Parathyroid Hormones and Calcuim & Phosphate Metabolism

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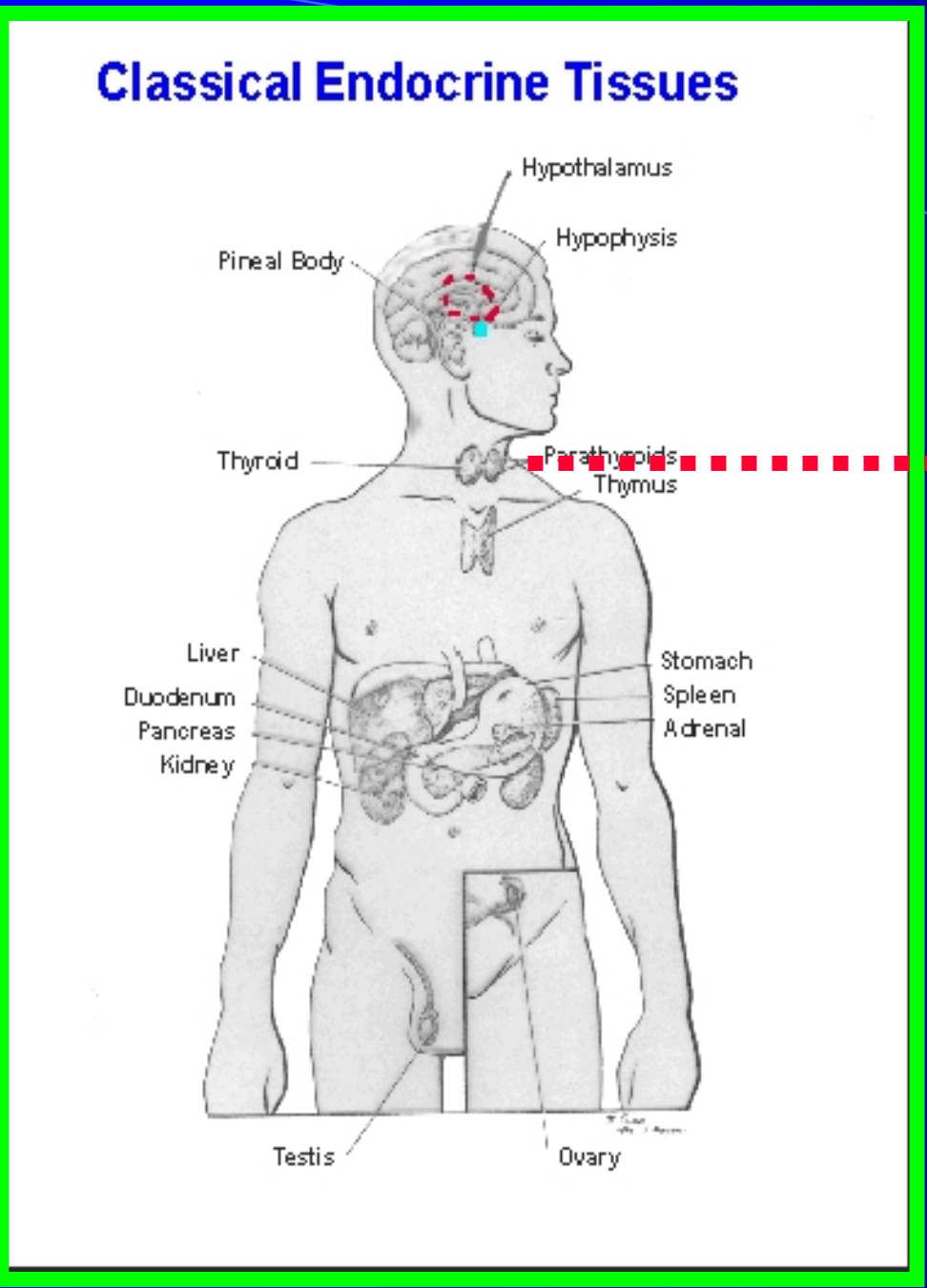
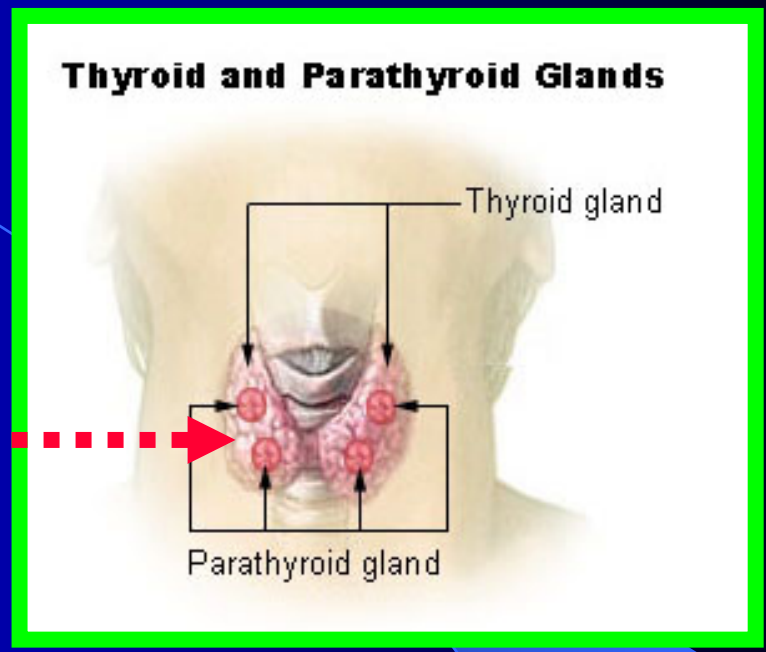
Important Spelling

