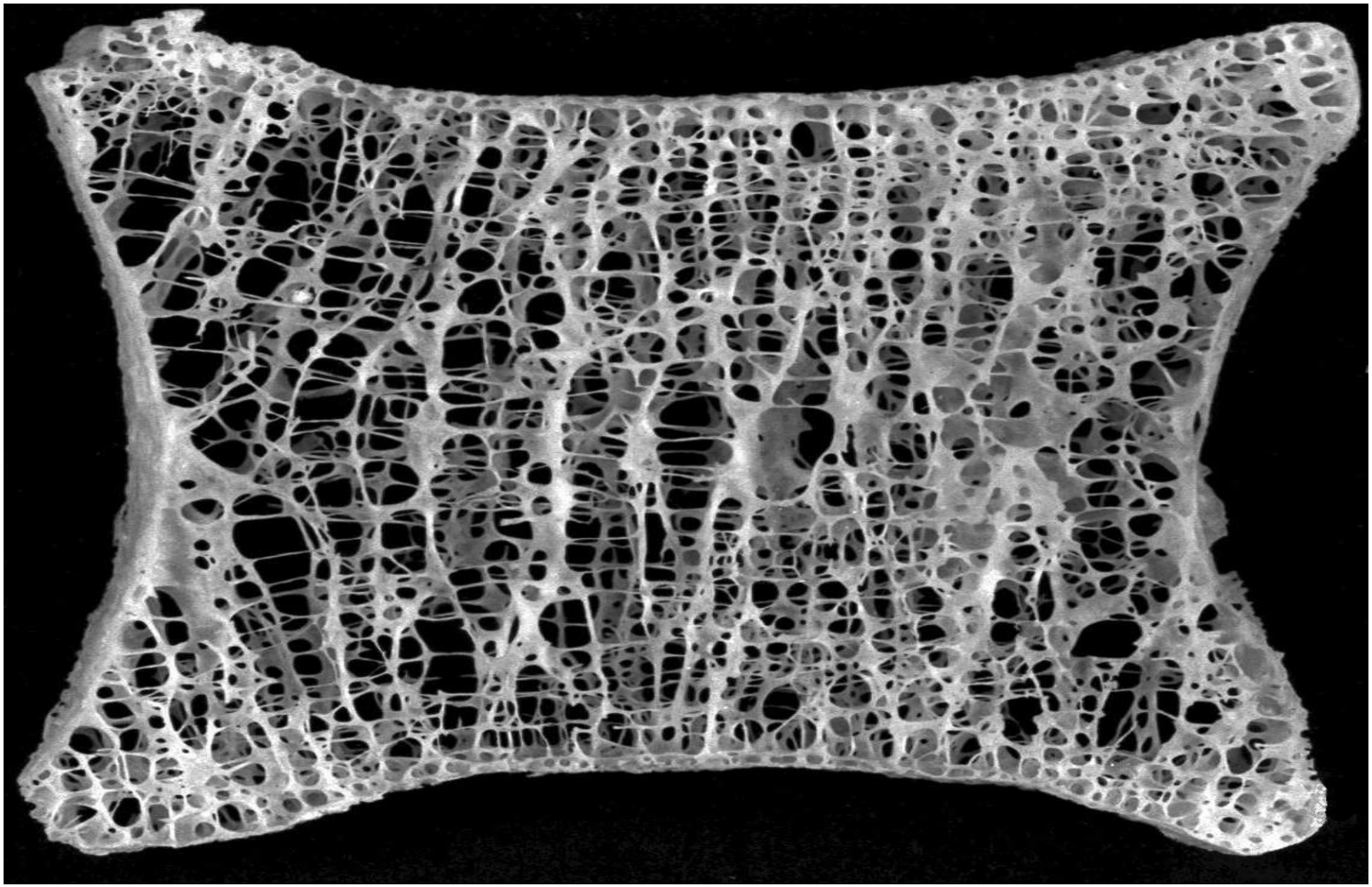
  Int’l Soc Clinical Densitometry 2007

Normal Bone



Female, age 30 years

Osteoporosis



Hormonal factors

Corticosteroid

Growth factors

Oestrogen

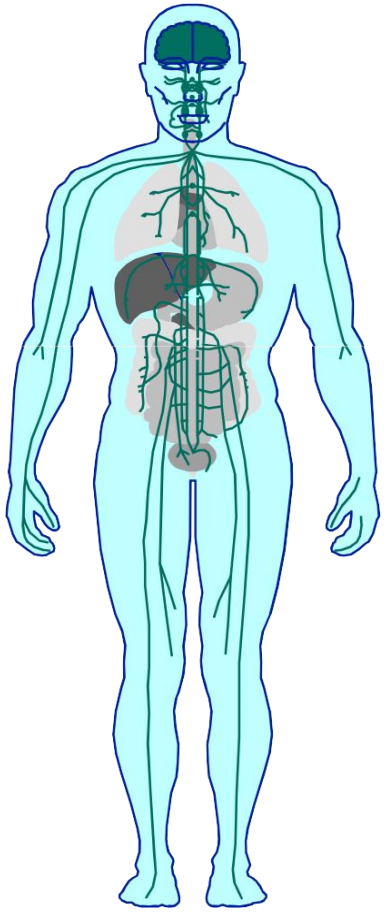
Pituitary hormones

PTH

Testosteron

Thyroxin

Vitamin Ds



Symptoms & Signs

- Bony aches (variable severity)
- Easy fractures (Low – Trauma)

  spine - lower radius - femoral neck- Rib fracture)
- Decreased mobility & impaired quality of life
  - Walking, sitting, go up& down stairs, daily life activities)
- Normal biochemistry including (normal calcium, phosphate, ALP, vitamin D and PTH)

Causes of Osteoporosis In Children

- Primary osteoporosis in children & adolescents is relatively uncommon and usually secondary to identifiable causal factors

- Primary
  - Heritability of bone loss
    - Osteogenesis imperfecta
    - Idiopathic juvenile osteoporosis

Secondary Osteoporosis

- Endocrine disorder / Metabolic
  - Estrogen deficiency
  - Testosterone deficiency
  - Cushing's syndrome
  - Primary hyperparathyroidism
  - Thyrotoxicosis
  - GH deficiency
  - Gaucher's disease
    - Malabsorption disorder
  - Gastrectomy
  - Celiac disease
  - Small bowel resection
  - Crohn's disease
  - Cystic fibrosis

Secondary Osteoporosis

- Malignancies
  - multiple Myeloma
- Autoimmune disorders
  - Rheumatoid arthritis, Lupus erythematosis
- Immobilization
  - CP / Neuromuscular disorders
- Drugs
  - Corticosteroids
  - loop diuretics
  - Anticonvulsants (phenytoin)
  - GnRH agonist
  - Chemotherapy (Methotrexate)
  - Heparin

Secondary Osteoporosis

- Nutritional factors
  - Calcium
  - Vitamin D
  - Vitamin C
  - Protein
- Lifestyle
  - Physical activity Vs sedentary life style
- Smoking / Alcohol
- Pregnancy
- Anorexia nervosa

Osteogenesis imperfecta

- At least 8distinct forms of OI representing extreme variation in severity from one person to another
- Inherited disorder of collagen 1 deficiency
- The most common features of OI include:
  - Bone that fracture easily
  - Family history usually present
  - Short stature common
  - Blue sclera common
  - Hearing loss
  - Dental problems
  - In mild form of the disease, with late onset, should be distinguished from “idiopathic Juvenile osteoporosis”

Osteogenesis Imperfecta

- Pathologic changes seen in all tissues in which type 1 collagen is an important constituent (e.g., bone, ligament, dentin, and sclera)
- Basic defect : qualitative or quantitative reduction in type 1 collagen
- Mutations in genes encoding type 1 collagen affect the coding of 1 of the 2 genes
- Mutations are either genetically inherited or new
- Inherited mutations : recurrence risk in subsequent pregnancies of 50% if a parent is affected
- New mutations unpredictable recurrence risk

Osteogenesis Imperfecta

- Incidence : 1 case for every 20,000 live births
- Equally common in males and females
- Described in every human population in which skeletal dysplasias have been studied
- No predilection for a particular race
- Family history , but most cases due to new mutations
- Commonly present with fractures after minor trauma

Osteogenesis Imperfecta

- **Osteogenesis imperfecta or "brittle bone disease" is a genetic condition characterized by fragile bones that break easily**
  - OI is caused by a mutation in the type I collagen genes, affecting the body's normal production of collagen leading to fragile bones

Clinical manifestations:

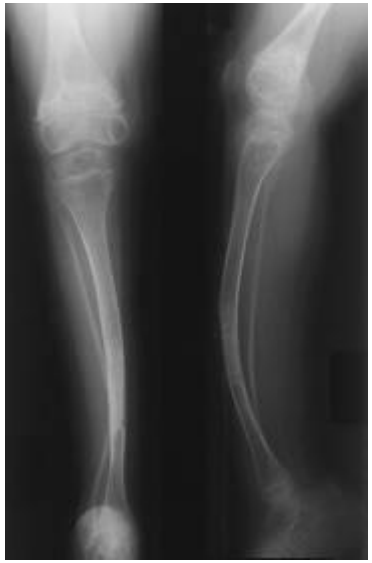
- Short stature
- Blue sclerae (pictured)
- Dentinogenesis imperfecta
- Wormian bones
- Hearing loss
- Osteopenia

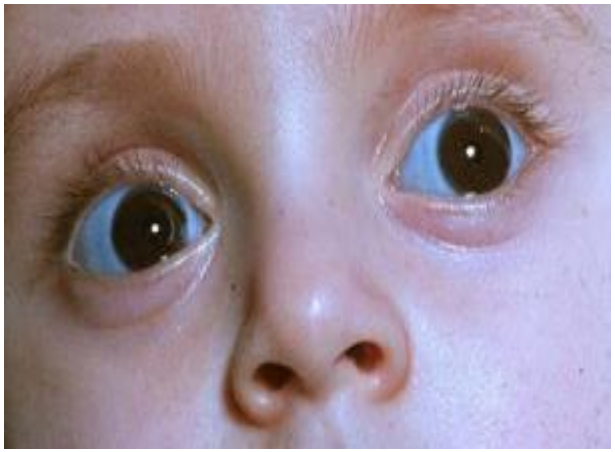
There is no cure for OI, but treatment focuses on:

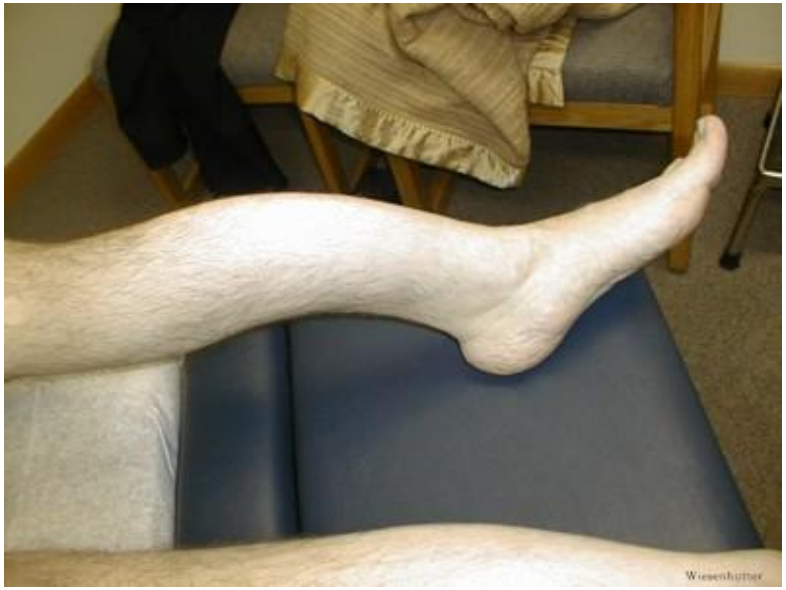
- Minimizing fractures
- Maximizing mobility, function, general health

Bisphosphonates are prescribed for OI

Osteogenesis Imperfecta







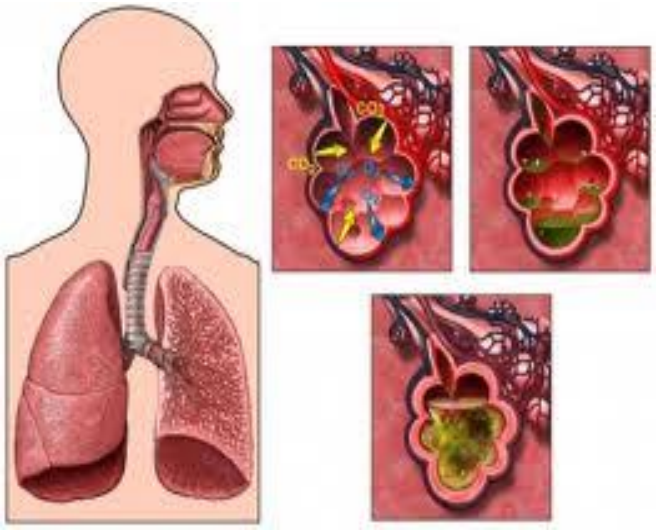

1x

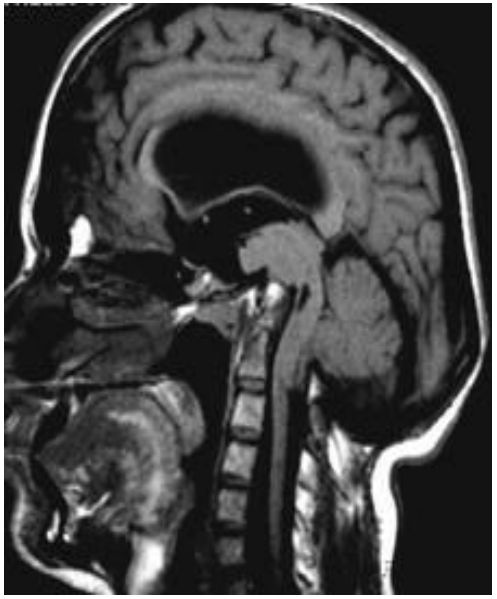
Type I

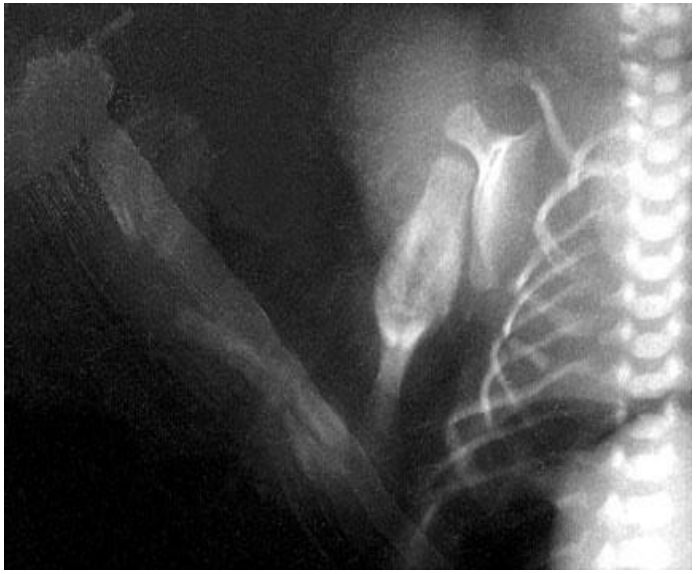
- Mildest and most common form
- 50% of the total OI population
- Mild bone fragility
- Relatively few fractures
- Minimal limb deformities
- Child might not fracture until he or she is learning to walk
- Some children have few obvious signs of OI or fractures while others experience multiple fractures of the long bones, compression fractures of the vertebrae, and chronic pain.
- Appear healthy yet need to accommodate for bone fragility

