Academic lectures – 3rd year of Medical faculty

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ENDOCRINOLOGY 4

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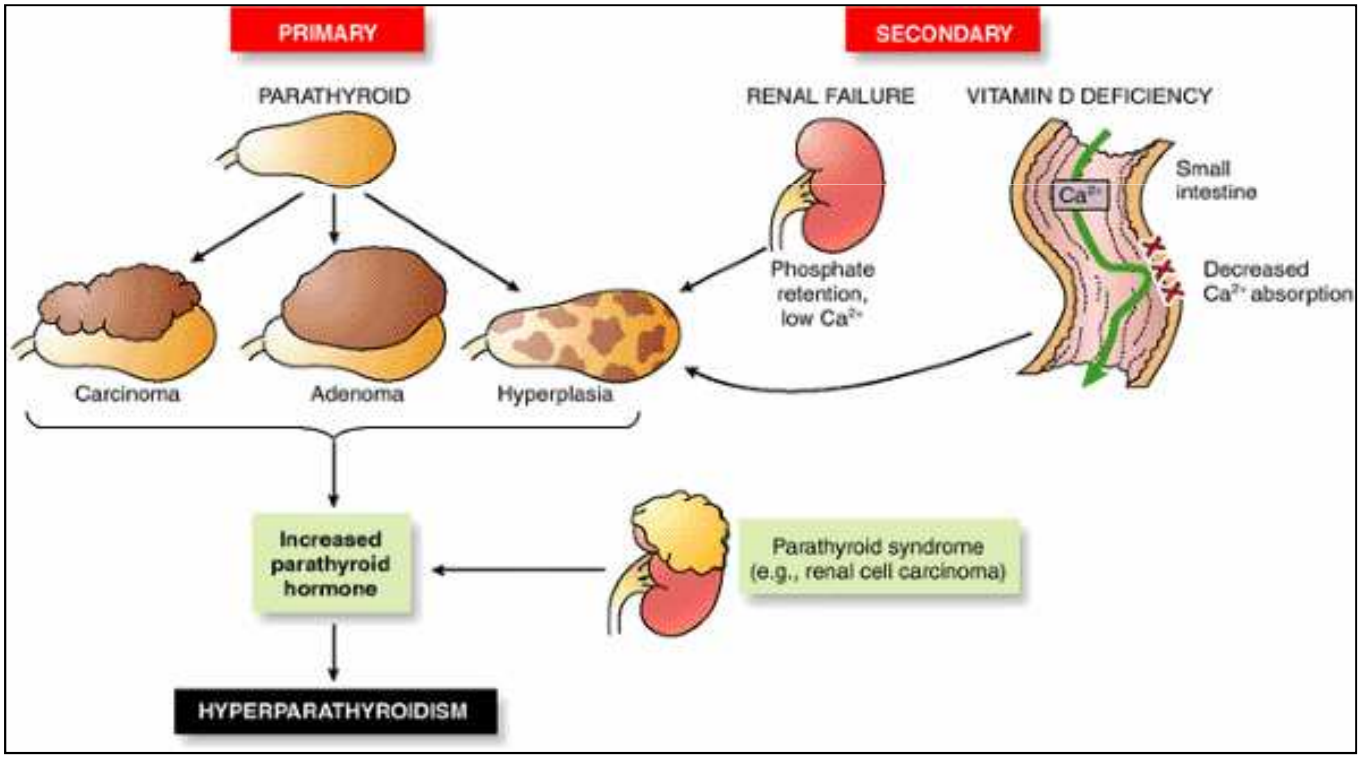
Paratyroid glands

- Physiological review
- Hypoparatyroidism
- Hyperparatyroidism

Primary hyperparathyroidism

Def PTH is produced in excess, even with normal or elevated serum calcium levels

Etio Condition caused by excessive parathormone ssecretion which can be sporadic or part of familial syndromes such as MEN-1 and MEN-2A.

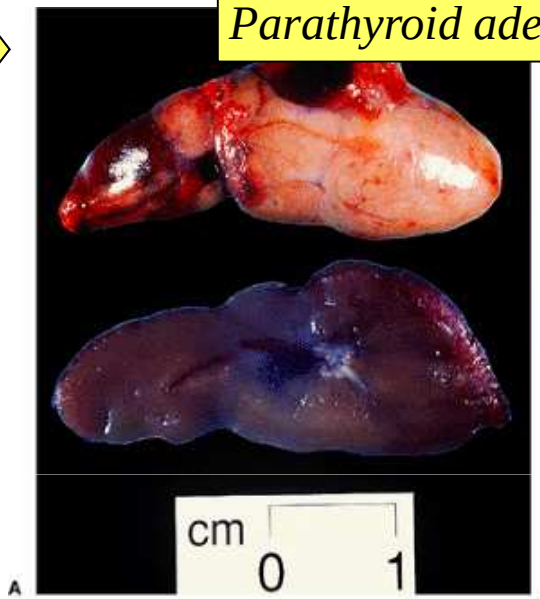


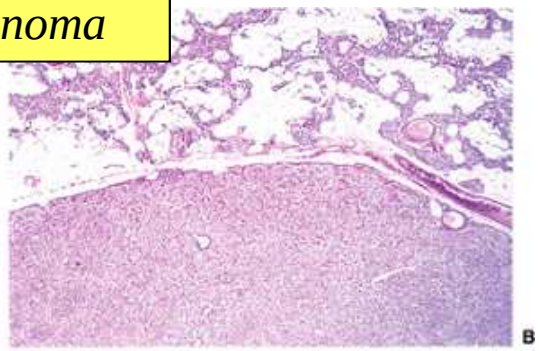
Primary hyperparathyroidism - Causes

1. Parathyroid adenoma (80-90%)

- mostly over 50 y. of age; sporadic (80-90%) or as MEN-1 (10-20%)
- rearrangement/ overexpression of the cyclin D1 (PRAD1; Ch 11) in some cases.