- Illicit = illegal
  Elicit = stimulate, provoke
- Protein not protien; related to Protean = big, large
- Gonadotrope (or gonadotroph) = cell type of the anterior pituitary
- Gonadotropin = hormone from the anterior pituitary
- Gonadotropism = a physiological state of gonadotropin hormone:
  - underproduction (hypogonadotropism)
  - overproduction (hypergonadotropism)
  - normal production (eugonadotropism)
- Hypertrophy = growth to large size, may refer to a tissue or to individual cells
- Hyperplasia = increased cell number
- Neoplasia = new, often irregular, growth

Objectives :

1. Microanatomy of Parathyroid gland
2. PTH synthesis
3. Action of PTH
4. Control of PTH secretion and actions
5. Laboratory tests
6. Hyper- and Hypoparathyroidism
7. Calcium and Phosphorus metabolism



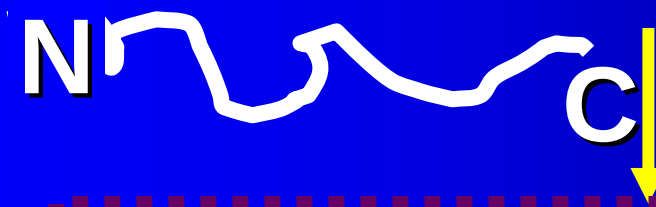


- Four parathyroid glands are embedded in the thyroid gland.
- 2 cell types:
  - Chief cells secret parathyroid hormone (PTH).
  - Oxyphil cells are believed to be old chief cells.