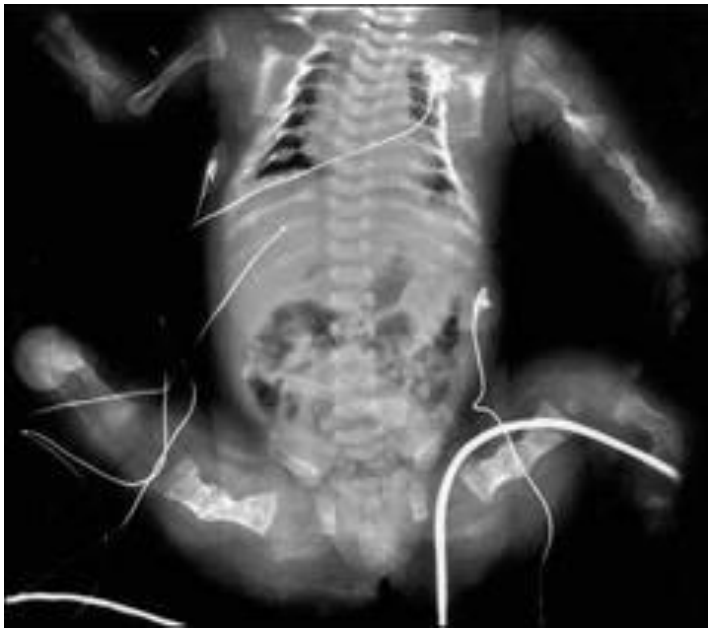
Complications

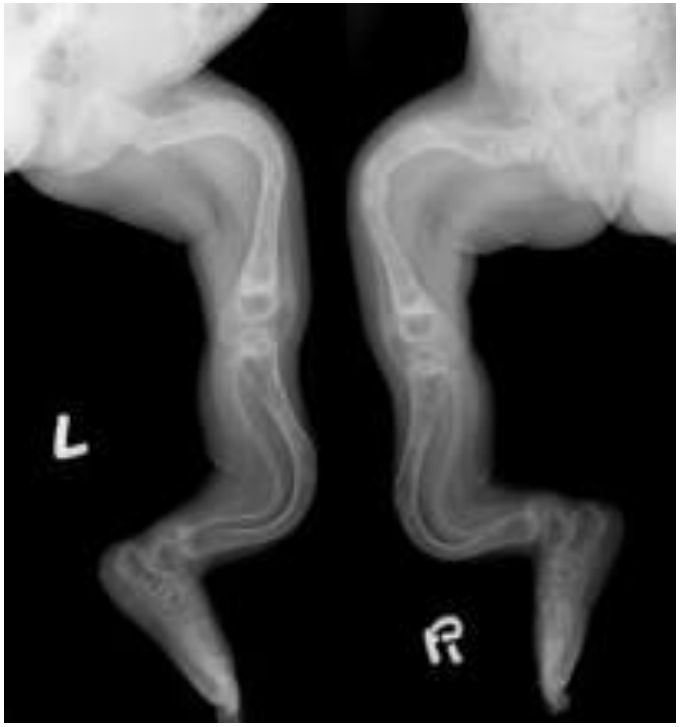
- Repeated respiratory infections
- Basilar impression caused by a large head, which causes brainstem compression
- Cerebral hemorrhage caused by birth trauma
- High risk for complications of anesthesia

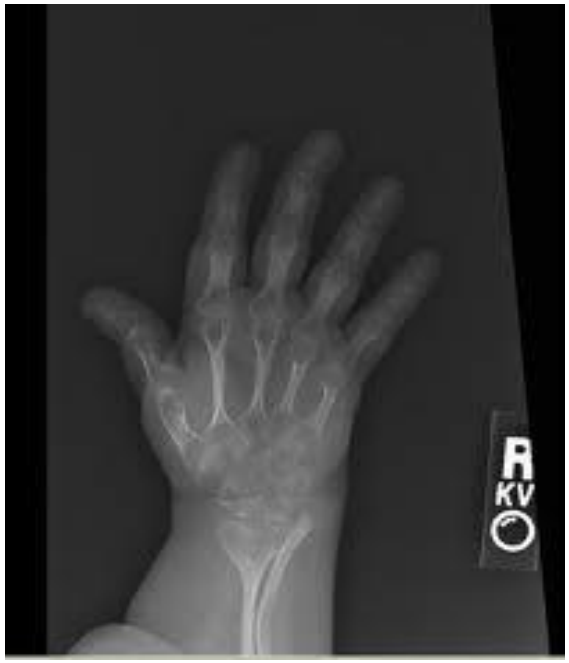


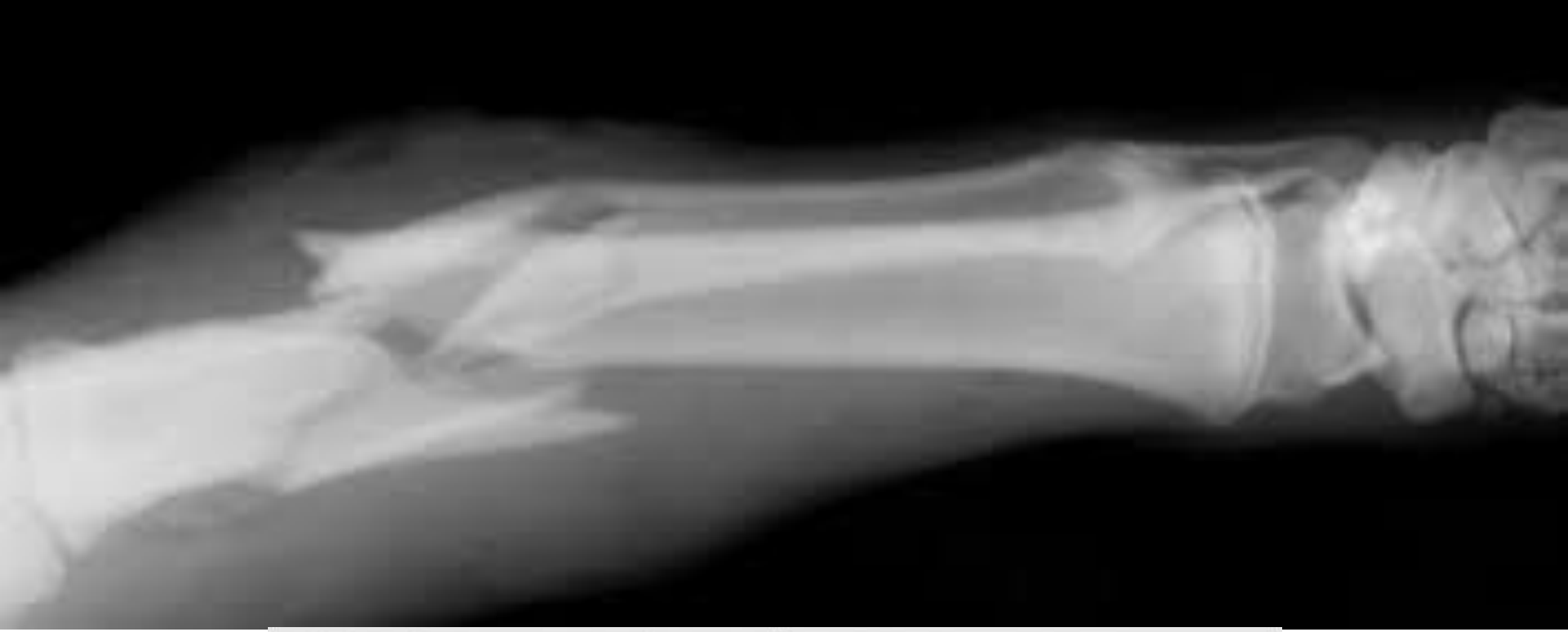


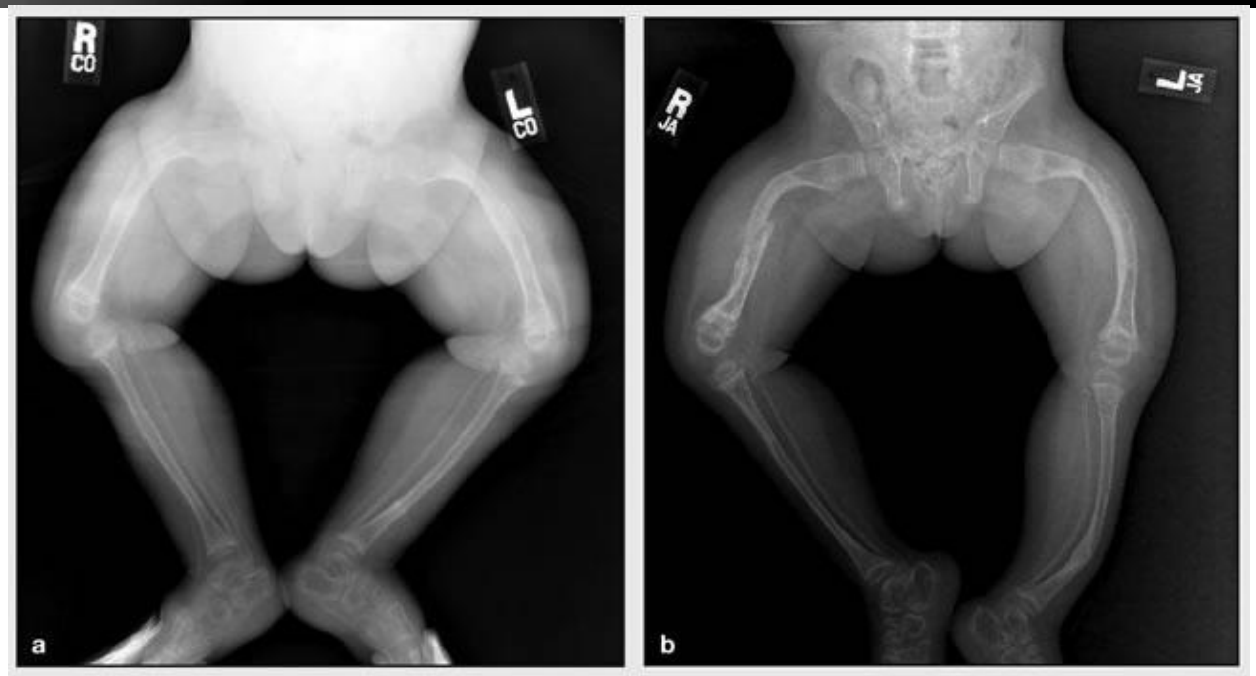





L
R


R
KV




R
CO
L
CO
a
R
JA
L
JA
b

Diagnosis of osteoporosis

- In addition to a thorough history and physical examination, the following should be performed:
  - Calcium, phosphorus, albumin, & liver enzymes
  - Bone-specific alkaline phosphatase
  - 25-hydroxyvitamin D
  - Intact parathyroid hormone (PTH)
  - Thyroid function test
  - 24–hour urinary calcium & creatinine values
  - ESR & CRP
  - LH / FSH & Sex hormones

Biochemical markers of bone turnover

- Formation (osteoblast products)
  - Serum
    - Bone specific alkaline phosphatase (BSAP)
    - Osteocalcin (OC)
    - Carboxyterminal propeptide of type I collagen (PICP)
    - Aminoterminal propeptide of type I collagen (PINP)
- Resorption (osteoclast products)
  - Urine
    - Hydroxyproline
    - Free and total pyridinolines (Pyd) & deoxypyridinolines (Dpd)
    - Free and total *N*-telopeptide of collagen cross-links (NTx)
    - *C*-telopeptide of collagen cross-links (CTx)
  - Serum
    - Cross-linked *C*-telopeptide of type I collagen
    - *N*-telopeptide of collagen cross-links
    - *C*-telopeptide of collagen cross-links

Imaging Assessment of Bone Strength in Children

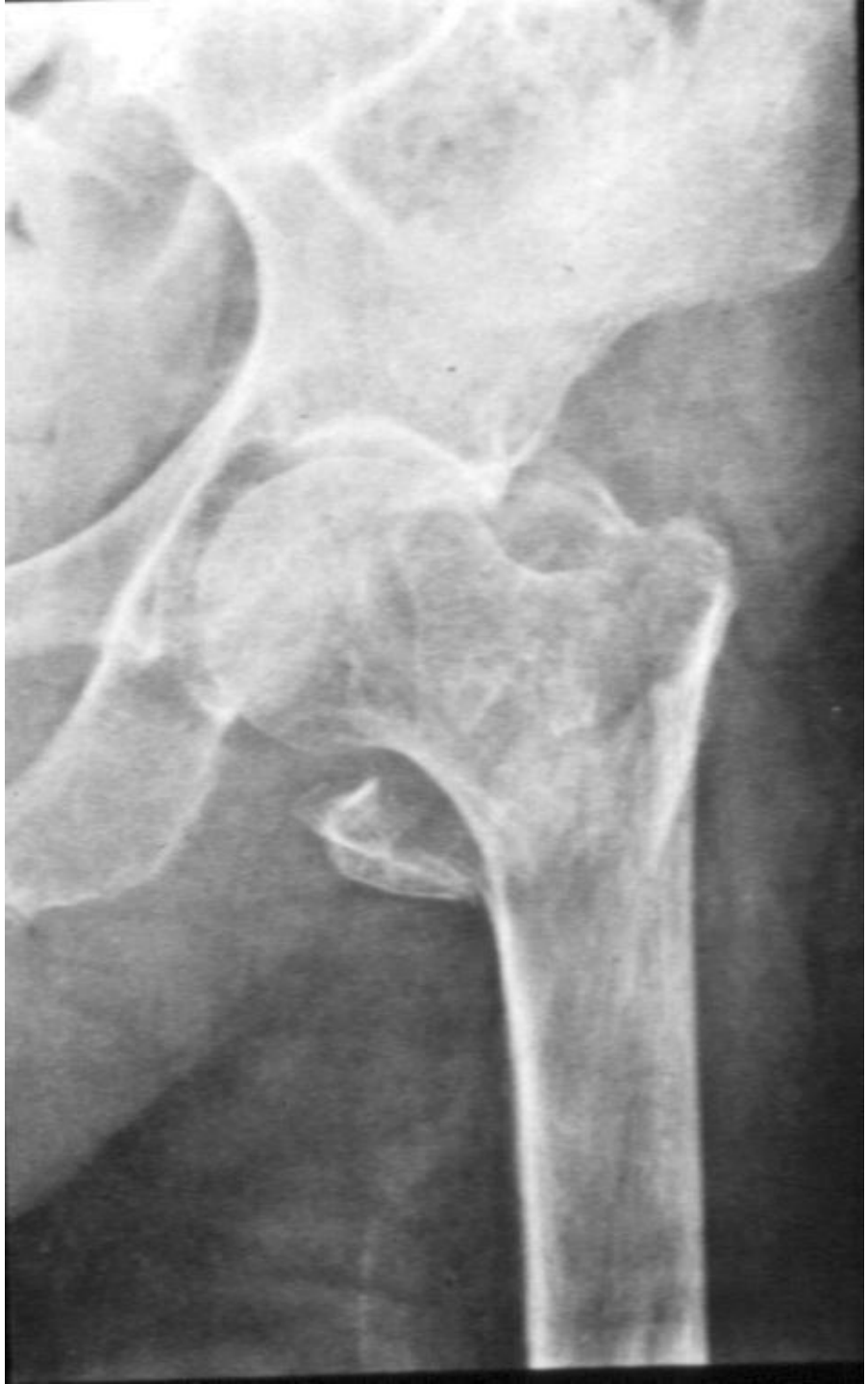
Techniques for Assessing Bone Mass

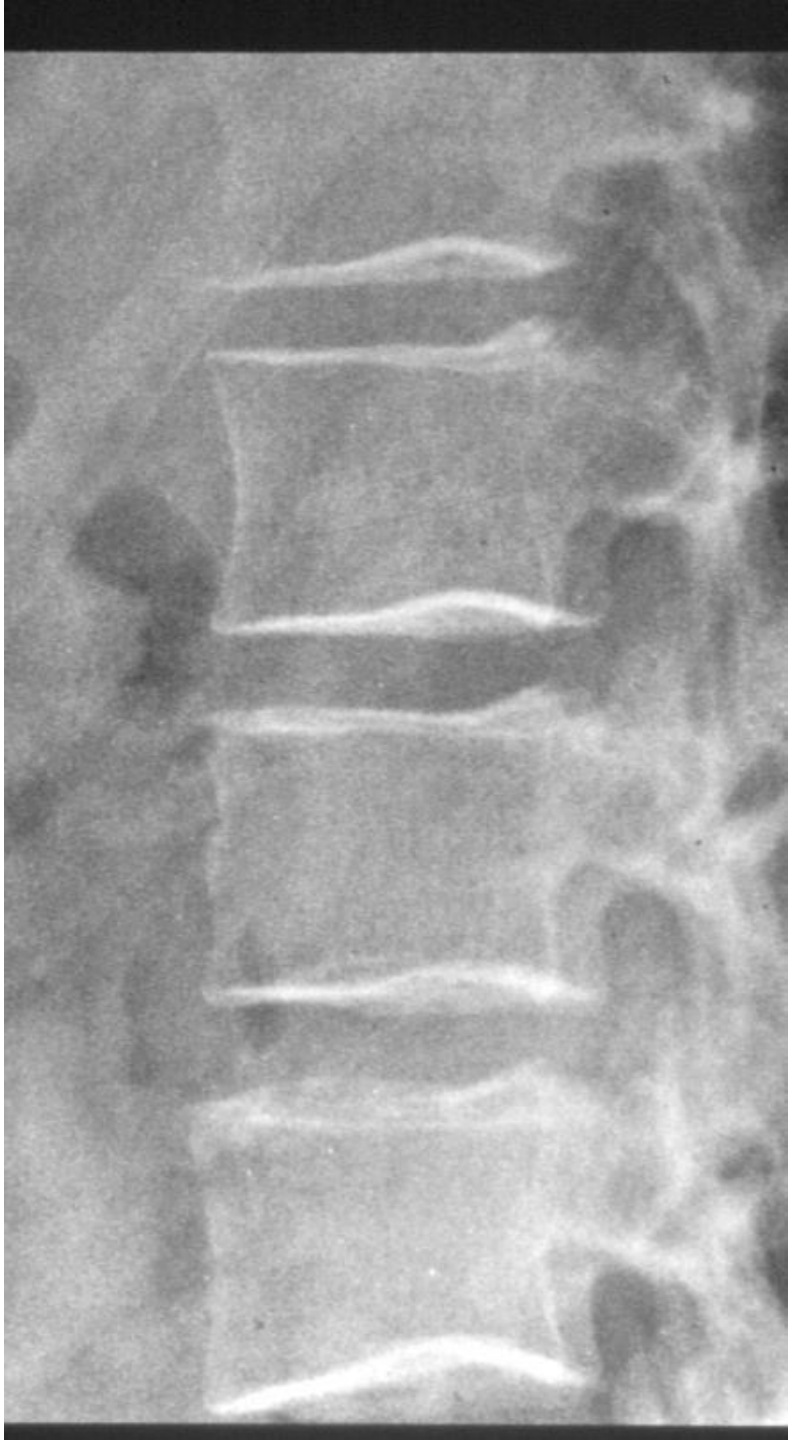
- A number of technologies can be used to assess mineral density including:
- Plain X-ray, especially of spine
- Assessment of bone mass
  - QCT (Quantitated Computer Tomography)
  - DPA (Dual Photon Absorptiometry)
  - DXA (Dual Energy X-ray Absorptiometry)
  - Ultrasound