Parathyroid adenoma





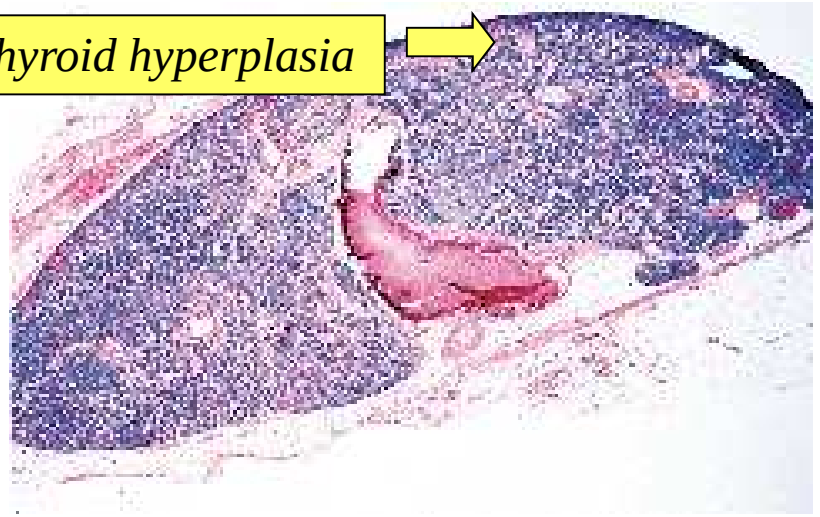
- all four parathyroid glands are enlarged, (weight 1 g to 10 g)

- In ½ one gland is larger than others

2. Primary hyperplasia (10-15%)

- mostly in women (75%); external radiation and lithium ingestion
- 20% familial hyperparathyroidism or MEN types 1 and 2A
- 1/3 of hyperplasias are monoclonal (neoplastic) - chief cell hyperplasia and multiple small adenomas

Parathyroid hyperplasia



3. Parathyroid carcinoma (1% to 5%)

- either sex; over 30 – 60 y); may develop from adenoma
- lobulated, firm, tannish, unencapsulated mass, adherent to surrounding soft tissues;
- after removal, local recurrence is common
- 1/3 of patients develop metastases to regional lymph nodes, lungs, liver, and bone.

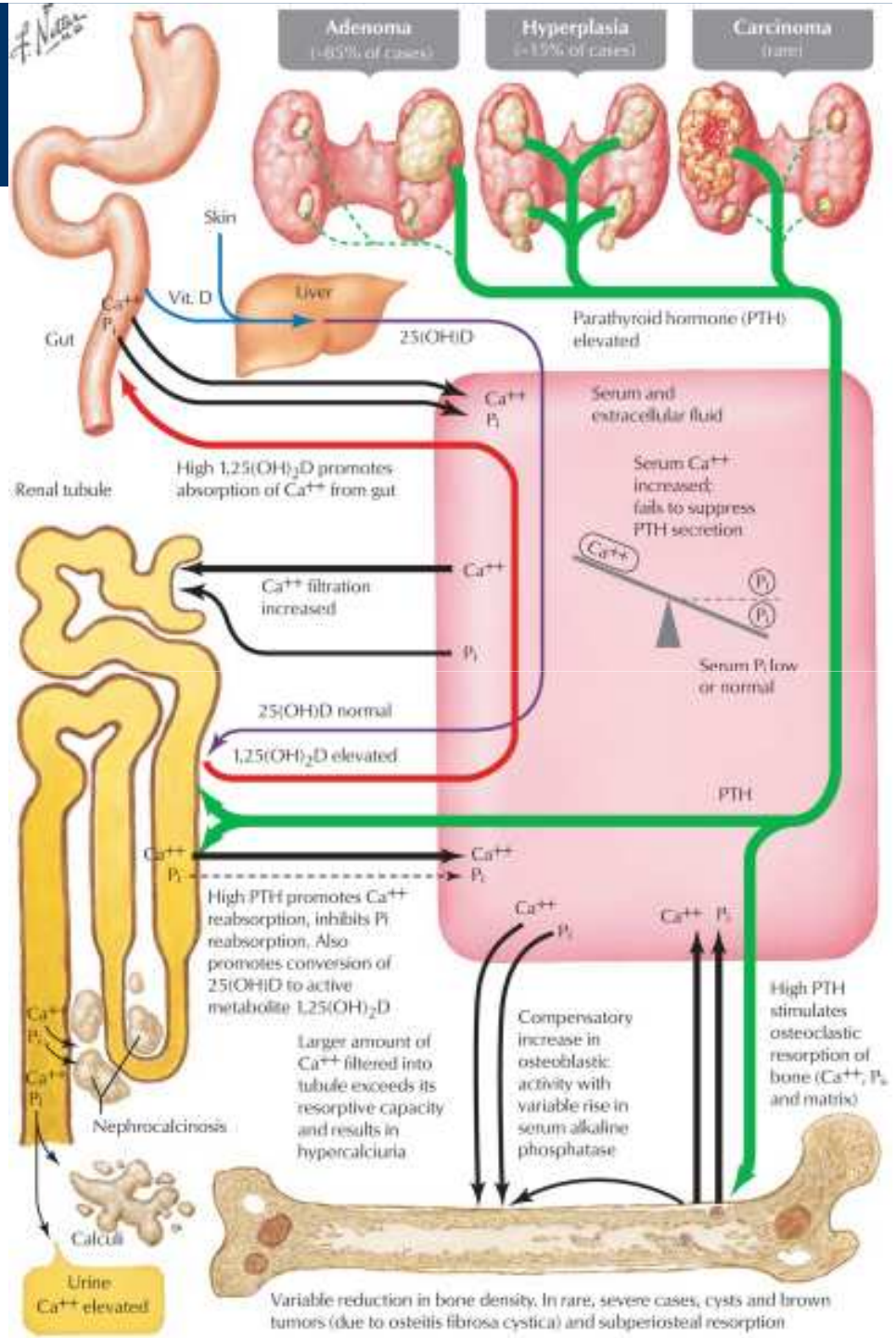
Secondary & terciary hyperparathyroidism