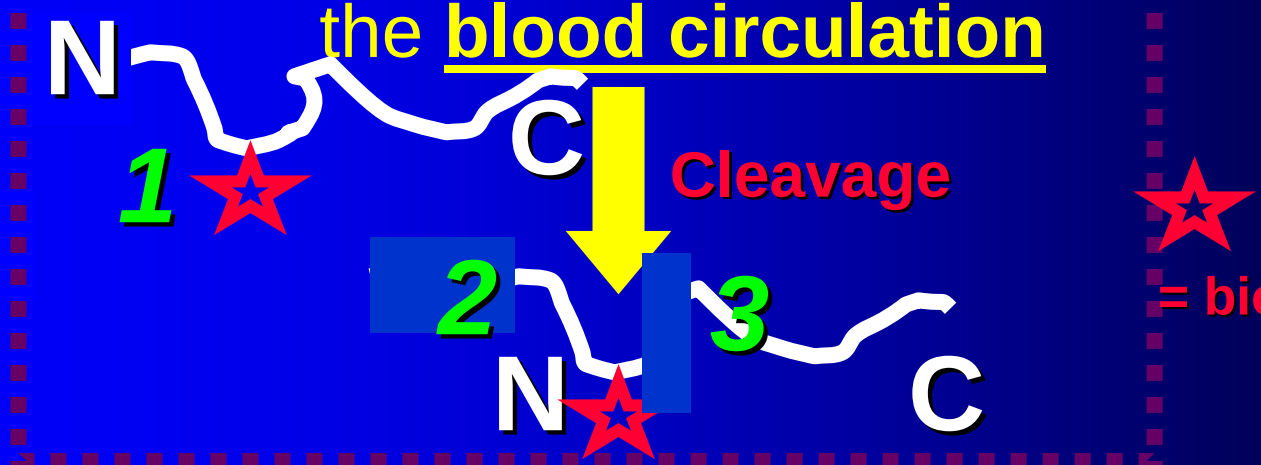
Biosynthesis and Metabolism of PTH

Pre-pro-PTH (115 aa) produced by chief cells

Pro-PTH (90 aa) in secretory vesicles



PTH (84 aa) secreted to the **blood circulation**

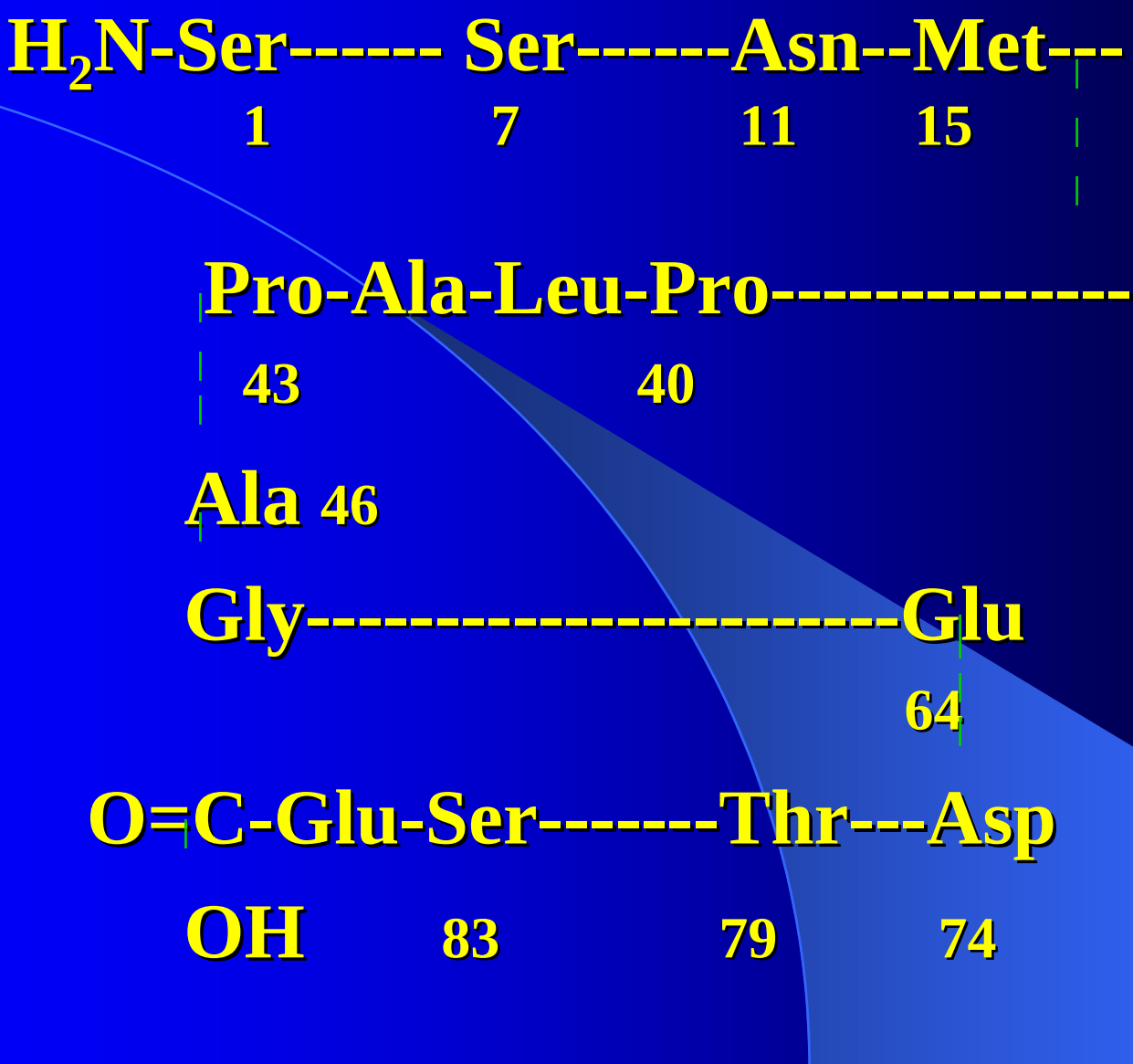


Three forms of PTH in blood

1. Intact PTH molecule
2. Amino-terminal fragment
3. Carboxyl-terminal fragment

Forms 1 and 2 are biologically active.

Human PTH Molecules



How are PTH production and secretion controlled?