Osteoporosis

X-rays

- Decrease bone density
- Wedging or biconcave vertebrae
- Thin cortex and deformities
- Dexa Scan
- Biopsy



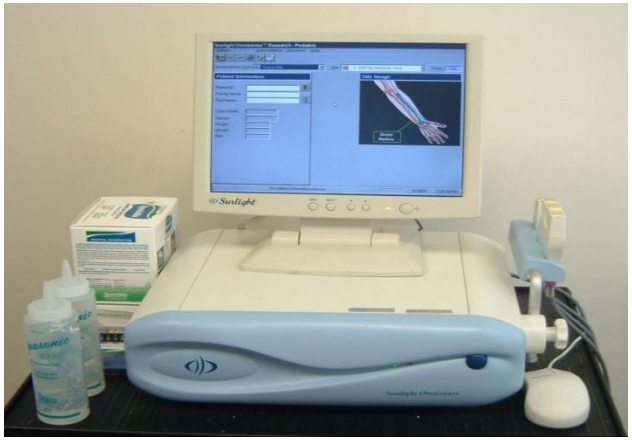


- Quantitative ultrasound (QUS) was also well tolerated and was technically easy to perform
- Speed of sound (SOS) shows a significant correlation with BMD as measured by DXA
- With the added advantage that it is free from radiation risk, further assessment of this potentially valuable tool for measuring bone status in children is warranted

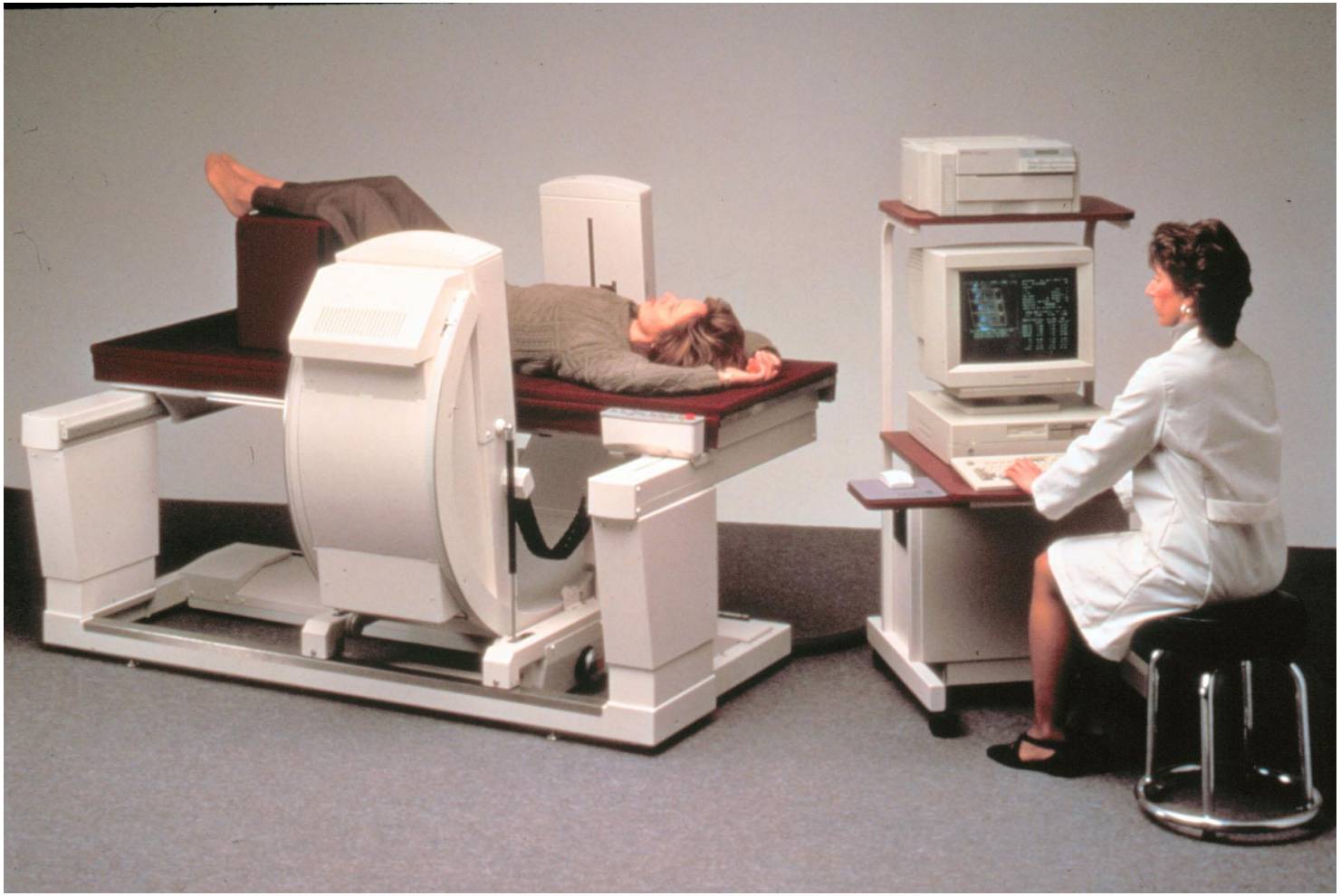
Quantitative ultrasound (QUS)