Secondary hyperparathyroidism

- patients with **chronic renal failure, vitamin D deficiency, intestinal malabsorption, Fanconi syndrome, and renal tubular acidosis**
- Chronic hypocalcemia owing to renal retention of phosphate, inadequate 1,25(OH)2D production by diseased kidneys, and some skeletal resistance to PTH all lead to compensatory PTH hypersecretion. Secondary hyperplasia of all parathyroids leads to excess levels of PTH, which cause osseous manifestations of hyperparathyroidism, termed renal osteodystrophy The morphology of parathyroids in secondary hyperplasia is like that in primary hyperplasia. Treatment is surgical removal of the enlarged glands with or without re-implantation.

Tertiary hyperparathyroidism

- development of autonomous parathyroid hyperplasia after long-standing hyperplasia secondary to renal failure
- parathyroid hyperplasia may not regress after renal transplantation, and surgery to remove parathyroids is required.
- 2/3 of patients with long-standing uremia have monoclonal hyperplastic parathyroid proliferations.


Adenoma
(~85% of cases)
Hyperplasia
(~15% of cases)
Carcinoma
(rare)
Skin
Vit. D
Liver
25(OH)D
Gut
Ca++
Pi
Parathyroid hormone (PTH) elevated
Serum and extracellular fluid
Serum Ca++ increased; fails to suppress PTH secretion
High 1,25(OH)2D promotes absorption of Ca++ from gut
Renal tubule
Ca++ filtration increased
Serum Pi low or normal
25(OH)D normal
1,25(OH)2D elevated
PTH
High PTH promotes Ca++ reabsorption, inhibits Pi reabsorption. Also promotes conversion of 25(OH)D to active metabolite 1,25(OH)2D
Larger amount of Ca++ filtered into tubule exceeds its resorptive capacity and results in hypercalciuria
Compensatory increase in osteoblastic activity with variable rise in serum alkaline phosphatase
High PTH stimulates osteoclastic resorption of bone (Ca++, Pi and matrix)
Nephrocalcinosis
Calculi
Urine
Ca++ elevated
Variable reduction in bone density. In rare, severe cases, cysts and brown tumors (due to osteitis fibrosa cystica) and subperiosteal resorption