- Stimulated by low levels of calcium in the blood.
- Inhibited by high levels of calcium in the blood.

- Stimulated by low levels of magnesium in the blood.
- Inhibited by high levels of magnesium in the blood.

- Stimulated by high levels of phosphorus in the blood.
- Inhibited by low levels of phosphorus in the blood.

Control of PTH (I)

1. Ca^{2+} < 4 mg/dL --- stimulate secretion
   > 12 mg/dL --- stop PTH synthesis
2. PO_4^{2-} High --> activate vit.D in kidney
   Low --> Low ATP --> Hypoparathyr.
3. Mg^{2+} -- aids PTH release and transfer into cell
4. Calcitonin (32 aa peptide, m.w.3590)
   from Parafollicular cell (C cell) of Thyroid gl.

Childhood - Bone mineralization of Ca-P
hydroxyapatite - making
lowering of plasma Ca, P

Control of PTH (II)

Childhood - Bone resorption by control & limit numbers of osteoclasts

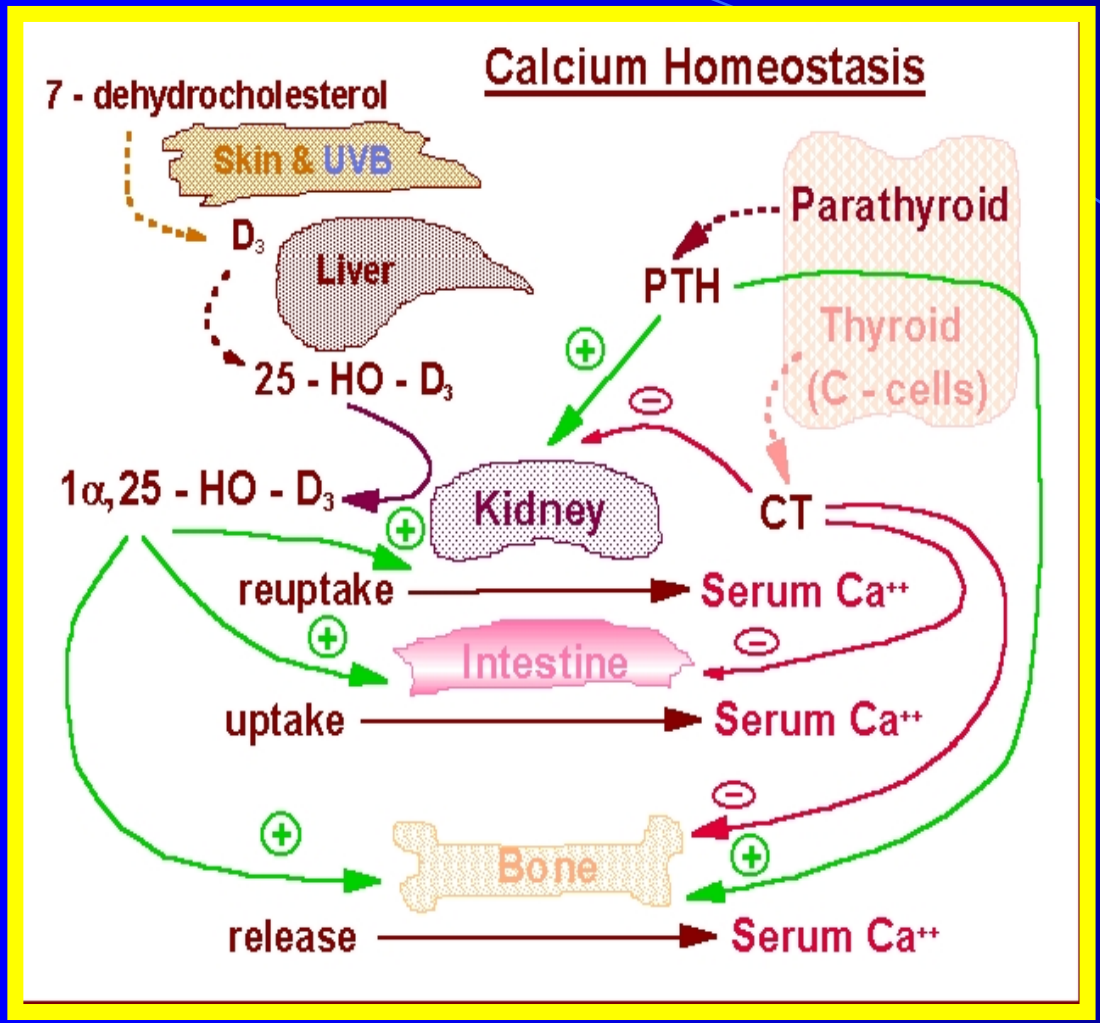
- Inhibit vit. D activation
- Inhibit P reabsorption by renal tubule