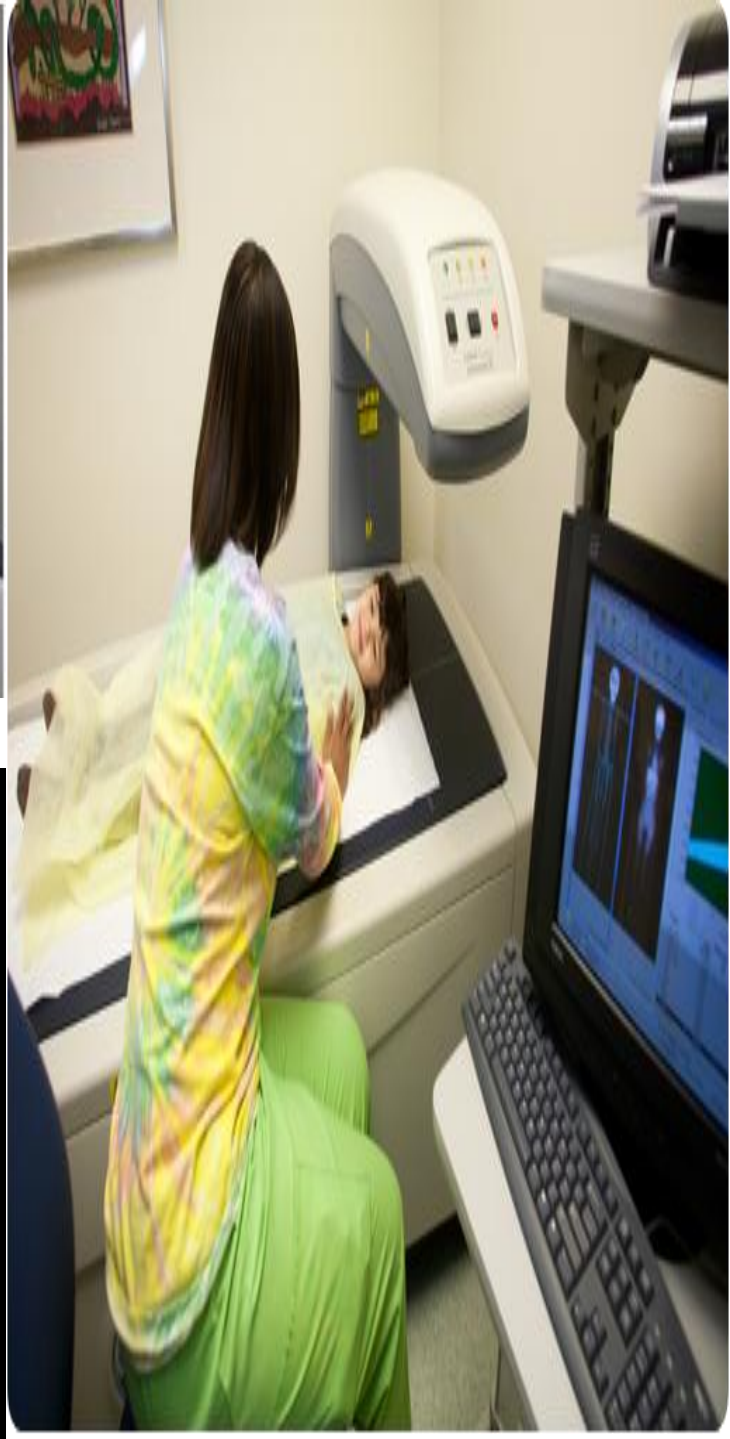
Peripheral QCT

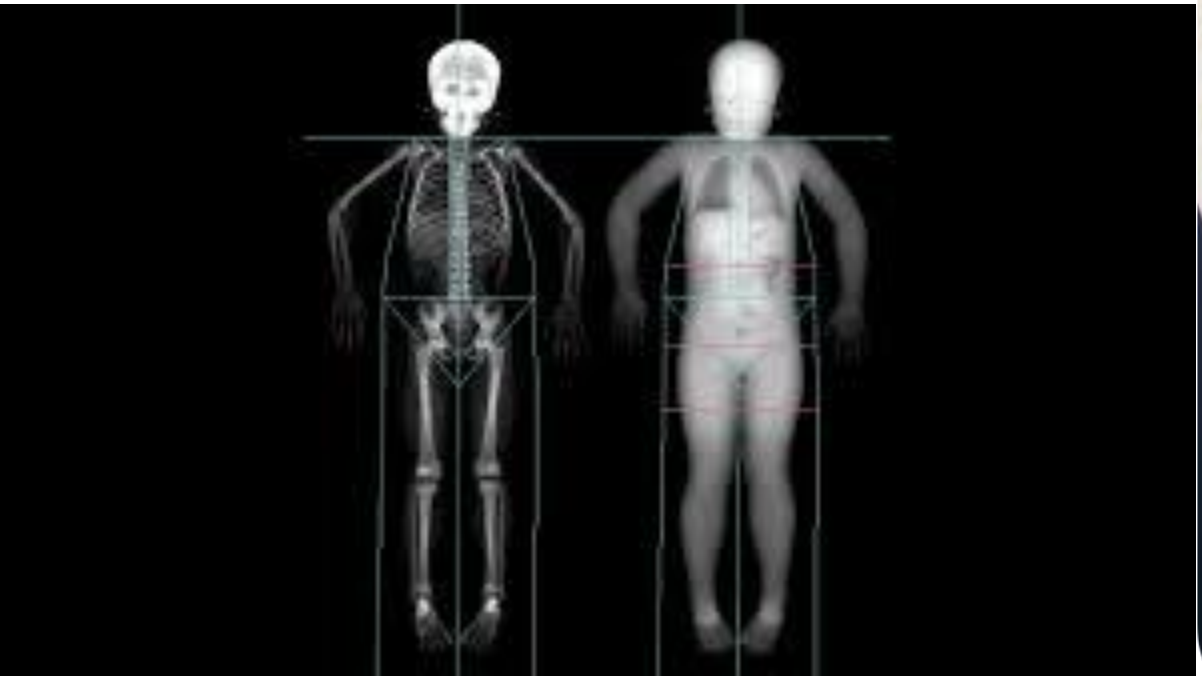
Quantitative Ultrasound



DXA scanner – open configuration







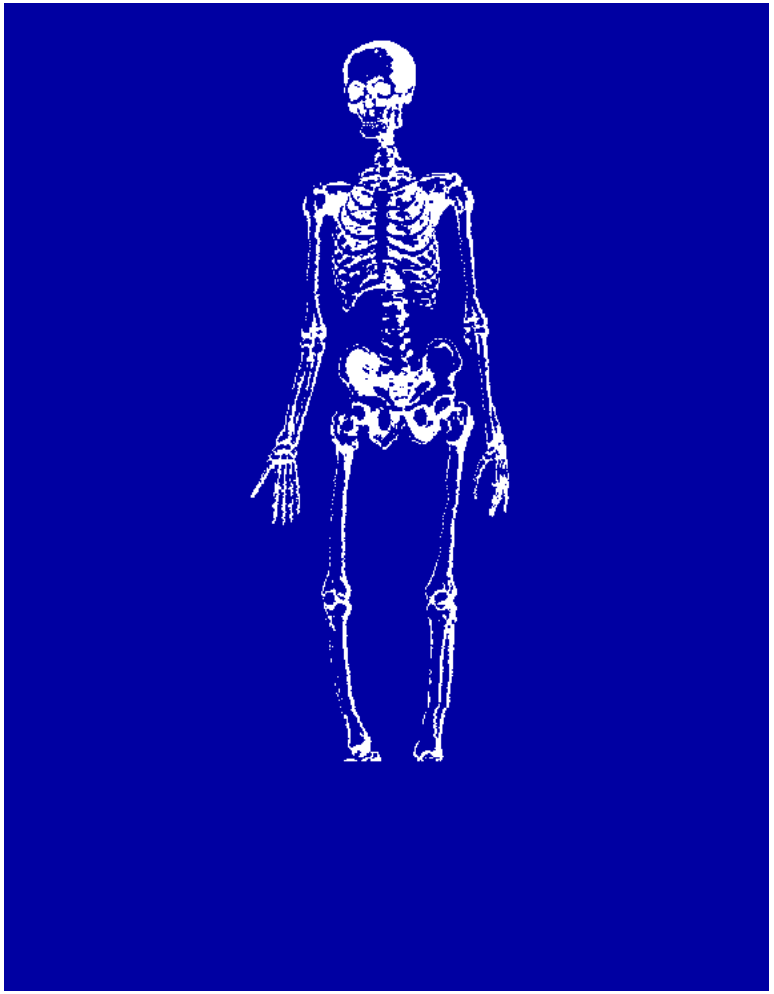
DXA software

total body

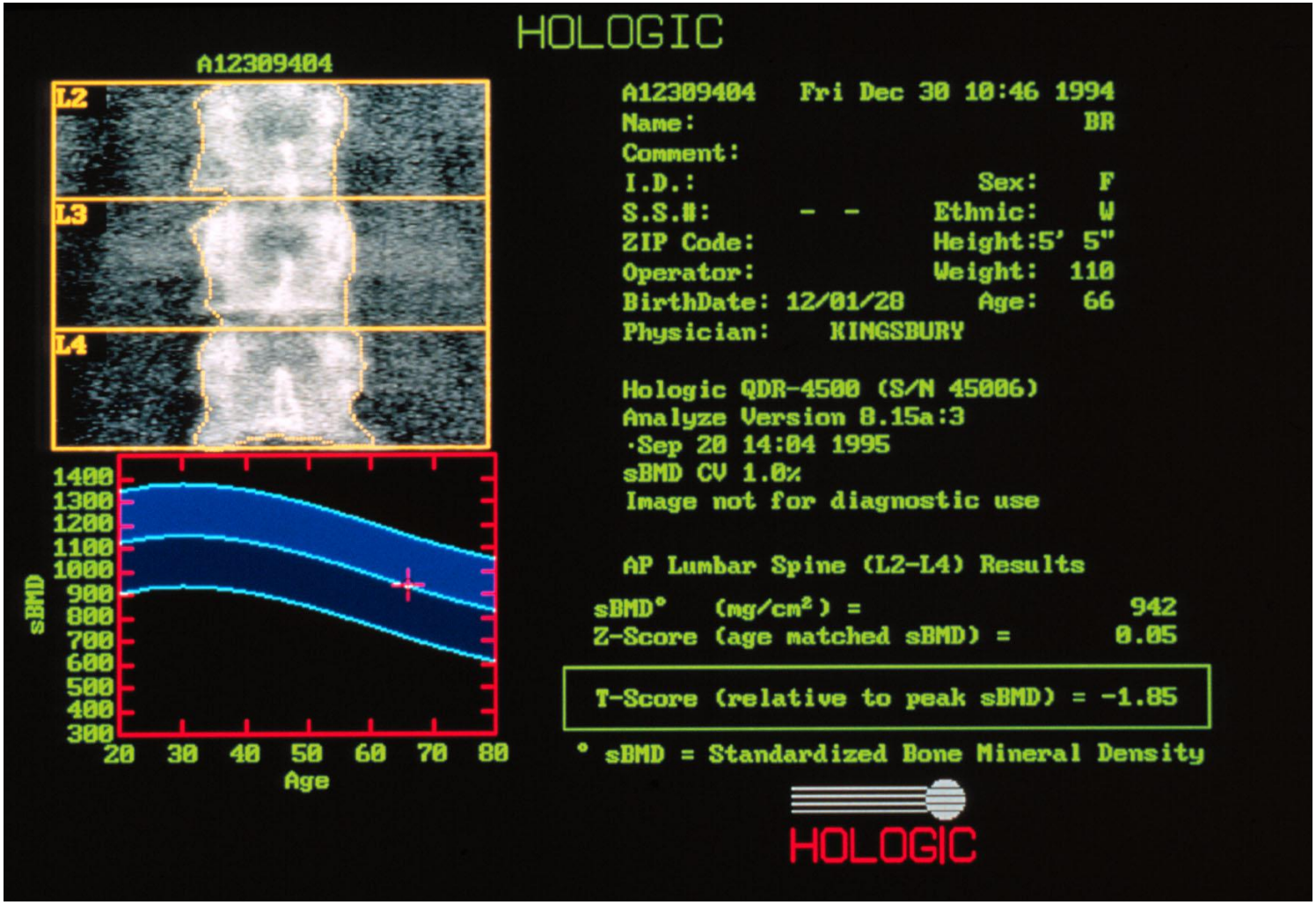
spine

femur

forearm



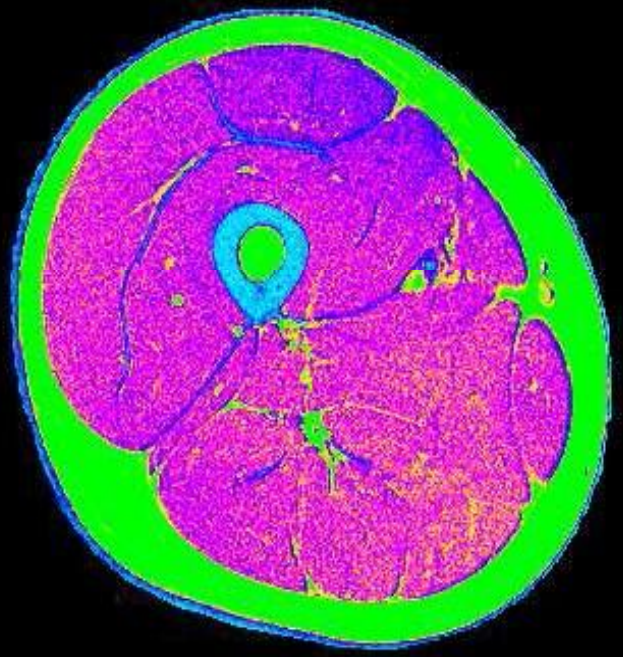
DXA Results: rate-of-change curve



- The interpretation of densitometry data in the young is difficult because "normal" BMD values has to be corrected for:
  - gender, body size, pubertal stage, skeletal maturation and ethnicity
- No regional references in children in most countries
- In children, we cannot use T- score, only Z score
- Radiologist reporting DXA scan for children, gave areal not BMD T scores !?

Geometry Assessment using MRI

Scout Scan

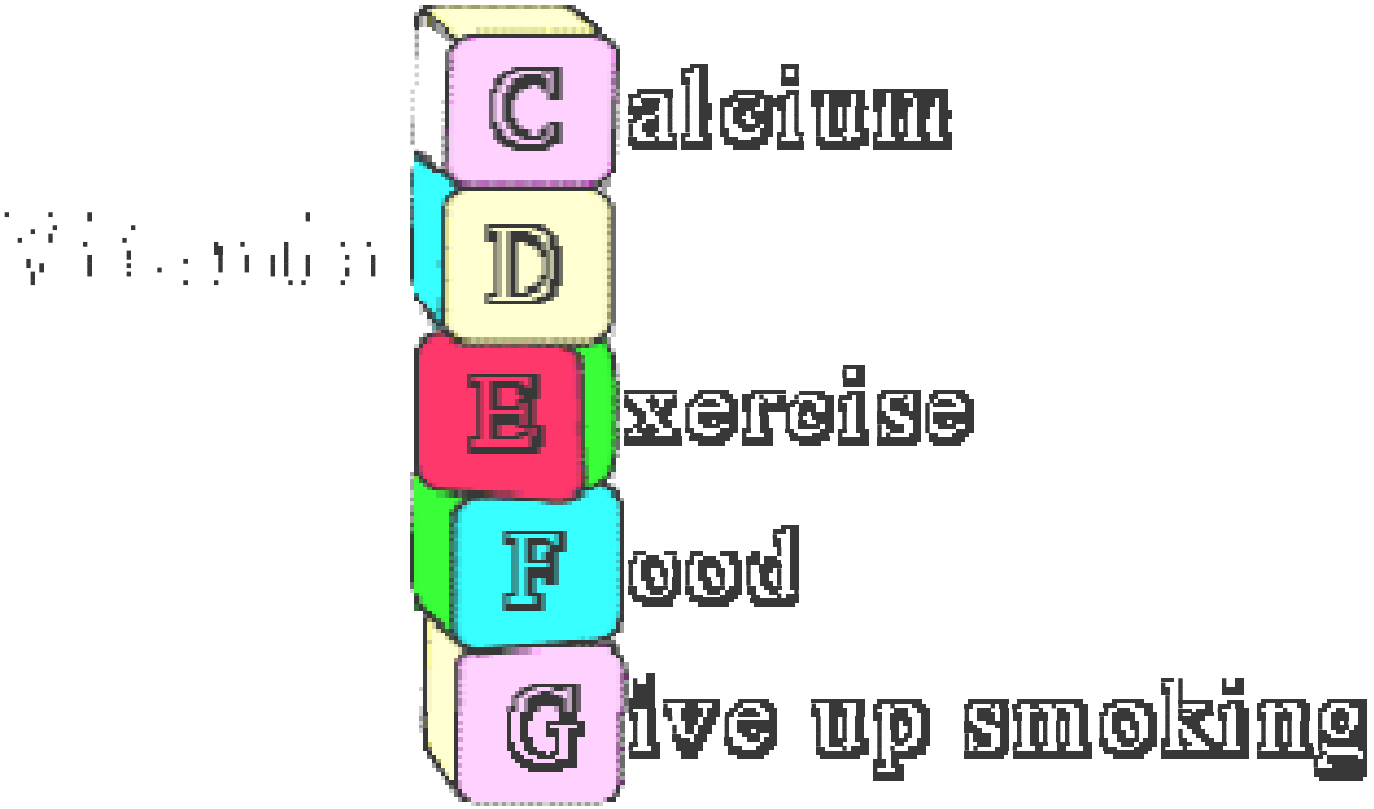


Middle Slice of Mid-Third Region

- MRI - Geometry (mid-femoral shaft)
  - cortical width/ area /volume
  - medullary cavity width
  - shape
  - muscle parameters

- MRI can be useful in the assessment of metabolic bone disease
- MRI can be used to discriminate between acute and chronic fractures of the vertebrae and occult stress fractures of the proximal femur
- These osteoporotic fractures demonstrate characteristic changes in the bone marrow that distinguish them from other uninvolved parts of the skeleton and the adjacent vertebrae

Prevention



Treatment

Established treatment

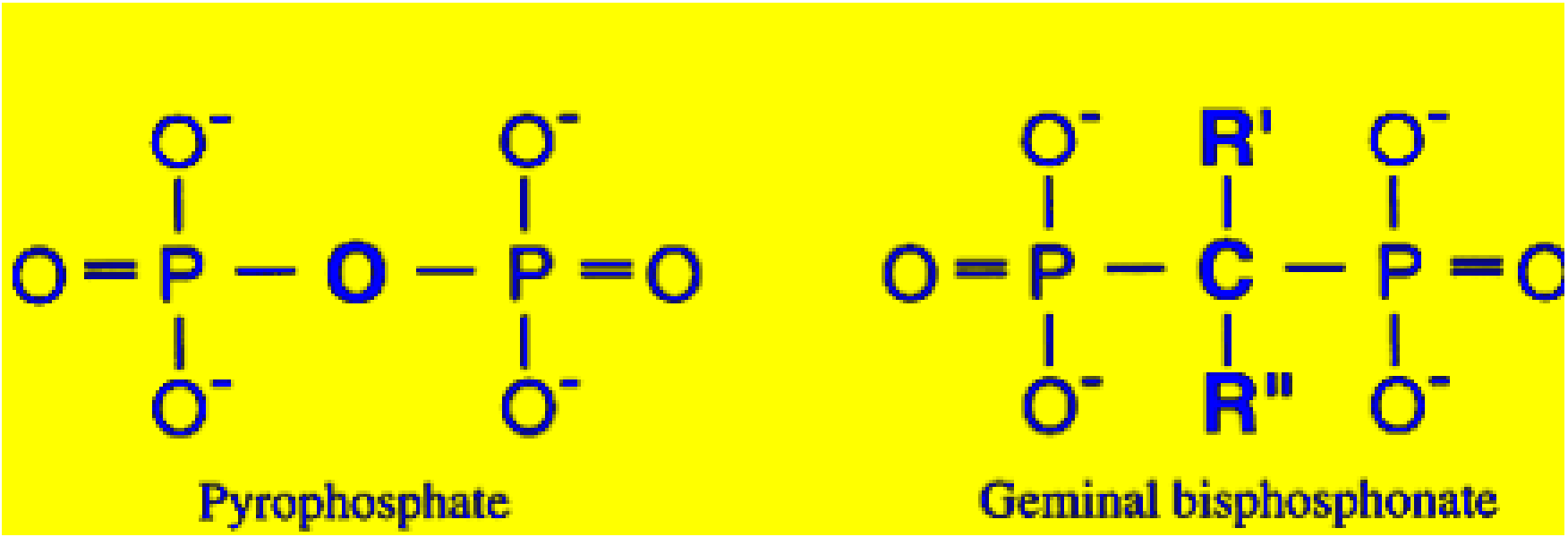
- calcium supplementation & vitamin D
- Calcitonin
- Bisphosphonates

Experimental treatment

- Combination therapy
- Thiazide
- Fluoride
- PTH
- GH

Bisphosphonates

Chemical structure of pyrophosphate and bisphosphonates

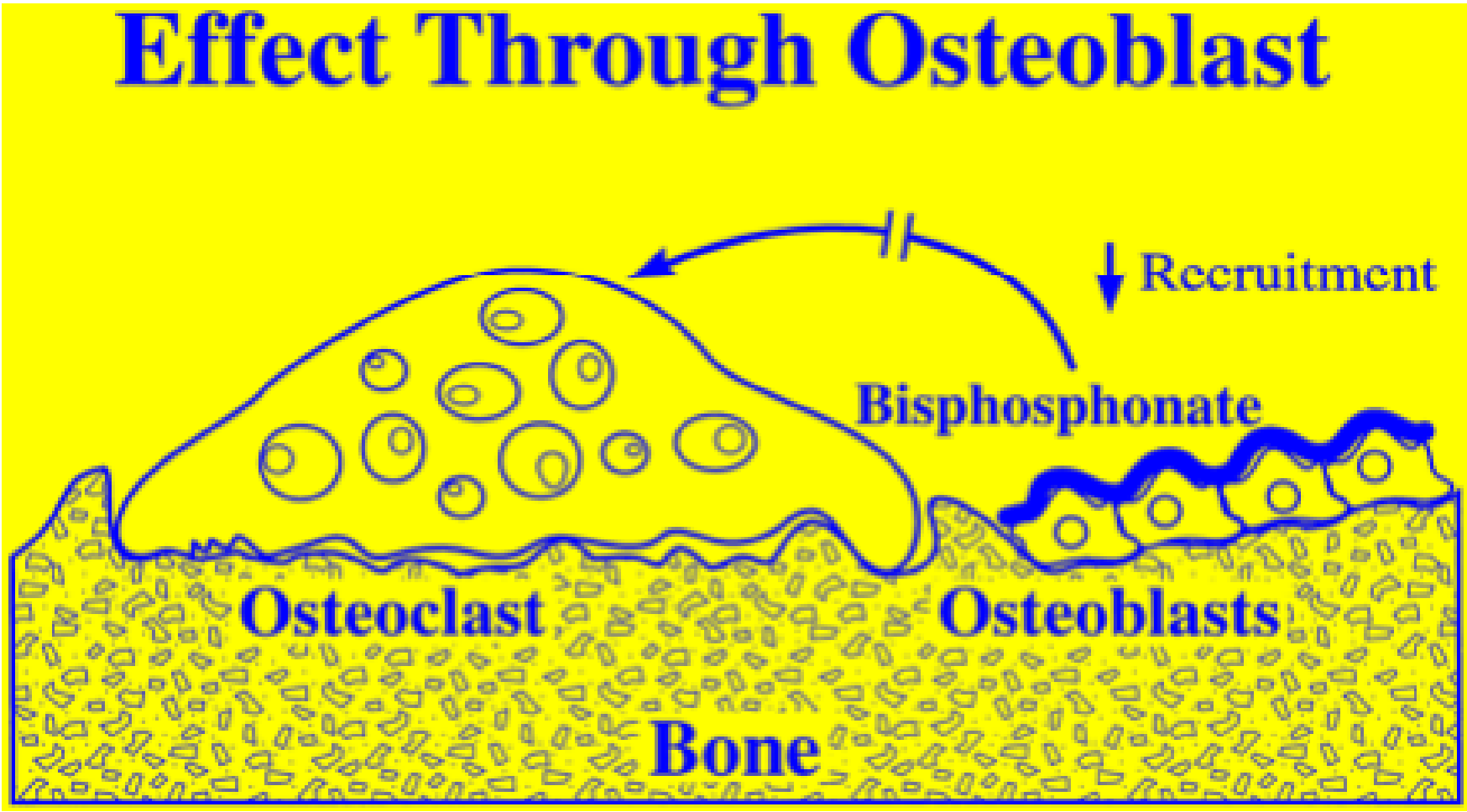


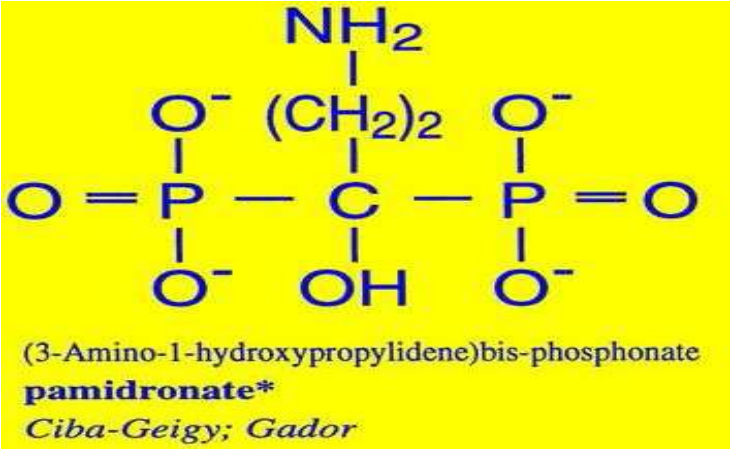
Bisphophonates

- Bisphosphonates are a class of medicines which mimic the structure of pyrophosphate, a natural component of normal bone

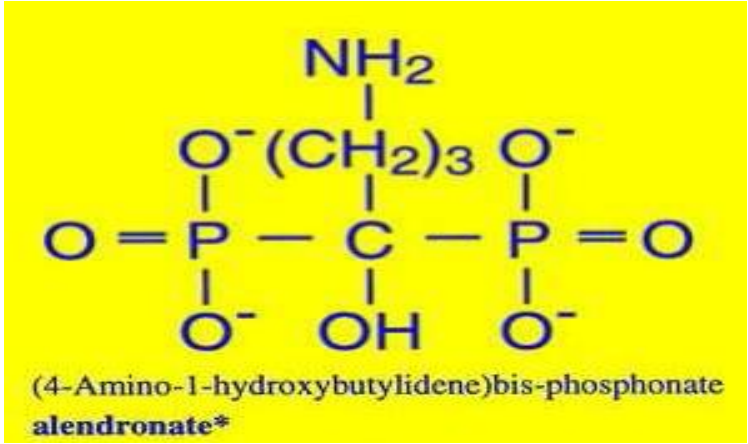
- Pamidronate or Zolodronate is selectively deposited in the skeleton
- The trials in children have all involved intravenous use
- It has turned out that intermittent use is particularly effective with children