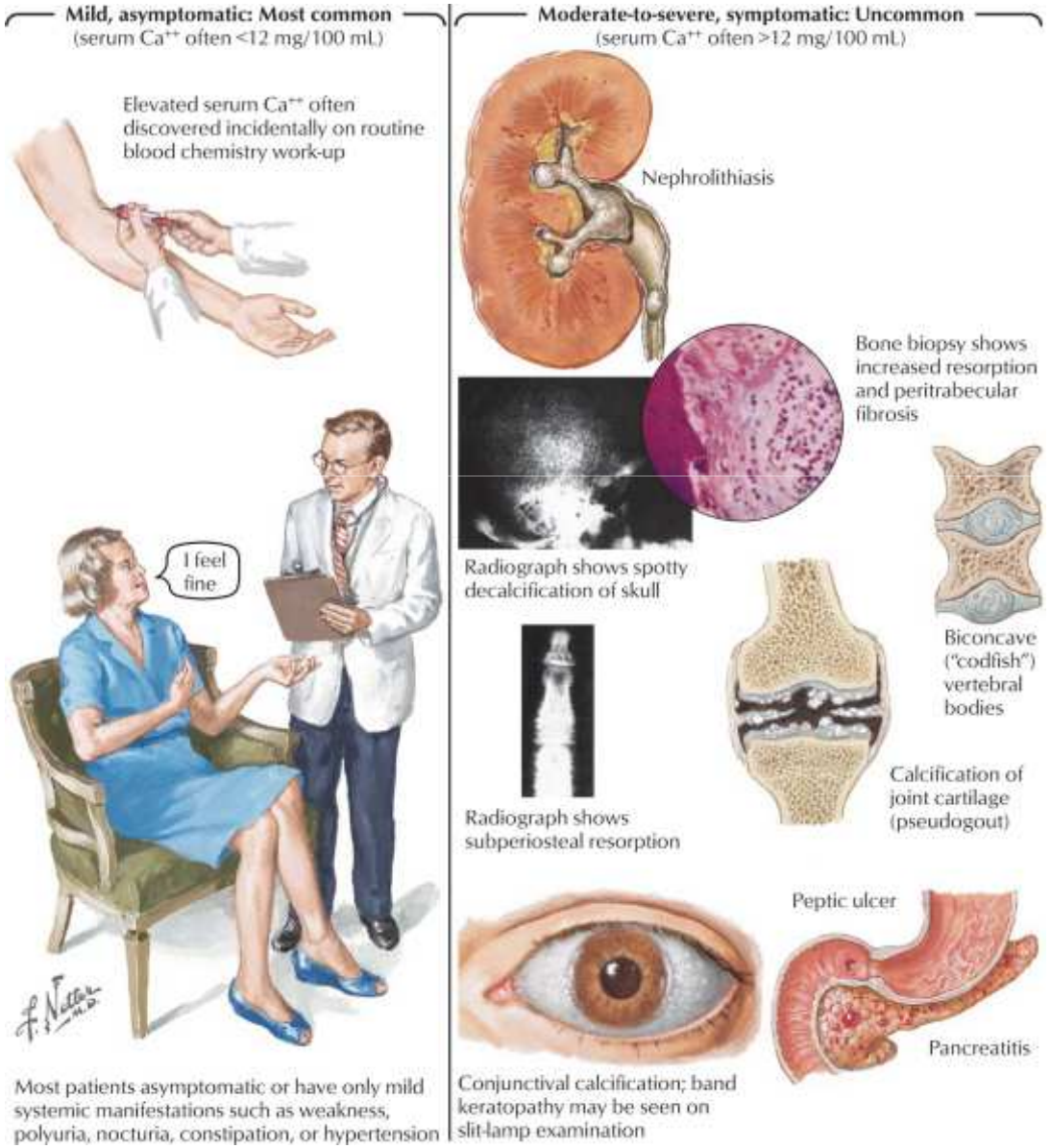
Hyperparathyroidism - Symptoms

MILD ASYMPTOMATIC HYPERCALCEMIA

- Very common accidental asymptomatic hypercalcaemia; Other symptoms: nausea, vomiting, fatigue, weight loss, anorhexia, polyuria, and/or polydipsia.
- A neck mass is palpable in many patients.

MODERATE TO SEVERE SYMPTOMS

- Sketeton: **Osteitis fibrosa cystica** (minority of patients in severe disease) - bone pain, bone cysts, pathologic fractures, localized bone swellings (brown tumors and epulis of the jaw). **Chondrocalcinosis (pseudogout)**
- Kidney: diffuse renal calcification **nephrocalcinosis** ; **renal colic** (10% of patients) due to kidney stones, polyuria is caused by hypercalciuria, and leads to polydipsia.
- Psychiatric: common (depression, emotional lability, poor mentation, and memory defects).
- Nervous: Hyperactive reflexes; Peripheral neuropathy with type 2 fiber atrophy of skeletal muscles leads to muscle weakness.



Primary hyperparathyroidism

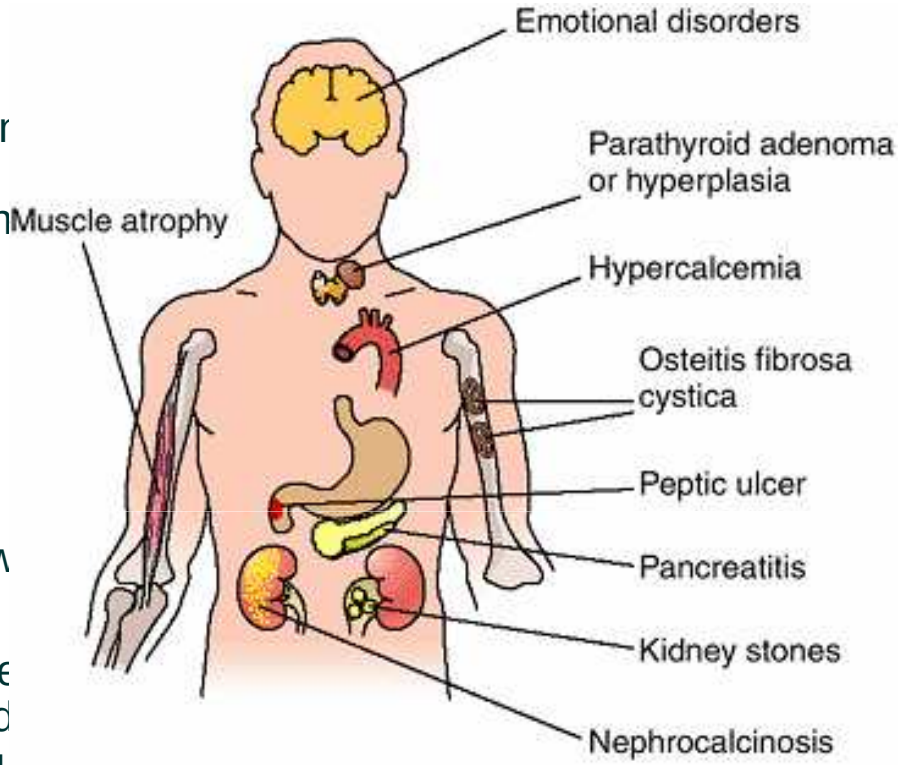
- Gastrointestinal - **peptic ulcer disease** is increased (? hypercalcemia increases serum gastrin, thereby stimulating gastric acid secretior case of MEN-1, - parathyroid hyperplasia or adenoma, may be secondary to Zollinger-Ellison syndrome Hypercalcemia may also cause **constipation** and **chronic pancreatitis**
- Other: **arterial hypertension** (50% of patients) **Anemia** of unknown cause is also frequent.

Dg

- Diagnosis of hyperparathyroidism is confirmed w an immunoassay for PTH.