5. Hormones - Glucocorticoid - vit. D antagonist
   - T4 increases bone resorption

6 Vitamin D

- Parathyroid gland uptake Ca
- GI absorption of Ca

Action Mechanisms of PTH



- **These actions are mediated by cAMP.**

- **Increasing resorption of Ca^{2+} from bone.**
  - **Osteoclasts.**
- **Stimulating retention of Ca^{2+}, hydrogen ions, magnesium, and ammonium by renal tubules.** Stimulating excretion of phosphate, sodium, potassium, and bicarbonate ion.
- **Promoting 1-hydroxylation of 25-OH-D_3 in kidney. 1,25$(OH)_2$-D_3 increases Ca^{2+} and phosphate absorption from intestine.**

Cellular Action of PTH

PTH

Receptor

Adenylcyclase at Cell membrane

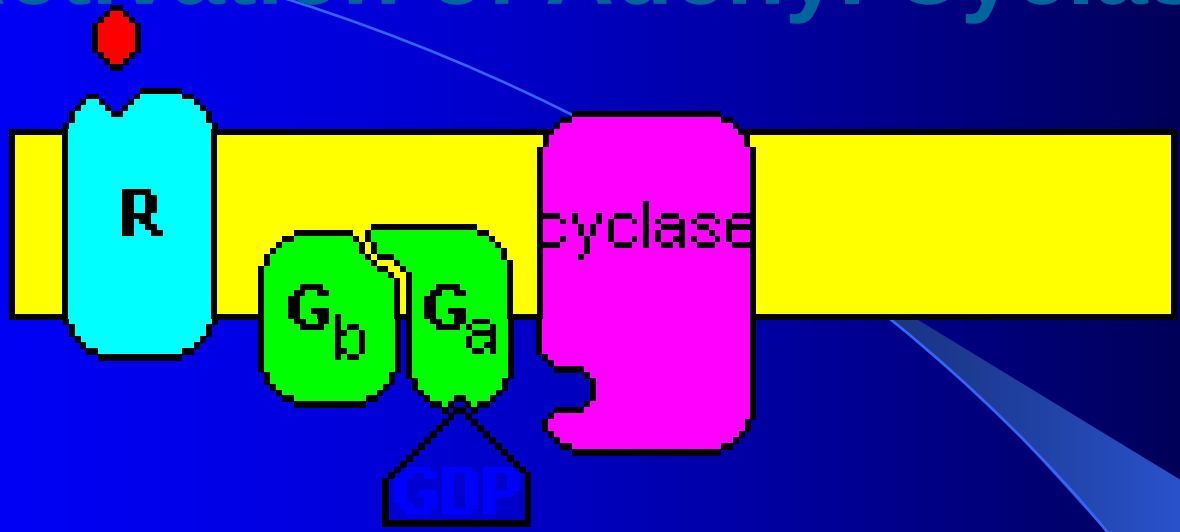
Mg^{2+}

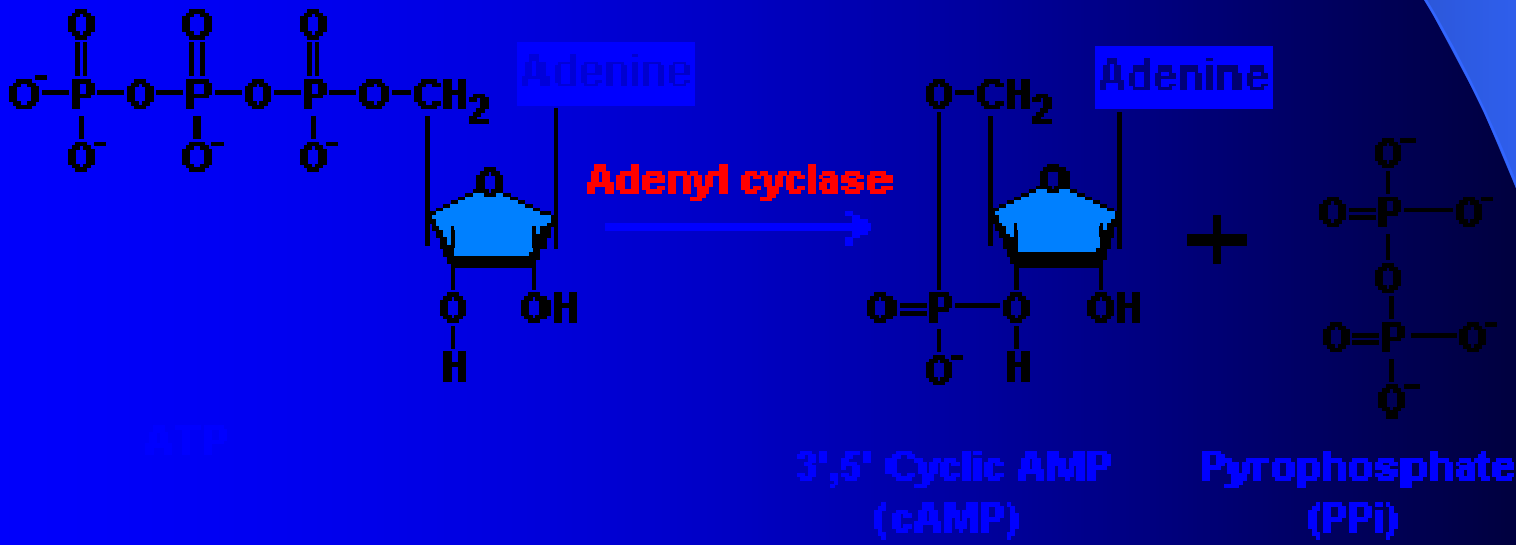
ATP -----> cAMP--------> 5'AMP
(active) (inactive)