Effect Through Osteoblast

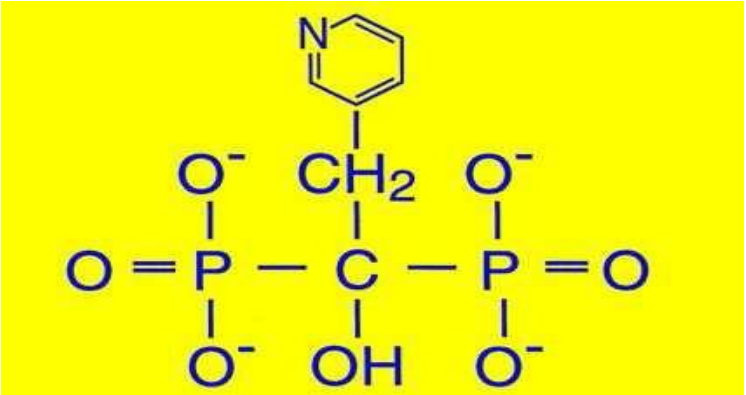




(3-Amino-1-hydroxypropylidene)bis-phosphonate
pamidronate*
Ciba-Geigy; Gador



(4-Amino-1-hydroxybutylidene)bis-phosphonate
alendronate*



[1-Hydroxy-2-(3-pyridinyl)-ethylidene]bis-phosphonate
risedronate

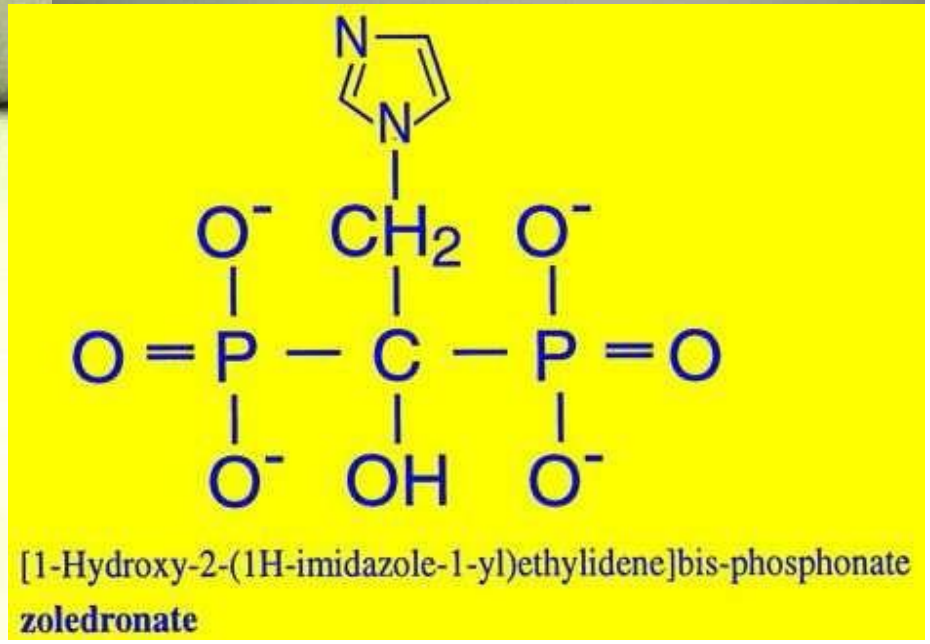
[1-Hydroxy-2-(1H-imidazole-1-yl)ethylidene]bis-phosphonate
zoledronate

Clinical indications for bisphophonate therapy

1. Treatment of acute hypercalcaemia (immobilization, malignancies -related)
2. Osteogenesis imperfecta
3. Juvenile idiopathic osteoporosis
4. Osteopenia (C.P, Paraplegia)
5. Fibrous dysplasia (McCune-Albright)
6. Steroid induced osteoporosis
7. Juvenile Rheumatoid arthritis

Clinical indications for bisphophonate therapy

8. Idiopathic infantile aortic calcification
9. Familial idiopathic hyperphosphatasia
10. Myositis Ossificans
11. Gaucher's disease "acute bone crisis"
12. Others ……etc



[1-Hydroxy-2-(1H-imidazole-1-yl)ethylidene]bis-phosphonate

zoledronate

Zoledronate

- Zoledronate is the most potent of the clinically tested compounds
- Third-generation bisphosphonate
- 100-850 times more active than pamidronate in several in vivo and in vitro pharmacological test
- The new generation of bisphosphonates are likely to increase clinical options in terms of administration regimens, but their real advantage over those already available in terms of clinical efficacy remains uncertain.
- The effective doses (in adults) ranged from 2 to 4 mg

Bisphosphonates

Side effects

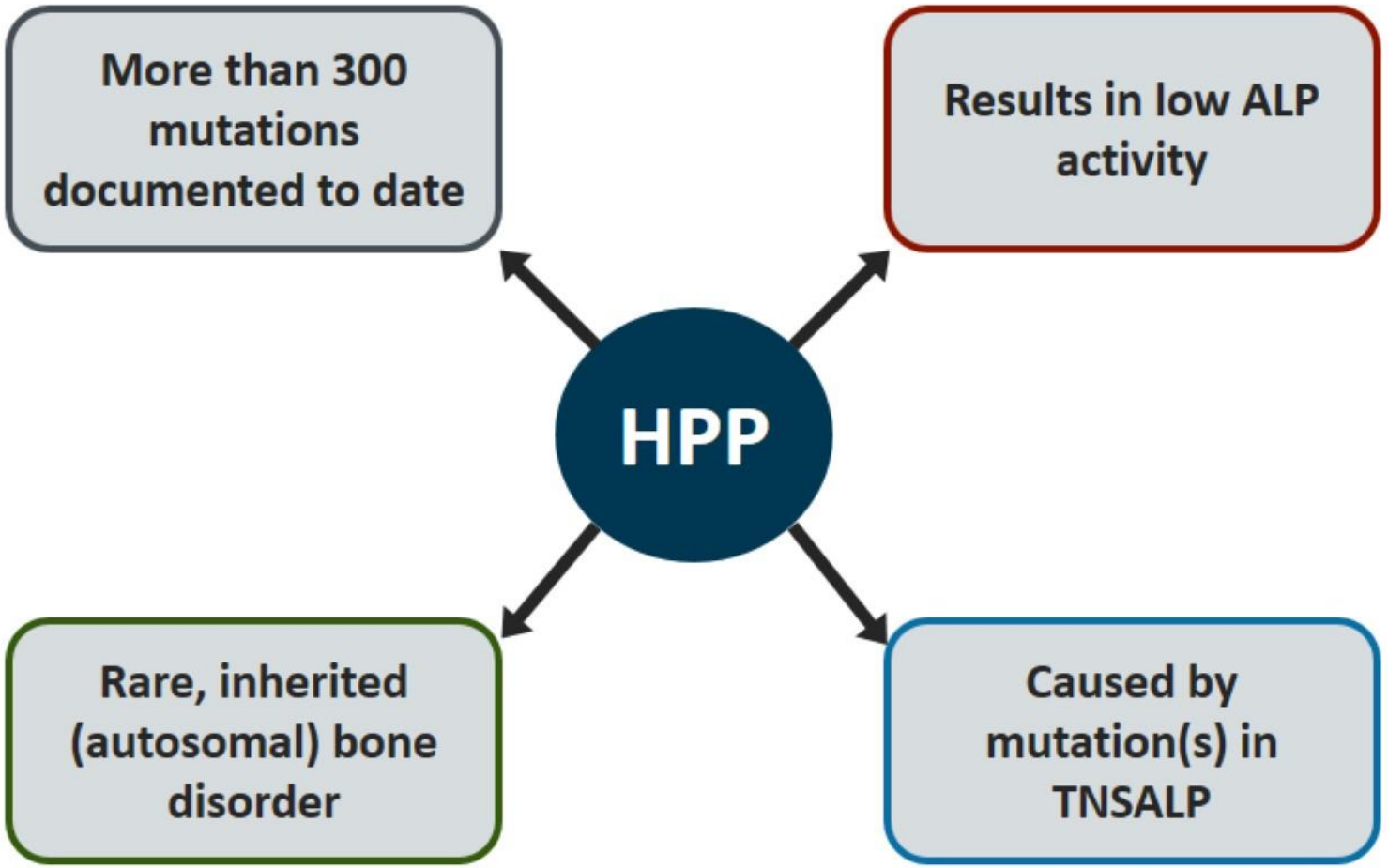
- long term safety uncertain

- Acute side effects include:
  - transient hypocalcemia (IV)
  - pyrexia (IV)
  - Myalgia & bone pain (IV)
  - GI disturbances (oral)
    - Esophagitis, GOR, oesophageal perforation

Hypophosphatasia

- Is an autosomal recessive inherited disorder characterized by a deficiency of the tissue-nonspecific (liver, bone, and kidney) isoenzyme of alkaline phosphatase
- The severity of clinical expression is remarkably variable and spans intrauterine death from profound skeletal hypomineralization at one extreme to lifelong absence of symptoms at the other.
- As a consequence, six clinical disease types are distinguished.
- The age at which skeletal disease is initially noted delineates, in large part, the perinatal (lethal), infantile, childhood, and adult variants of the disorder
- affected children and adults may manifest only the unique dental abnormalities of the syndrome and, accordingly, are classified as having odontohypophosphatasia.

What is HPP?



Bianchi ML. *Osteoporos Int*. 2015;26:2743-2757.

Radiographic Findings of HPP[1]: Progressive Skeletal Demineralization (example 1)

Birth 5 months old 7 months old

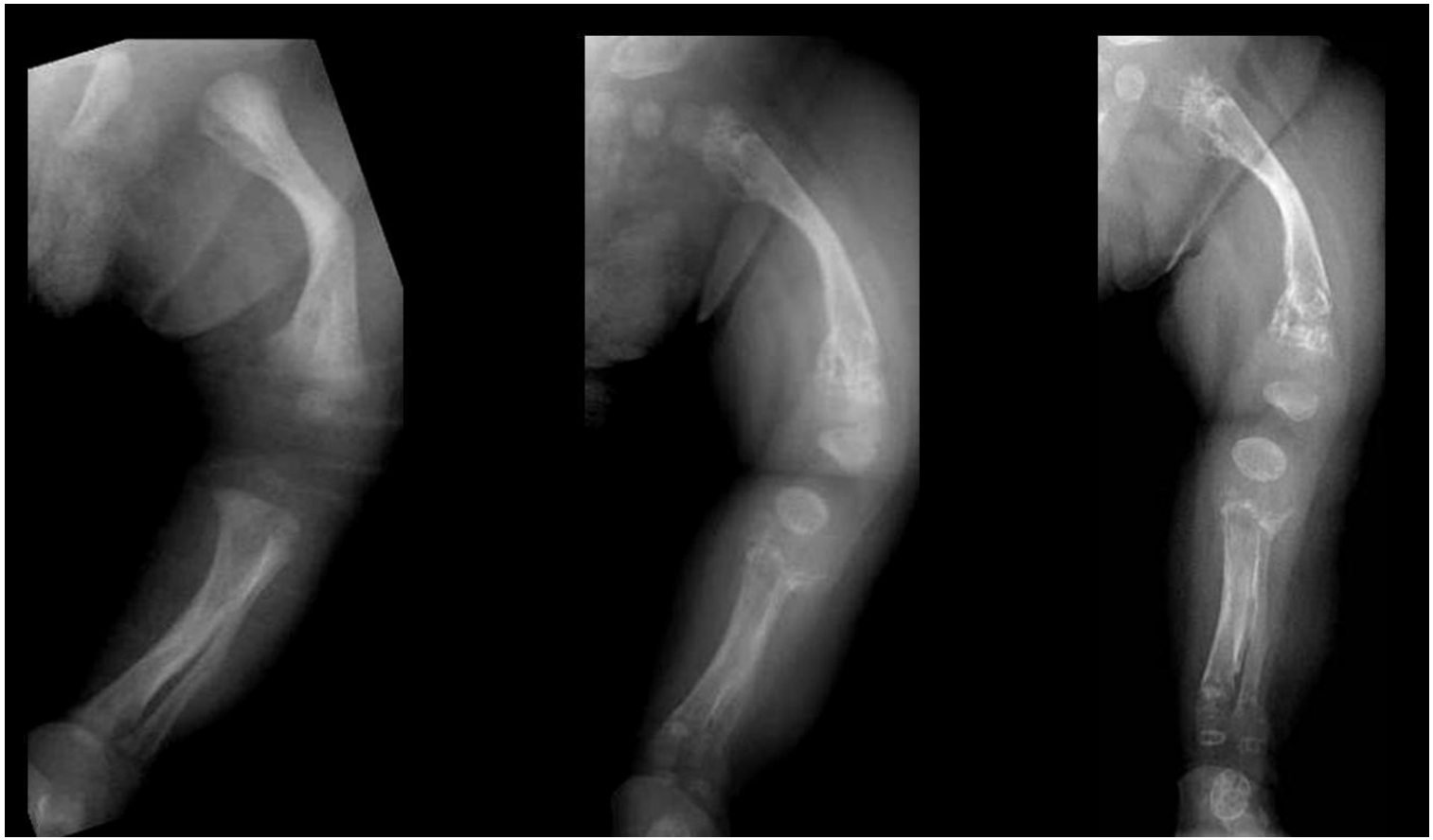
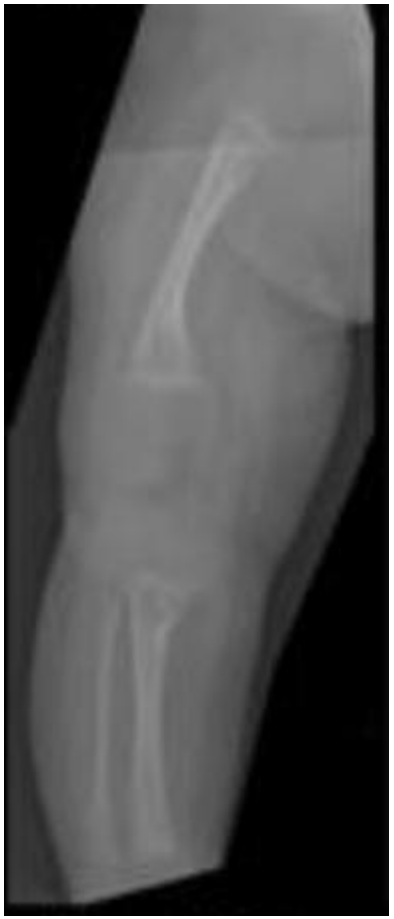


Figure Permission provided by Copyright Clearance Center for License Agreement from Massachusetts Medical Society, The New England Journal of Medicine: License #3332610589774 and #3544470213379

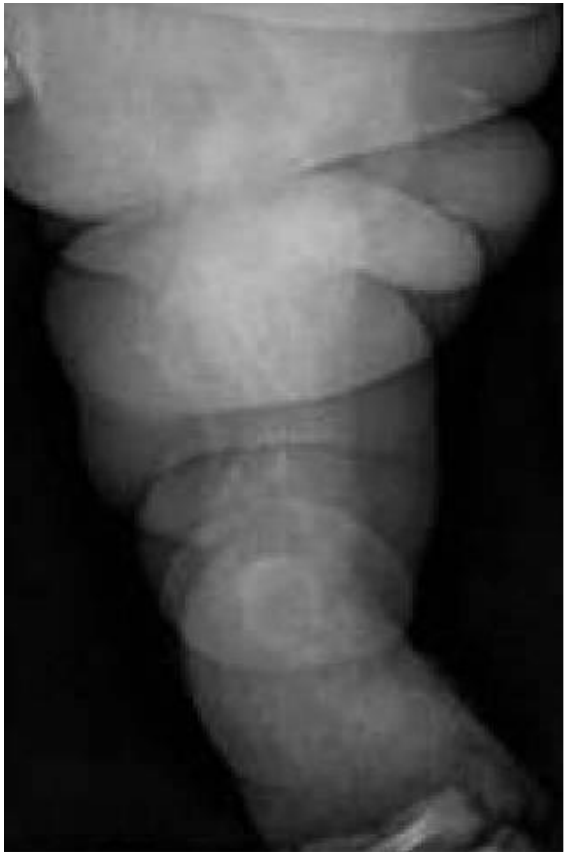
1. Whyte, M. (2012)

Radiographic Findings of HPP[1]: Progressive Skeletal Demineralization (example 2)