Th

- **Treatment** includes surgery to remove either the adenoma or 3½ of the 4 hyperplastic parathyroid glands. ***Postoperative hypocalcemia*** may occu but is usually mild and does not require treatment.
- Humoral *hypercalcemia of malignancy* can be a difficult problem to manage. Most cases are caused by the tumor producing *PTH-related protein*. Because PTH and PTH-related protein have similar amino acid sequences in their amino terminal domains, these two molecules bind to and activate the same receptors.



- PTH: excessive loss of calcium from bones + enhanced calcium resorption by renal tubules → **hypercalcemia** + **hypophosphatemia**
- PTH: increased production of kalcitriol by renal tubules → increasing intestinal calcium absorption → **hypercalcemia**

Hypoparathyroidism

Def Condition clinically characterized by **hypocalcemia** and **hyperphosphatemia** and caused by **decreased secretion of PTH** /or **end-organ insensitivity** to it due to congenital or acquired conditions.

Etio

- **Primary hypoparathyrodism**
  - **Iatrogenic** - surgical removal of the parathyroids during thyroidectomy
  - **Familial hypoparathyroidism** a) may be part of a polyglandular syndrome (adrenal insufficiency + mucocutaneous candidiasis b) **Isolated hypoparathyroidism** – rare; variable trait; deficient PTH secretion.
  - **Idiopathic hypoparathyroidism** - heterogeneous group of rare disorders, sporadic and familial. Agenesis of the parathyroid glands is part of the **DiGeorge syndrome**
- **Pseudohypoparathyroidism** - hereditary conditions; insensitivity to PTH → inadequate resorption of calcium from glomerular filtrate ensues.
  - ***a) type 1a*** - decreased activity of $G_{s\alpha}$ (GNAS1 mutation; Ch20p) → impaired renal tubular epithelium production of cAMP in response to PTH ; decreased sensitivity to other cAMP-coupled hormones **(TSH, glucagon, FSH, and LH)**
  - ***b) type 1b*** - reduced expression of the PTH receptor
  - ***c) type 1c*** - impaired activity of adenyl cyclase, which synthesizes cAMP and other uncharacterized defects in PTH end-organ response.

  Individuals with pseudohypoparathyroidism type 1a and type 1c also have ***Albright's hereditary osteodystrophy***
- **Pseudopseudohypoparathyroidism** - rare cases; reduced G_S activity (Ch20p but no GNAS1 mutations; normal cAMP response to PTH;)

Hypoparathyroidism - Symptoms

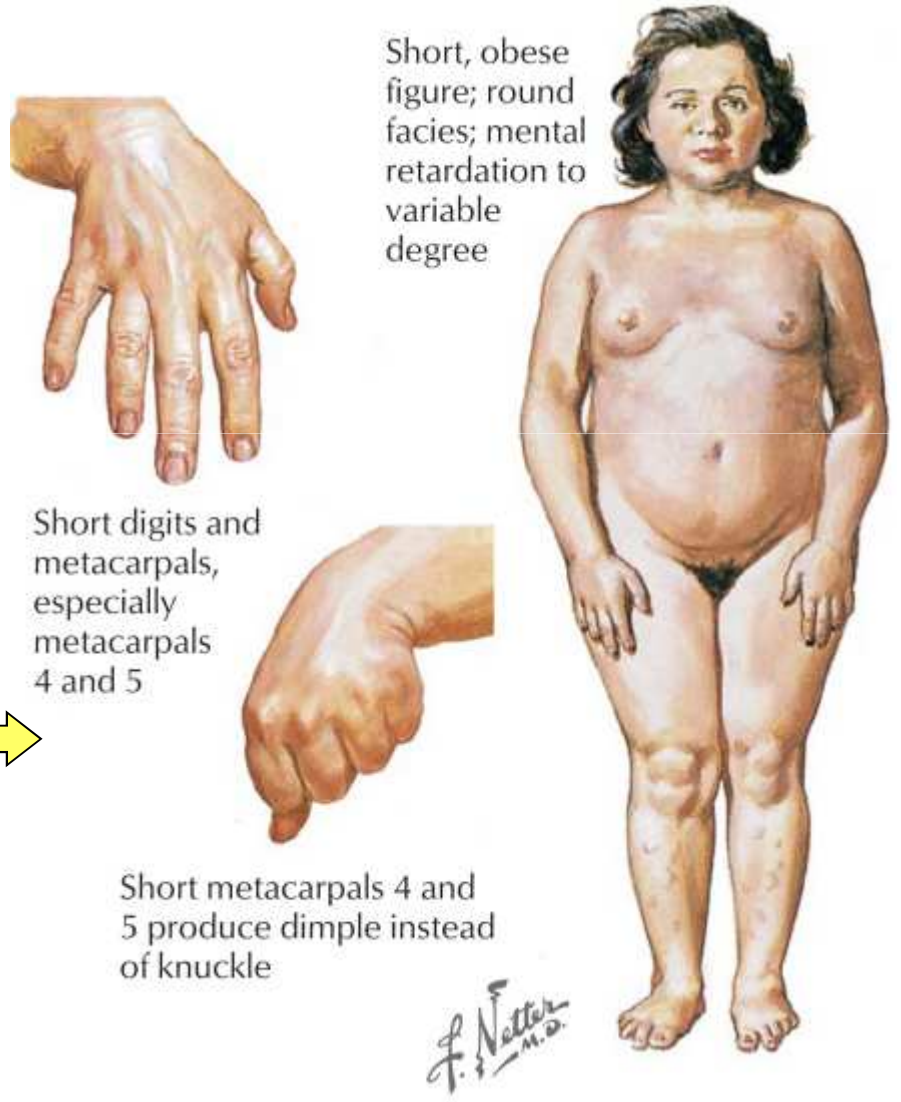
Chronic hypoparathyroidism

- Increased neural and muscular excitability: (due to hypocalcemia)
  - mild tingling in the hands and feet,
  - severe muscle cramps, tetany, convulsions
  - laryngeal stridor
- Nonspecific psychiatric manifestations:
  - lethargy, depression, paranoia, and psychoses.
  - high cerebrospinal fluid pressure, papilledema (mimic brain tumor)
- Other:
  - cataracts, alopecia, poor tooth formation.
  - Bony changes are minimal.

Albright's hereditary osteodystrophy

- congenital short stature, abnormally short metacarpals and metatarsals, subcutaneous calcification
- mental retardation + obesity

- **Therapy:** vitamin D, calcium, radioactive iodine; 1% of patients develop irreversible hypoparathyroidism

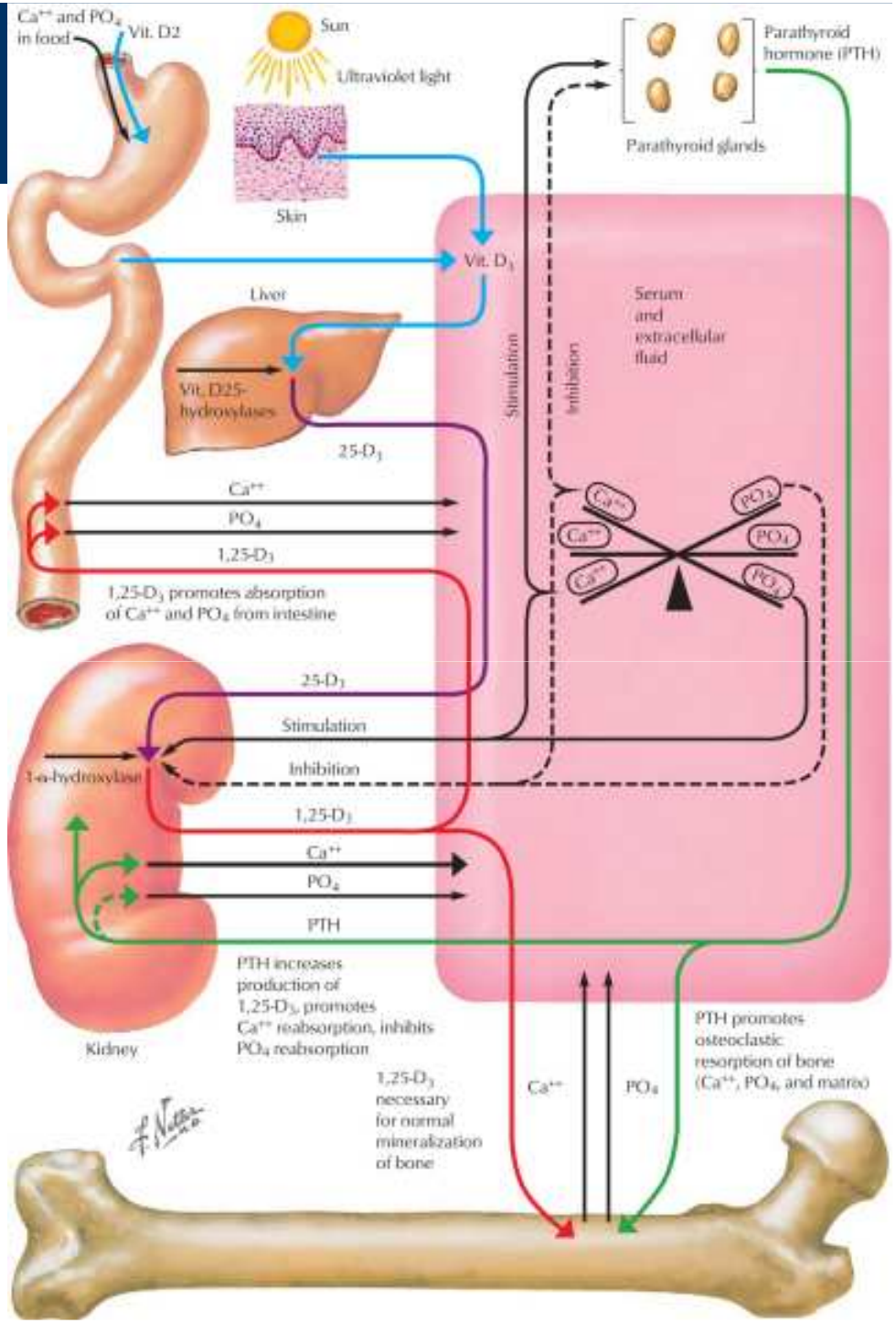


Vitamin D3 hormone (calcitriol)

- Physiological overview
- Rickets
- Osteomalacia

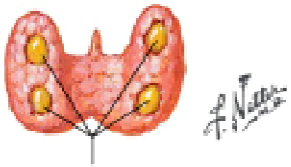
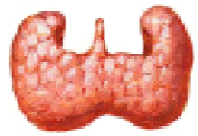
Vitamin D

- *Vitamin D* is a steroid hormone that may be produced endogenously or via dietary sources Ultraviolet light converts *7-dehydrocholesterol* in the skin to *cholecalciferol* (*vitamin D3*).
- Individuals who wear heavy garments designed to cover most of their skin may receive insufficient sun exposure for adequate vitamin D production. This condition is uncommon, however, because the sunlight exposure to the face and hands necessary to produce daily requirements is only 10 to 15 minutes in fair-skinned people. Dark-skinned persons, however, require more prolonged exposure.
- *Vitamin D2* (*ergocalciferol*) may be obtained through diet. Therefore, nutritional rickets is rare in countries that supplement milk and other food products with vitamin D2.
- Vitamins D2 and D3 undergo hydroxylation initially at the 25-position in the liver, then in the kidneys at the 1-position, to become *1,25-D3*, a major calcium-regulating hormone. 1,25-D3 upregulates production of the calcium-binding proteins essential for calcium transport and absorption in the gut. This hormone also stimulates bone resorption in a manner similar to PTH.