7 weeks old

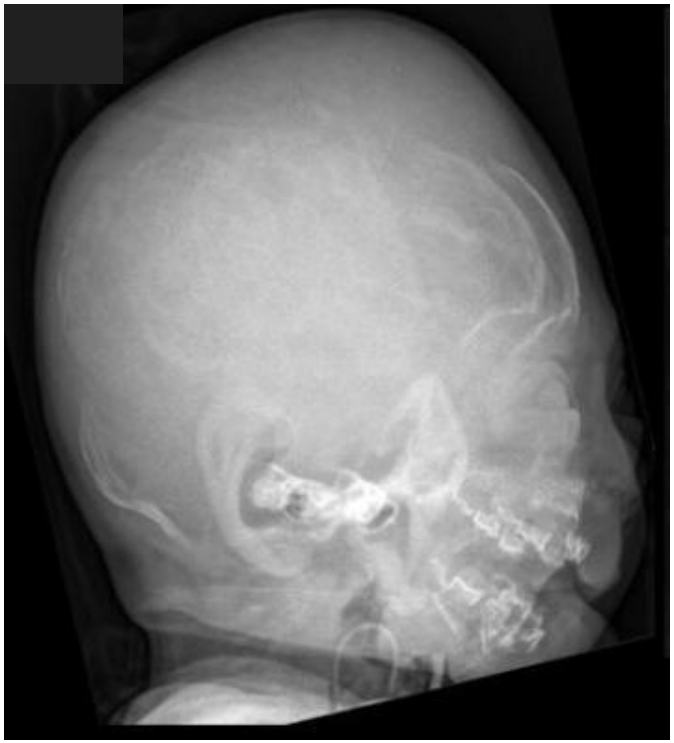


33 months old

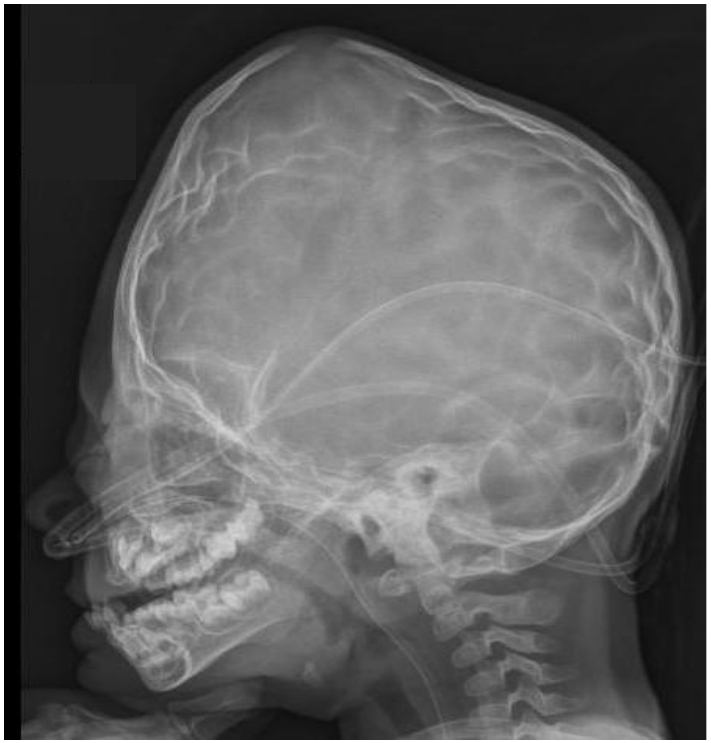


1. Whyte, M. (2012)

20 months old

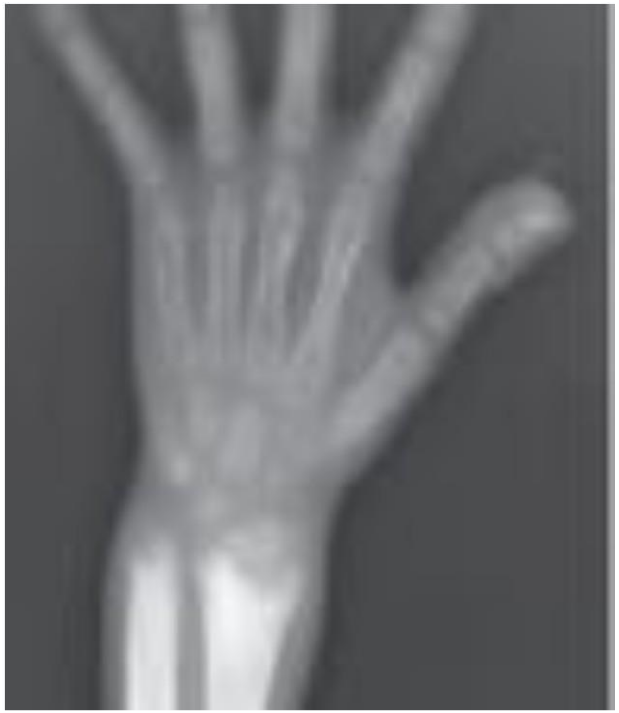


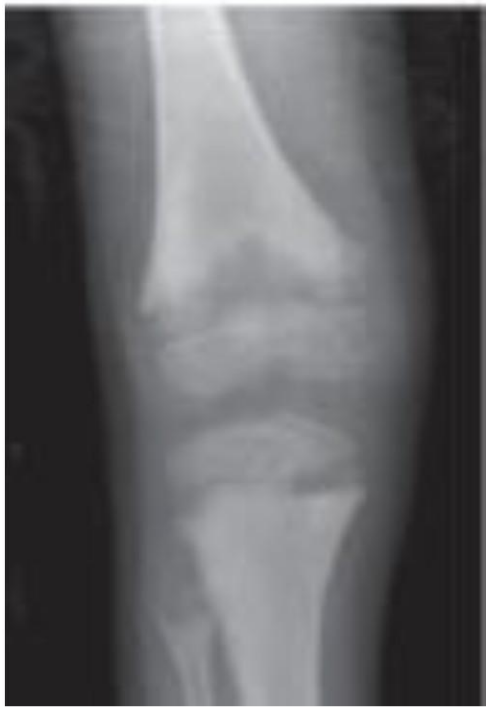
33 months old



1. Whyte, M. (2012)

Radiographic Findings in Children with HPP[1]

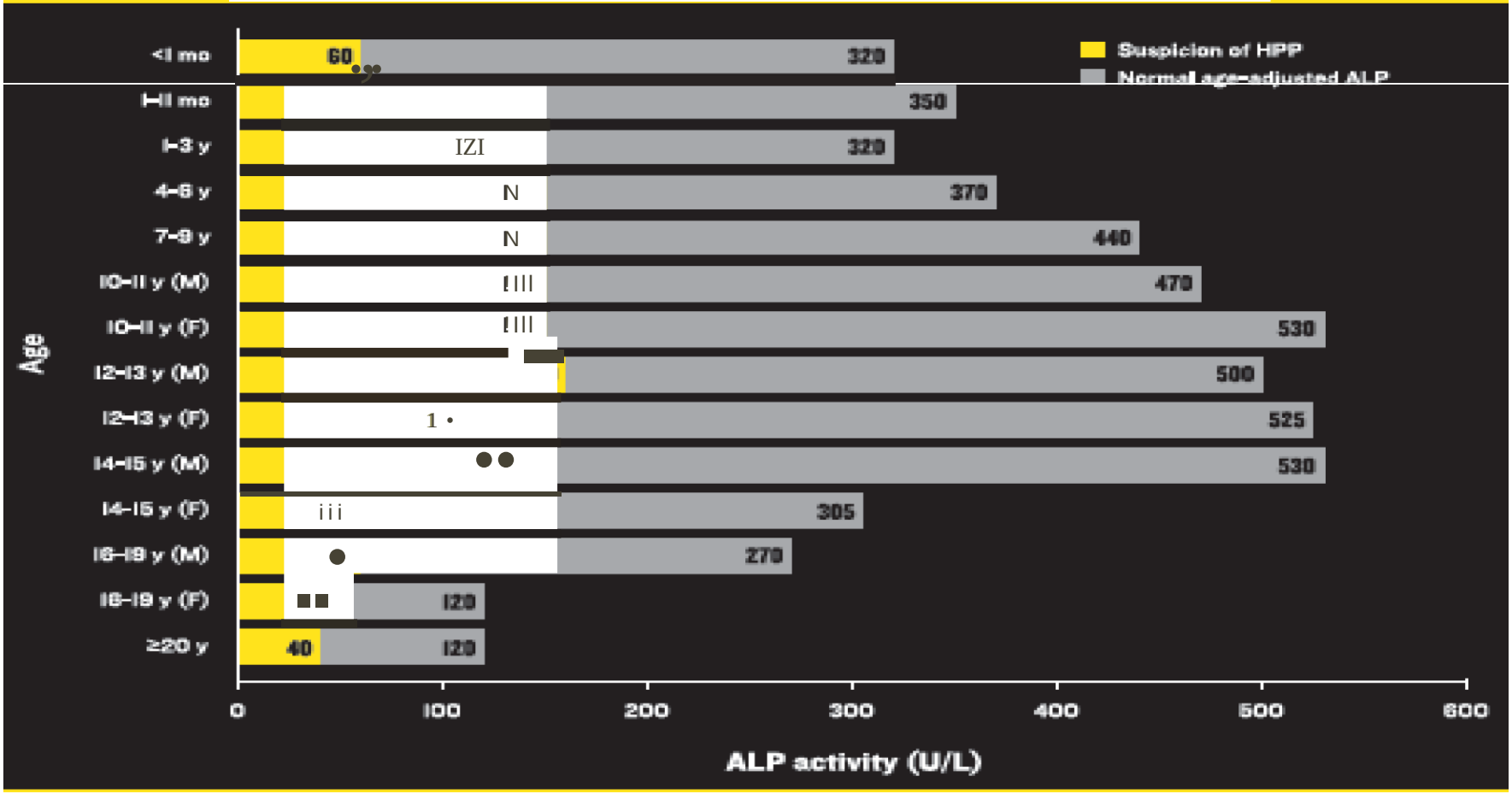




1. Madson , K. (2014)

ALP varies with Age and Gender

AGE- AND GENDER-ADJUSTED ALP REFERENCE RANGES (U/L) [3,23]



ALP activity is higher in infants, children, and adolescents than in adults

Treatment

Asfotase Alfa (Strensiq) NOW APPROVED.

- S/C injection 3 or 6 times a week.

Calcium Disorders

Neonatal Hypocalcaemia

- Early Neonatal Hypocalcaemia (48-72 hour of birth)
  - Prematurity
  - small for gestational age
  - Birth asphyxia
  - infant of GDM
  - Sepsis

Neonatal Hypocalcaemia

- Late Neonatal Hypocalcaemia (3-7 Days of birth & as late as 6 weeks of age)
  - Exogenous phosphate load which is the most commonly seen in developing countries.
    - Feeding with phosphate-rich formula or whole cow's milk which has seven times phosphate load of breast milk.
  - Magnesium deficiency leads to functional hypoparathyroidism
  - Transient or permanent hypoparathyroidism of newborn
  - Maternal hyperparathyroidism
  - Congenital vitamin D deficiency

Hypocalcaemia in children

- The most common causes of hypocalcaemia
  - Vitamin D deficiency
  - Chronic renal failure
  - Hypomagnesaemia
  - Hypoparathyroidism
  - Pseudohypoparathyrodism
  - Acute pancreatitis
  - Less frequently, seen in critically ill patients with sepsis, burns, and acute renal failure
  - Transient hypocalcaemia can be observed after administration of a number of drugs
    - heparin, glucagon & protamine
    - massive transfusions of citrated blood products
    - Bisphosphonate therapy

Hypocalcaemia in children

- Activation mutation of the calcium sensing receptor (CaSR) which is inherited as an autosomal dominant, results in hypocalcaemia & hypomagnesaemia
  - gain-of-function mutation inhibits calcium reabsorption in the renal tubule, which results in urinary loss of calcium and magnesium
- Deletion 22q11.2 syndrome, where there is developmental defect of the parathyroid glands lead to hypoparathyroidism

Hypocalcaemia in children

- Hungry bone Phenomenon
  - State of severe hypocalcaemia, often after starting vitamin D therapy in nutritional rickets which might persists for few weeks after commencing vitamin D therapy or post surgical removal of parathyroid gland
  - Serum calcium is rapidly taken from the circulation and deposited into the bones
  - Usually takes 10-14 days to resolve
  - Vitamin d therapy should combine with calcium in first 2 weeks then vitamin D alone

Hypoparathyroidism

Transient hypoparathyroidism

- Preterm and low birth neonates are at increased risk, and as many as 50% of them might have a deficient surge in PTH that results in hypocalcaemia
- Occurs at (1-8 wk of age)
- PTH level is significantly lower than those in normal infants
- Due to functional immaturity of a delay in development of the enzymes that convert glandular PTH to secreted PTH
- Maternal Hypercalcemia from hyperparathyroidism can also cause prolonged suppression of PTH secretion in the neonate

Permanent Hypoparathyroidism

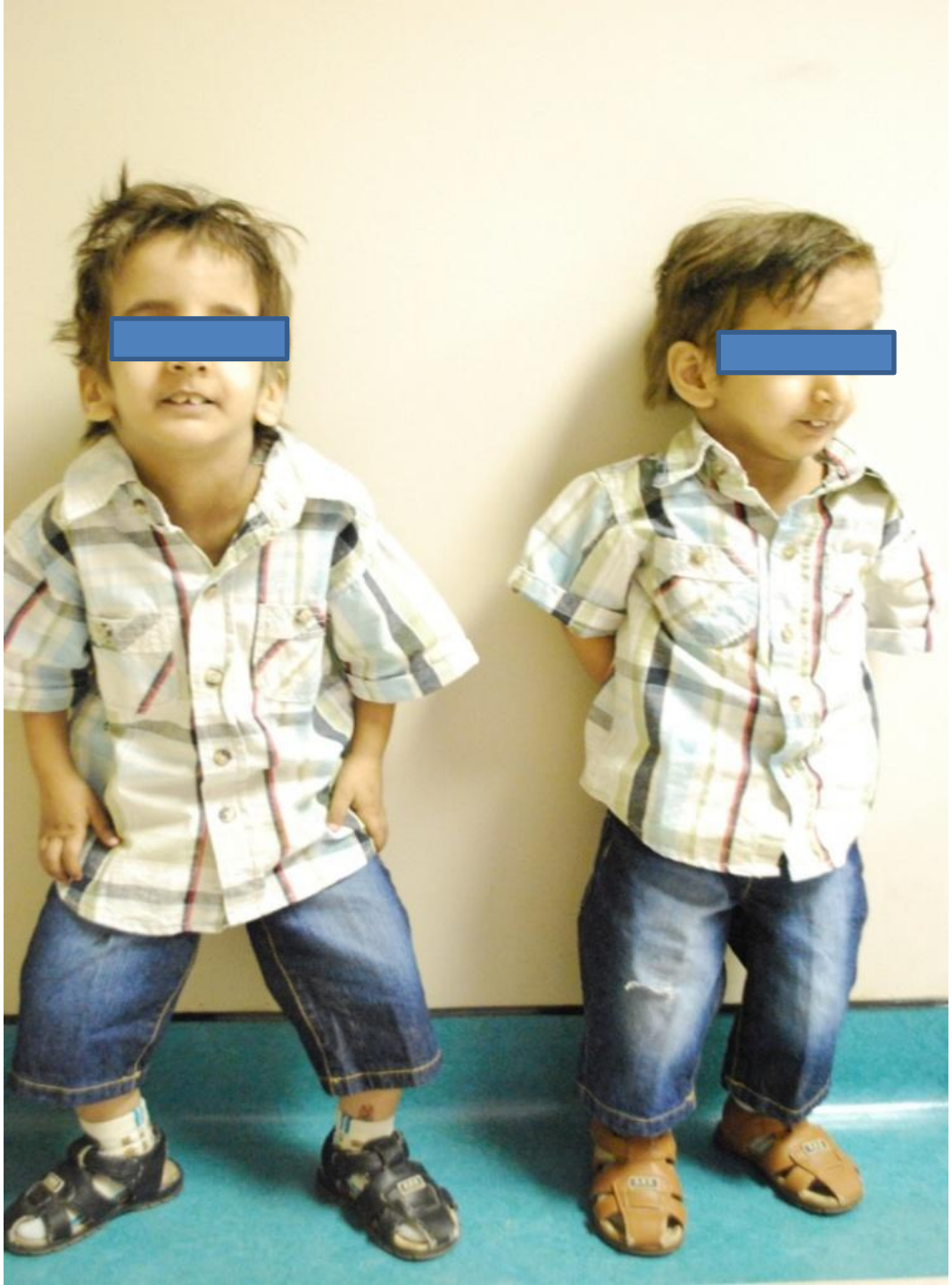
- DiGeorge syndrome
- X-linked recessive hypoparathyroidism
- HDR syndrome
  - hypoparathyroidism, deafness, &renal dysplasia
- Mitochondrial cytopathies, such as Kearns-Sayre syndrome (external ophthalmoplegia, ataxia, sensorineural deafness, heart block, and elevated cerebral spinal fluid protein

DiGeorge / velocardiofacial syndrome

- Prevalence of (1/4000)
- In 90% of patients, the condition is caused by a deletion of chromosome 22q11.2.
- Is associated with recurrent infections related to T-cell abnormalities& conotruncal abnormalities, such as tetralogy of Fallots & truncus arteriosus
- Aplasia of the thymus with severe immunodeficiency
- Cleft palate in 9%
- Renal anomalies in 35%
- Velopharyngeal insufficiency in 32%

Sanjad Sakati syndrome (SSS)

- Autosomal recessive disorder found exclusively in people of Arabian origin.
- It was first reported from the Kingdom of Saudi Arabia in 1988 as a newly described syndrome mainly from the Middle East and the Arabian Gulf countries.
- Children affected with this condition are born small for gestational age and present with hypocalcemic tetany or seizures due to hypoparathyroidism at an early stage in their lives.
- They have typical physical features
  - long narrow face, deep set small eyes, beaked nose, large floppy ears, micrognathia, severe failure to grow both intrauterine and extra uterine and mild to moderate mental retardation



Acquired Hypoparathyroidism

- Hypoparathyroidism incurred during neck surgery
- Radioactive iodine ablation of the thyroid
- Parathyroid gland destruction due to iron deposition (hemosiderosis) or copper deposition (Wilson's disease)
- Autoimmune polyendocrinopathy syndrome, type 1 (APS)

Autoimmune Hypoparathyroidism

- Parathyroid antibodies
- Autoimmune polyglandular disease type I

  autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APCED).
- Autosomal recessive
- *AIRE gene (autoimmune regulator);* chromosome 21q22
- One third of patients with this syndrome have all 3 components; 66% have only 2 of 3 conditions.