OSTEOMALACIA AND RICKETS

- **Vitamin D–deficient conditions**
  - Dietary lack of vitamin D
  - Insufficient exposure to sunlight
  - Vitamin D deficiency of prematurity
  - Use of seizure medications
  - Liver disease
  - Intestinal disease or surgery
  - Vitamin D–dependent rickets
  - Renal osteodystrophy
- **Hypophosphatemic rachitic syndromes**
  - X-linked hypophosphatemic rickets
  - AD - linked hypophosphatemic rickets
  - Fanconi syndrome
  - Use of aluminum-containing antacids
- **Impaired mineralization**
  - Hypophosphatasia
  - Use of bisphosphonates

	Parathyroid hormone (PTH) (peptide)	$1,25\text{-}O_3$ (steroid)	Calcitonin (peptide)
Hormone	 From chief cells of parathyroid glands	 From proximal tubule of kidney	 From parafollicular cells of thyroid gland
Factors stimulating production	Decreased serum Ca^{++}	Elevated PTH Decreased serum Ca^{++} Decreased serum P_i	Elevated serum Ca^{++}
Factors inhibiting production	Elevated serum Ca^{++} Elevated $1,25(OH)_2D$	Decreased PTH Elevated serum Ca^{++} Elevated serum P_i	Decreased serum Ca^{++}
End organs for hormone action — **Intestine**	No direct effect Acts indirectly on bowel by stimulating production of $1,25(OH)_2D$ in kidney	Strongly stimulates intestinal absorption of Ca^{++} and P_i	
Kidney	Stimulates $25(OH)D\text{-}1\alpha\text{-}OH_{ase}$ in mitochondria of proximal tubular cells to convert $25(OH)D$ to $1,25(OH)_2D$ Increases fractional reabsorption of filtered Ca^{++} Promotes urinary excretion of P_i		Increases renal calcium excretion
Bone	Increases bone resorption indirectly by up-regulating osteoblast production of autocrine cytokines such as interleukin-6, which results in increased production of paracrine cytokines that stimulate osteoclast production and activity. PTH also has an anabolic effect on osteoblasts that results in overproduction of osteoid in chronic hyperparathyroidism	Stimulates bone resorption in a similar fashion to PTH and also other membrane receptors	Inhibits bone resorption by direct inhibition of osteoclast differentiation and activity
Net effect on calcium and phosphate concentrations in extracellular fluid and serum	**Increased serum calcium** **Decreased serum phosphate**	**Increased serum calcium**	**Decreased serum calcium (transient)**

Rickets and osteomalacia

- **Genetic disorders:** the synthesis of active vitamin D
  - ***Type I vitamin D–dependent rickets*** results from a *deficiency in renal 1α-hydroxylase.*
  - ***Type II vitamin D–dependent rickets*** results from a *defect in the vitamin D receptor*, with resultant deficiency in response to 1,25-D2.
- **Anticonvulsant medications** that activate the P-450 oxidases in the liver increase the rate of vitamin D catabolism, with resultant decreased 25-hydroxyvitamin D3 levels
- *Hypophosphatemia*.
  - ***X-linked hypophosphatemic rickets*** - renal tubular defect caused by a mutation in the endopeptidase gene *PEX*.
  - ***Fanconi syndrome -*** hypophosphatemia with acidosis
  - ***phosphate-binding antacids containing aluminum*** were used to treat hyperphosphatemia in patients undergoing dialysis. Aluminum from these medications is deposited in bone and disrupts normal bone mineralization.
- ***Vitamin D–deficiency osteomalacia*** is seen primarily in elderly adults. Contributing factors include decreased production of 25-hydroxyvitamin D3 with aging; reduced renal function with aging, leading to reduced levels of 1α-hydroxylase enzyme; and the greater incidence of malabsorption abnormalities that occur in the elderly.

Lab: normal calcium levels, low vitamin D levels, elevated PTH levels, and elevated alkaline phosphatase levels. Normal calcium levels are important in distinguishing osteomalacia and rickets from primary hyperparathyroidism (calcium is elevated). Measurements of serum levels of *25-hydroxyvitamin D* and *1,25-dihydroxyvitamin D.*

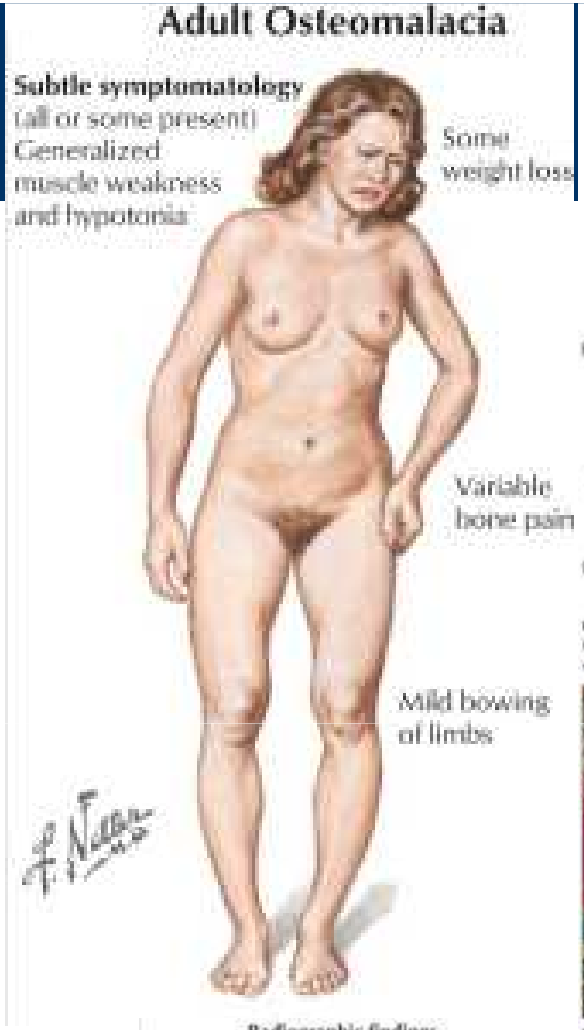
Osteomalacia & rickets

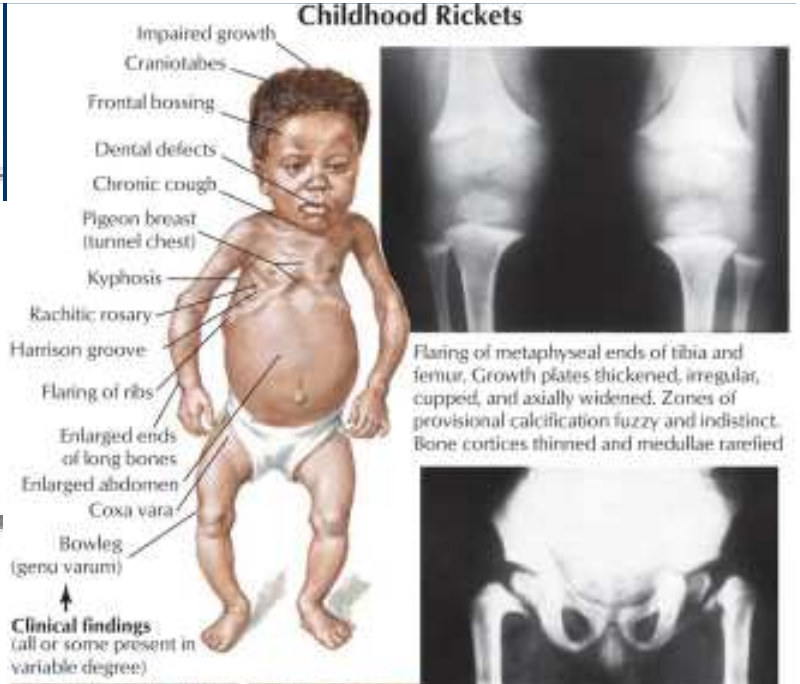
Sy:

- ***Pseudofractures*** result from stress fractures that heal with unmineralized bone and are seen as radiolucent lines on the compression side of bones.

- ***Multiple pseudofractures*** may be seen bilaterally, with radiolucent lines perpendicular to the axis of long bones developing from healing stress fractures. ("*Milkman syndrome*")

- Multiple stress fractures may result in a bowing **deformity of long bones**, and the spine may develop **increased thoracic kyphosis.**



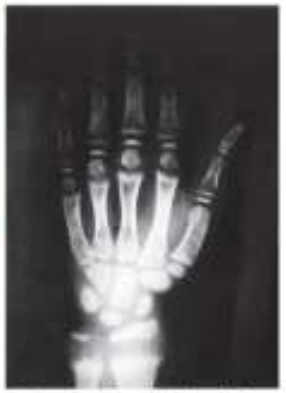


Flaring of metaphyseal ends of tibia and femur. Growth plates thickened, irregular, cupped, and axially widened. Zones of provisional calcification fuzzy and indistinct. Bone cortices thinned and medullae rarefied

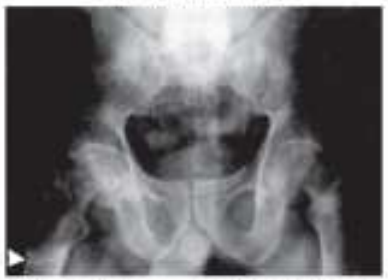
Coxa vara and slipped capital femoral epiphysis. Mottled areas of lucency and density in pelvic bones


Cartilage of epiphyseal plate in immature normal rat. Cells of middle (maturation) zone in orderly columns, with calcified cartilage between columns


After 6 weeks of vitamin D–and phosphate-deficient diet. Large increase in axial height of maturation zone, with cells closely packed and irregularly arranged


Radiograph of rachitic hand shows decreased bone density, irregular trabeculation, and thin cortices of metacarpals and proximal phalanges. Note increased axial width of epiphyseal line, especially in radius and ulna

Radiographic findings


Radiograph shows variegated rarefaction of pelvic bones, coxa vara, deepened acetabula, and subtrochanteric pseudofracture of right femur


Section of rachitic bone shows sparse, thin trabeculae surrounded by much uncalcified osteoid (osteoid seams) and cavities caused by increased resorption