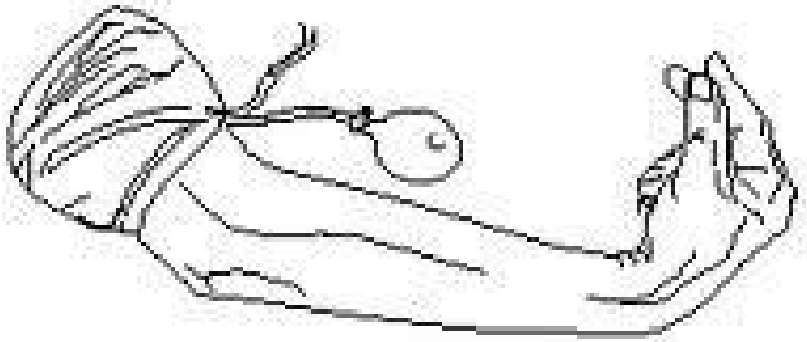
- The candidiasis almost always precedes the other disorders (70% of cases occur in children <5 yr of age);
- The hypoparathyroidism (90% after 3 yr of age) usually occurs before Addison disease (90% after 6 yr of age).
- Alopecia areata or totalis, malabsorption disorder, pernicious anemia, gonadal failure, chronic active hepatitis, vitiligo, and insulin dependent diabetes

Clinical Manifestations of Hypocalcaemia

- Manifestations of hypocalcaemia are primarily related to increased neuromuscular irritability
- Tetany is the classical sign of hypocalcaemia, but it is not always present
- Paresthesia is more common and often first occurs around the mouth or in the fingertips.
- They may progress to overt muscle spasm in the face and extremities, the latter typified by carpo-pedal spasm
- Muscular pain & cramps
- Numbness, stiffness, tingling of the hands & feet
- Convulsions with/without loss of consciousness

Clinical Manifestations of Hypocalcaemia

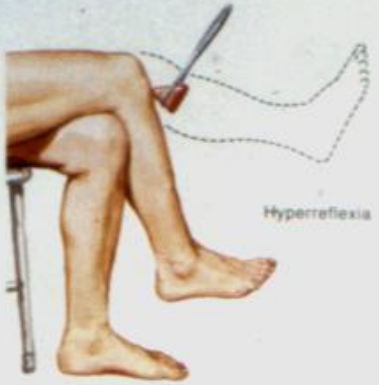
- Muscular pain and cramps
- Numbness, stiffness, tingling of hands & feet
- Convulsions with/without loss of consciousness
  - Trousseau's sign which is by induction of carpal spasm within 3 - 5 minutes of inflating a sphygmomanometer above systolic blood pressure while,
  - Chvostek's sign is by percussion of the facial nerve to induce involuntary contraction of the facial muscles including the corner of the mouth, nose, and eye on the same side



Clinical Manifestations of Hypocalcemia

Trousseau's sign

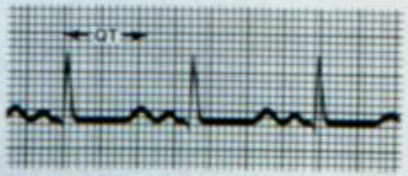
Chvostek's sign



Hyperreflexia

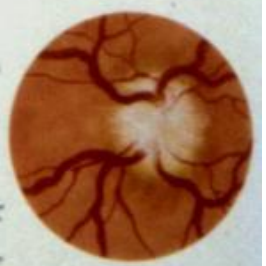
Stridor due to laryngeal spasm

Seizures



Electrocardiogram shows prolonged QT interval

Papilledema



Investigations of Hypocalcaemia

- Serum total and ionized calcium levels
- Serum albumin concentration should also be tested, as over 40% of circulating calcium is bound to albumin
- Intact parathyroid hormone levels should be tested in any patient with hypocalcaemia
- 25-hydroxyvitamin D, 1, 25 dihydroxyvitamin D, and alkaline phosphates levels may be useful in patients suspected of vitamin D deficiency
- Elevated urea and creatinine can indicate renal dysfunction.
- Amylase and lipase levels
- ECG should be performed which may show prolonged QT intervals, that may be the only sign of hypocalcaemia

Investigations of Hypocalcaemia

- Total lymphocyte and T-cell subset analyses: Findings are decreased in patients with DiGeorge syndrome and chest x-ray looking for the presence of thymus.
- Karyotype to assess for 22q11 and 10p13 deletion in cases of hypoparathyroidism.
- Maternal and family screening in familial forms of hypocalcaemia, such as those caused by activating mutations of the calcium-sensing receptor.
- X-rays should be performed when multiple fractures or signs of rickets or Osteomalacia are observed.
- DXA scans may be done in patients with suspected osteoporosis

Practical points

- Vitamin D deficiency is commonly seen in the developing countries and its supplement should be given to all age groups either as prophylactic or therapeutic doses depending on their vitamin D serum levels
- Congenital vitamin D deficiency in neonates & infants is not uncommon and best prevented by routine screening of the pregnant mothers
- Prophylactic or therapeutic doses of vitamin D during pregnancy and lactation is indicated to decrease the consequences of congenital vitamin D deficiencies in their babies especially tetany and seizures manifested because of hypocalcaemia

Practical points

- Intravenous infusion with calcium-containing solutions can cause severe tissue necrosis
- Necrosis of liver can occur after calcium infusion through an umbilical vein catheter placed in a branch of the portal vein.
  - The position of all umbilical vein catheters must be confirmed radiological before infusing calcium-containing solutions
- Rapid infusion of calcium-containing solutions through arterial lines can cause arterial spasm and, if administered via an umbilical artery catheter, intestinal necrosis.

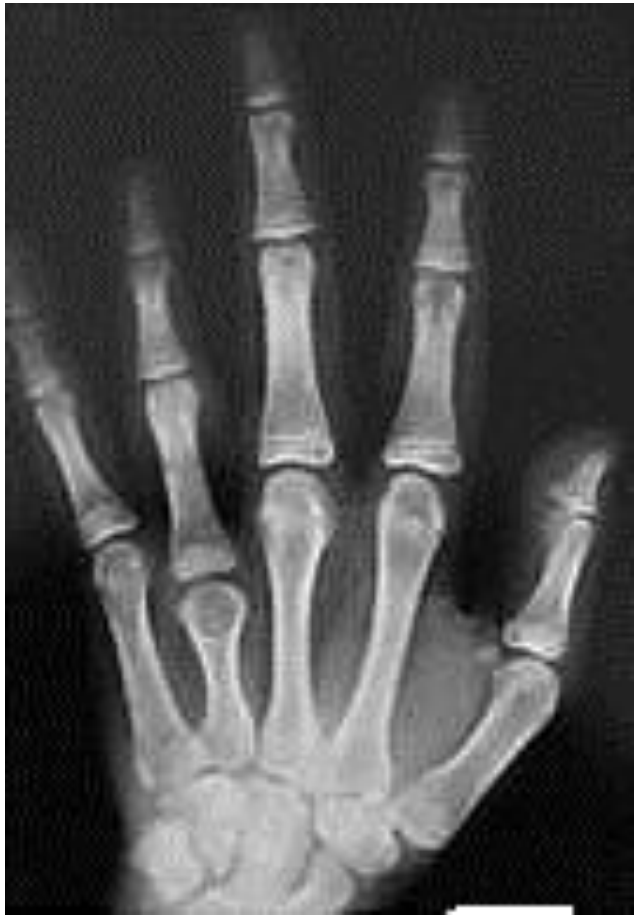
Pseudohypoparathyroidism

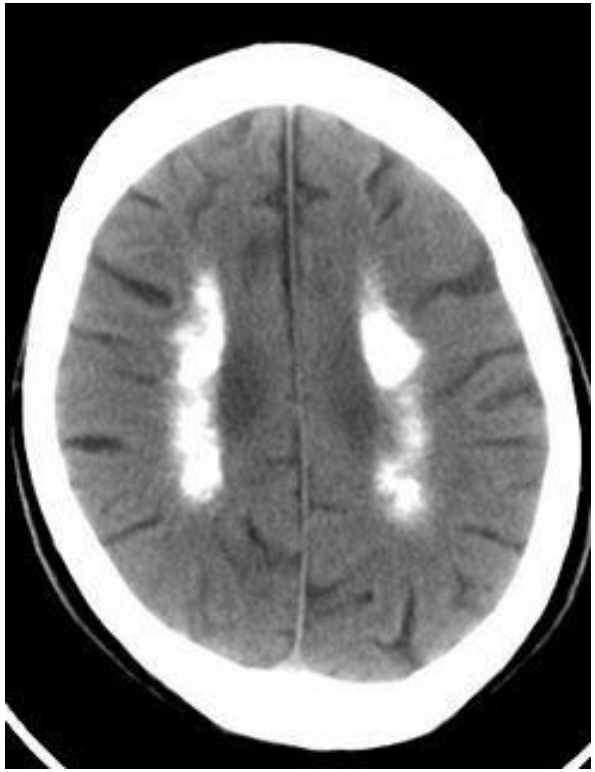
(Albright Hereditary Osteodystrophy)

Pseudohypoparathyroidism (Albright Hereditary Osteodystrophy)

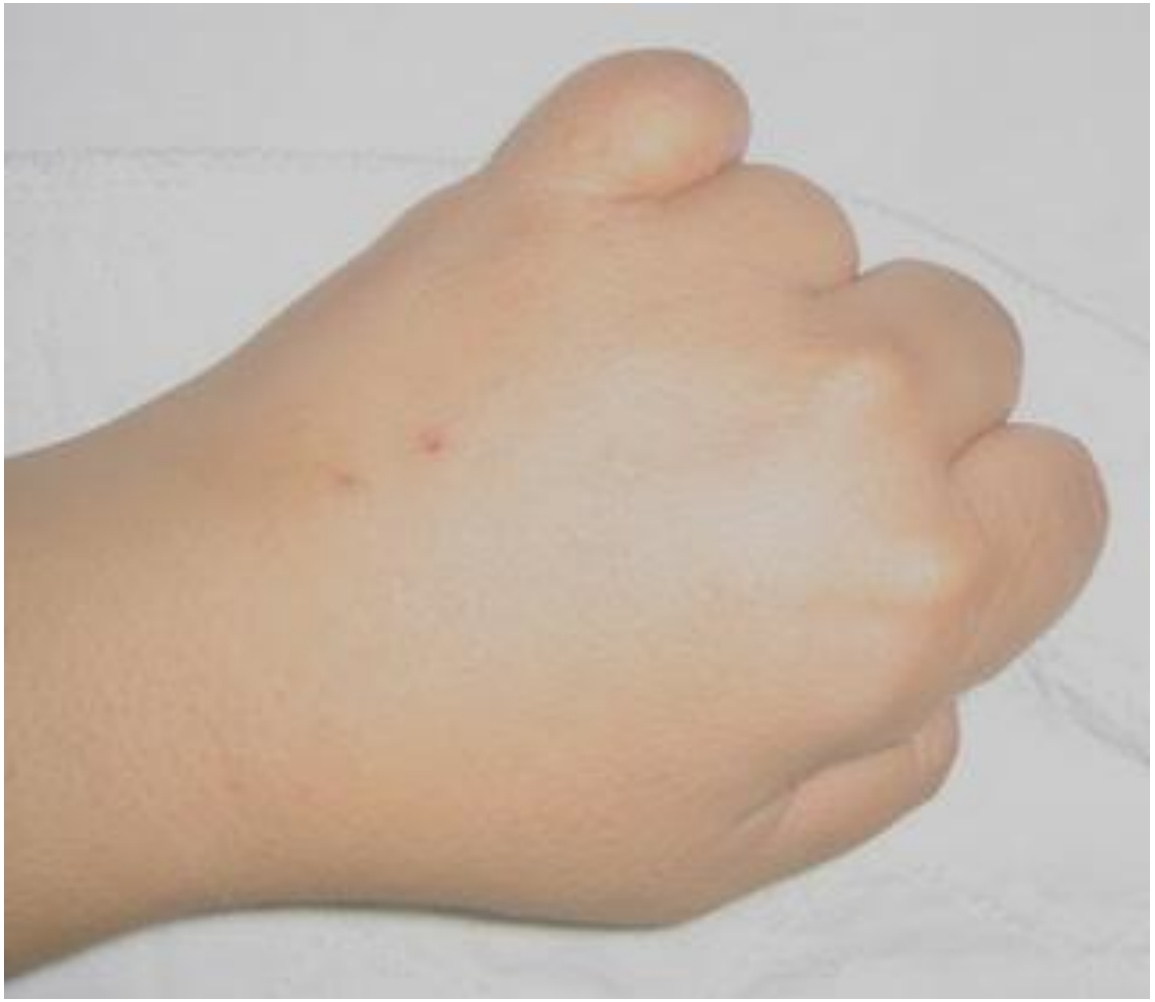
- In 1942, Fuller Albright first described the term Pseudohypoparathyroidism
  - describe patients who presented with PTH-resistant hypocalcaemia and hyperphosphatemia
  - constellation of developmental and skeletal defects, collectively termed Albright hereditary Osteodystrophy (AHO)
  - short stature, rounded face, shortened fourth metacarpals and other bones of the hands and feet, obesity, dental hypoplasia, and soft-tissue calcifications/ossifications
- administration of PTH failed to produce the expected phosphaturia or to stimulate renal production of cyclic adenosine monophosphate (cAMP)

Pseudohypoparathyroidism





Pseudohypoparathyroidism



Hypercalcemia

Transient neonatal hyperparathyroidism

- has occurred in a few infants born to mothers with hypoparathyroidism or with pseudohypoparathyroidism
- condition is chronic intrauterine exposure to hypocalcaemia with resultant hyperplasia of the fetal parathyroid glands.
- In the newborn, manifestations involve the bones primarily and healing occurs between 4 and 7 months of age.

Causes of Hypercalcemia in Children

- Primary hyperparathyroidism
- Inactivation mutations of a CaSR gene
- Granulomatous disease, including sarcoidosis, tuberculosis, and Wegener disease
- Thyrotoxicosis
- Adrenal insufficiency can decrease the renal clearance of calcium
- Vitamin A in high doses
- Milk-alkali syndrome (Burnett syndrome)

Causes of Hypercalcemia in Children

- Oncogenic Hypercalcemia
- Vitamin D intoxication
- Thiazide diuretics
- Immobilization
- Total parenteral nutrition
- Excessive supplementation of calcium

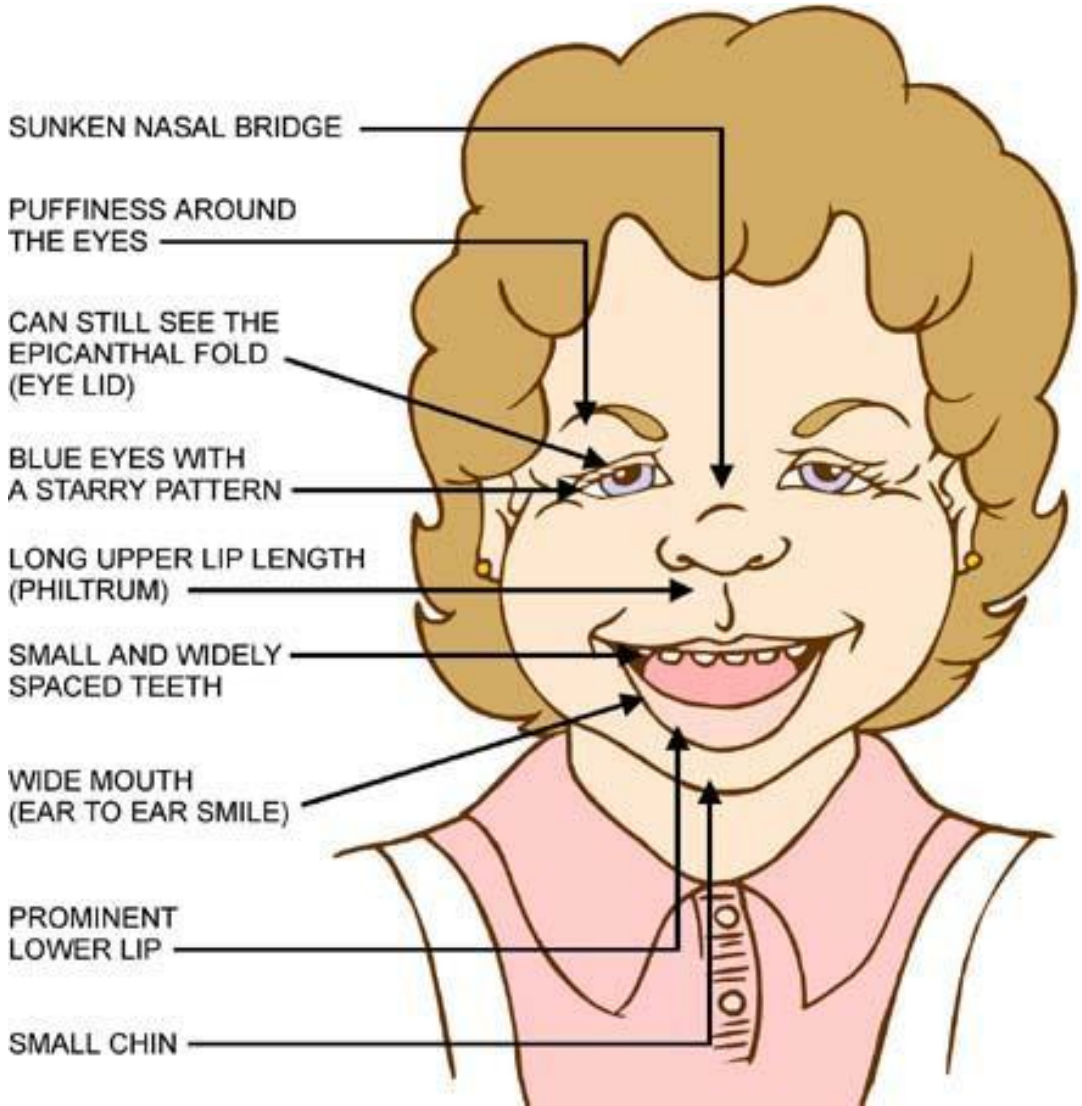
Subcutaneous fat necrosis

- Manifests in neonate as violaceous plaques or nodules overlying fatty areas, can lead to life-threatening Hypercalcemia at age 1-6 months
- It is likely mediated by prostaglandin E or due to macrophage production of 1, 25-dihydroxyvitamin D
- Treatment includes corticosteroids and symptomatic support of patient.

William‘s syndrome

- Associated with a deletion of elastin genes on chromosome 7
- Transient neonatal Hypercalcemia
- ? secondary to increased sensitivity to vitamin D
- The syndrome is associated with characteristic elfin facies, mental retardation, and supravalvar aortic stenosis
- Generally, Hypercalcemia is symptomatic, with poor feeding and constipation, and spontaneously remits by age 9-18 months

William syndrome



Familial benign hypocalciuric hypercalcemia (FHH)

- Inactivation mutations of a CaSR gene
- generally asymptomatic
- does not require treatment when present in heterozygote
- Patients who are homozygous for CaSR inactivating mutations have more severe hypercalcemia

Hyperparathyroidism

Hyperparathyroidism

- Primary
  - hyperplasia - adenoma - carcinoma
- Secondary
  - persistent hypocalcaemia
- Tertiary
  - secondary leads to hyperplasia

Hyperparathyroidism

Pathology

- PTH overproduction
- Increased renal tubular absorption , intestinal absorption and bone resorption of Ca
- Hypercalcaemia and hypercalciuria
- Suppressed phosphate tubular reabsorption
- Hypophosphataemia and hyperphosphaturia

Primary hyperparathyroidism

- Rare in children, with estimated incidence of 2-5 / 100,000.
- It is most often sporadic and caused by a parathyroid adenoma.
- It may also occur due to hyperplasia of glands, especially in multiple endocrine neoplasias (MEN)-I and II syndromes.
- Multiple endocrine neoplasia (MEN) type I (Wermer syndrome) is rare autosomal dominant constellation of hyperparathyroidism, pancreatic tumors, and pituitary tumors treated by subtotal parathyroidectomy
- Molecular diagnosis is now available for (MEN)-I and II

Etiology

- Childhood hyperparathyroidism is rare.
- Onset during childhood is usually the result of a single benign adenoma.
- It usually becomes manifested after 10 yr of age.
- Autosomal dominant
- Multiple endocrine neoplasia (MEN)
- Hyperparathyroidism–jaw tumor syndrome
- Neonatal severe hyperparathyroidism (rare)

Neonatal severe hyperparathyroidism

- Symptoms develop shortly after birth
- Anorexia, irritability, lethargy, constipation, and failure to thrive.
- Radiographs reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures.

MEN

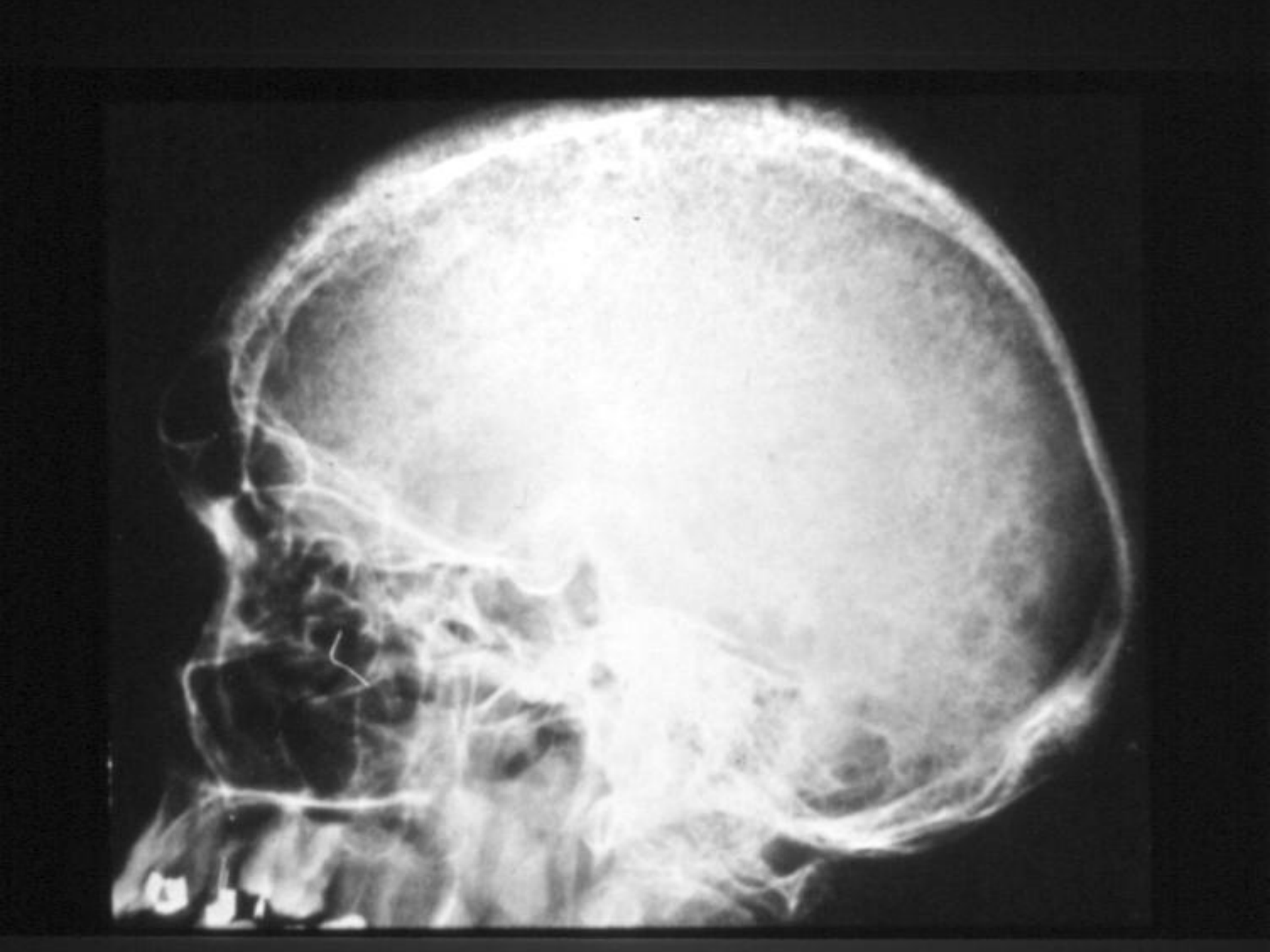
- MEN type I- Autosomal dominant
- Hyperplasia or neoplasia of the
  - –endocrine pancreas (which secretes gastrin, insulin, pancreatic polypeptide, and occasionally glucagon),
  - –anterior pituitary (which usually secretes prolactin),
  - –parathyroid glands.
- In most kindreds occurr only rarely in children <18 yr of age.
- With appropriate DNA probes, it is possible to detect carriers of the gene with 99% accuracy at birth, avoiding unnecessary biochemical screening programs.

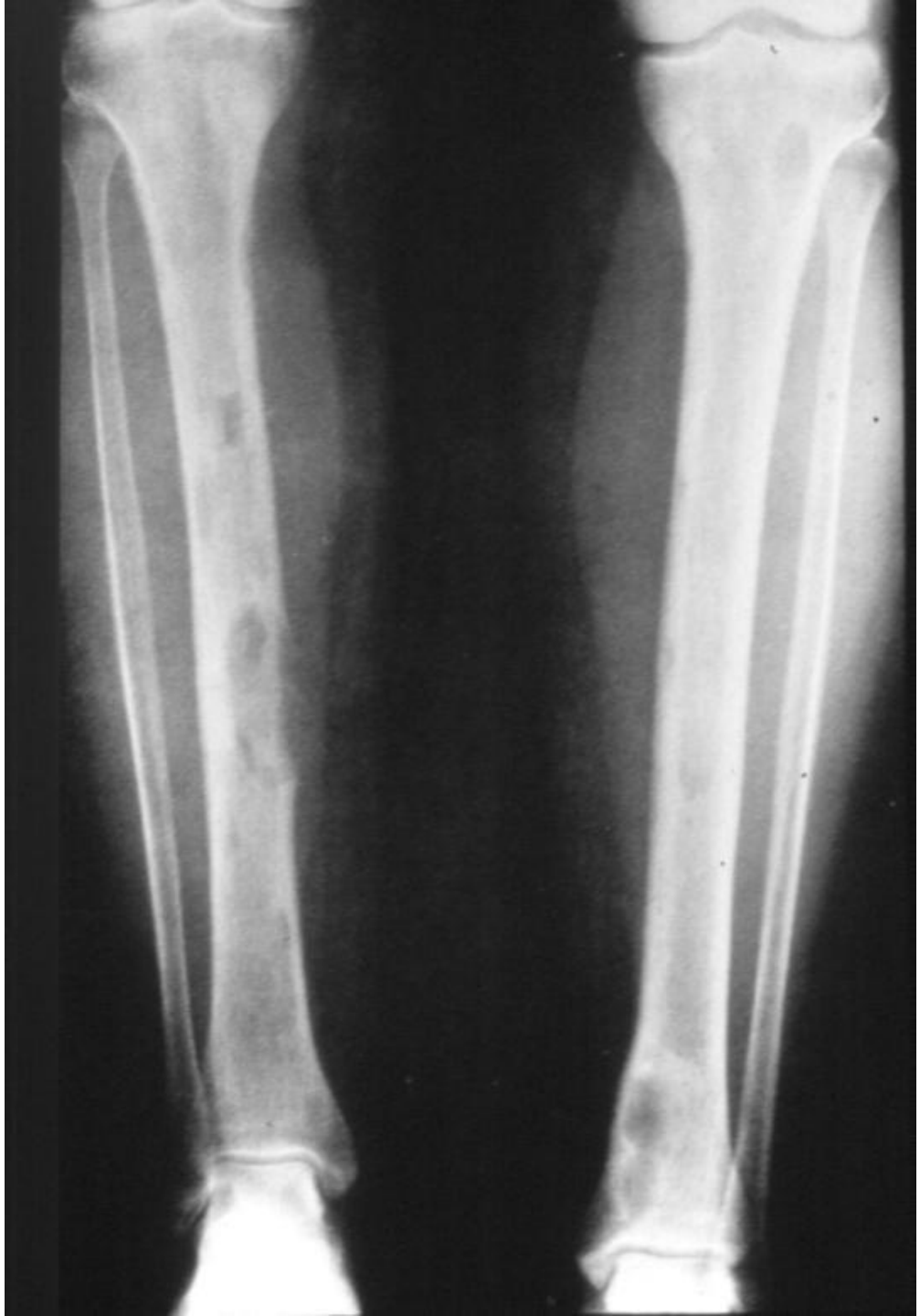
Clinical Manifestations of Hypercalcemia

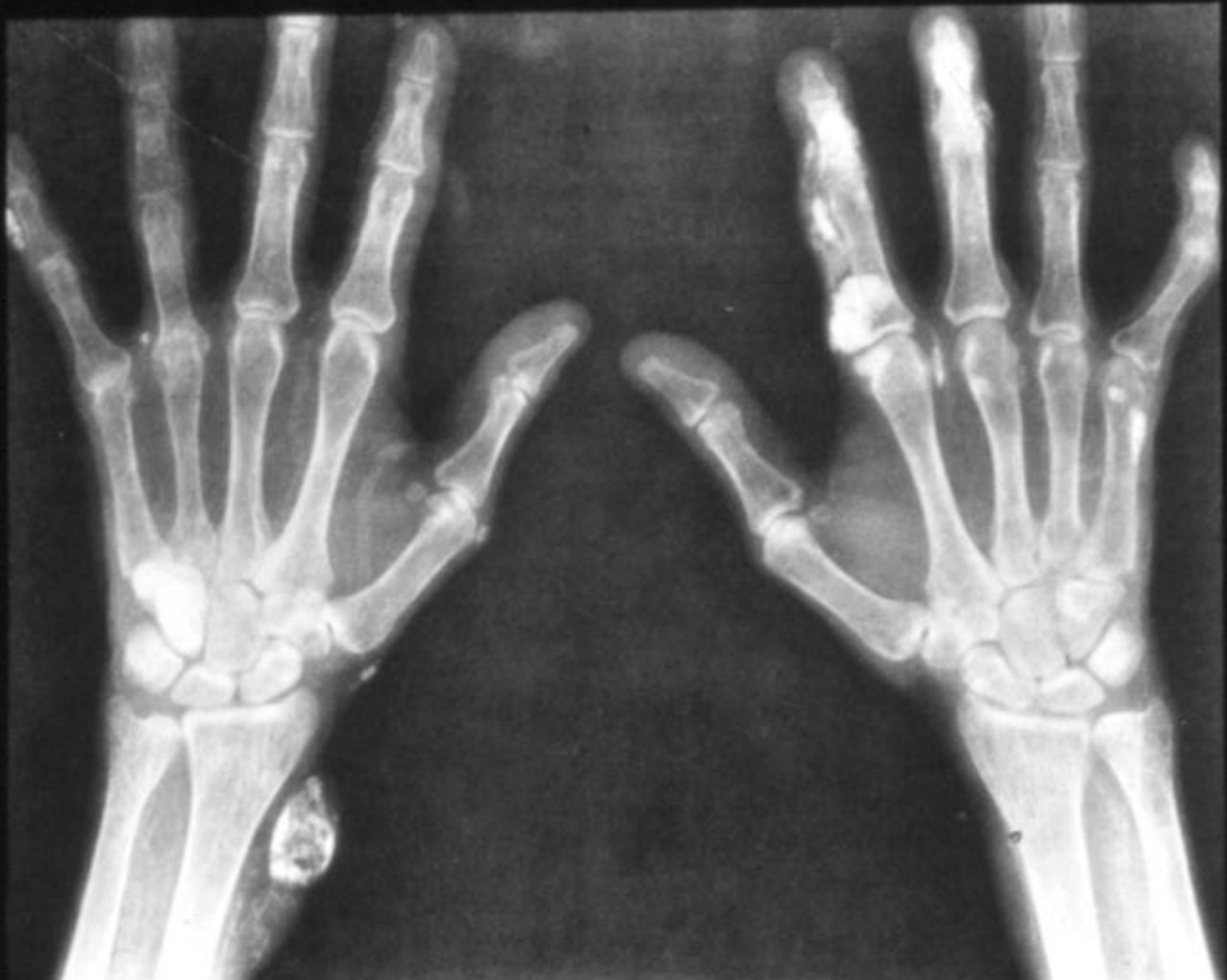
- At all ages, the clinical manifestations of hypercalcemia of any cause include:
  - muscular weakness, fatigue, headache, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia, polyuria, loss of weight, and fever
- When hypercalcemia is of long duration:
  - nephrocalcinosis with progressively diminished renal function & Renal calculi
  - Mental retardation, convulsions, and blindness
  - depression, confusion, dementia, stupor, and psychosis
- Abdominal pain is occasionally prominent and may be associated with acute pancreatitis

Hyperparathyroidism

- Hypercalcaemia
  - calcinosis , stone formation , recurrent infection ,& soft tissue calcification
- Bone resorption
- loss of bone substance , subperiosteal erosion
- osteitis fibrosa cystica " brown tumor"







Thank you