Phosphodiesterase

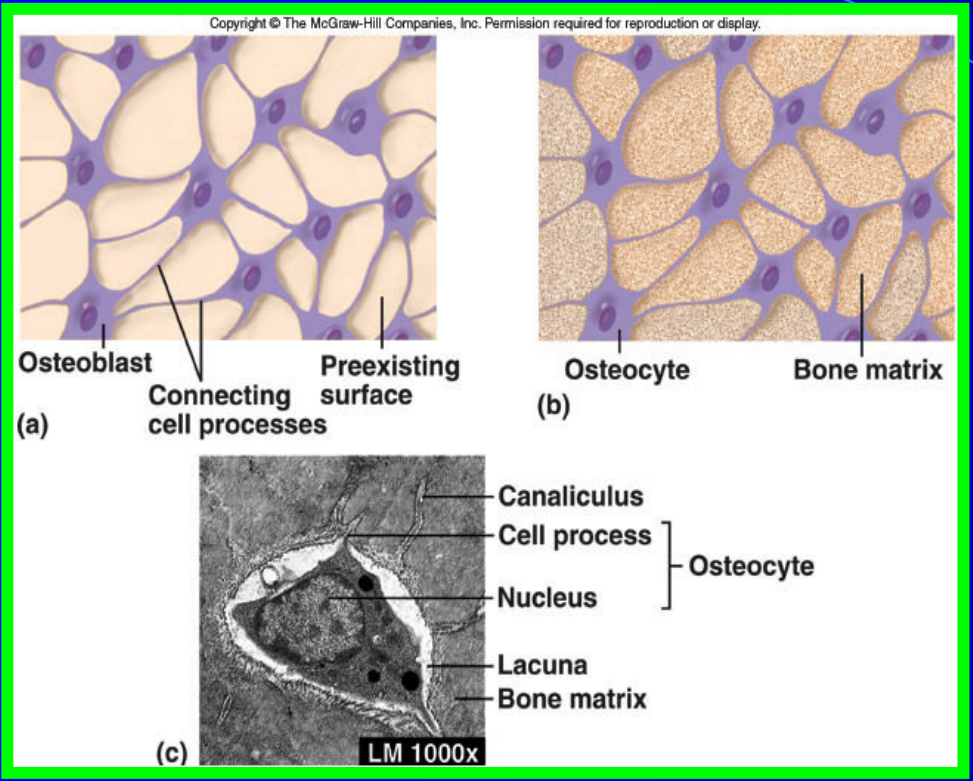
Biochemical change : Bone resorption

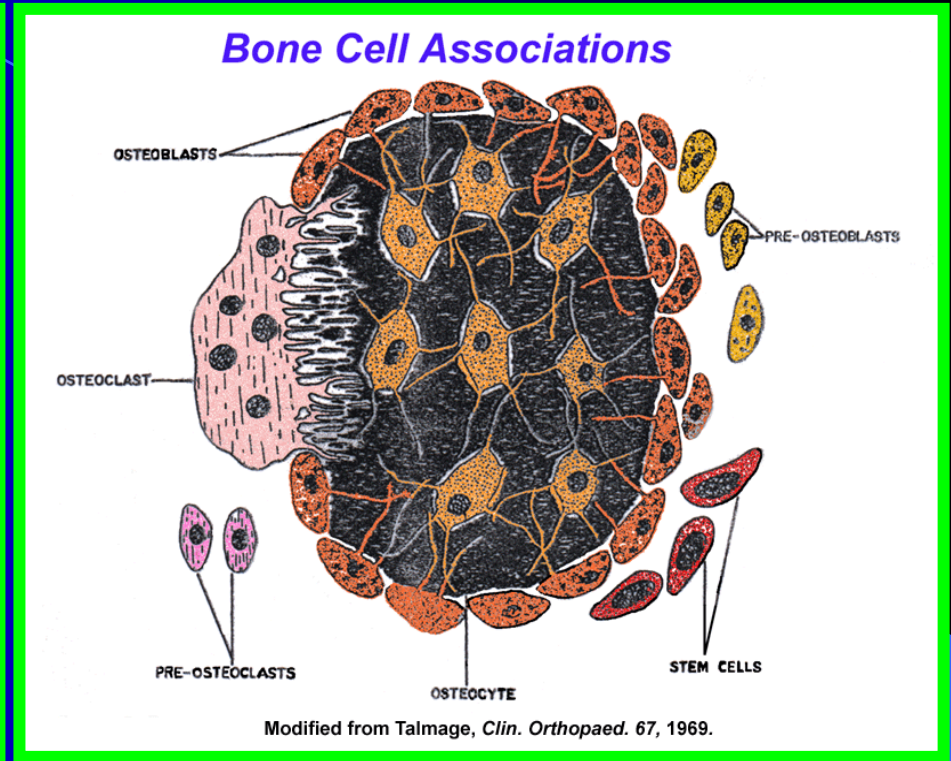
Activation of Adenyl Cyclase





Bone Cells



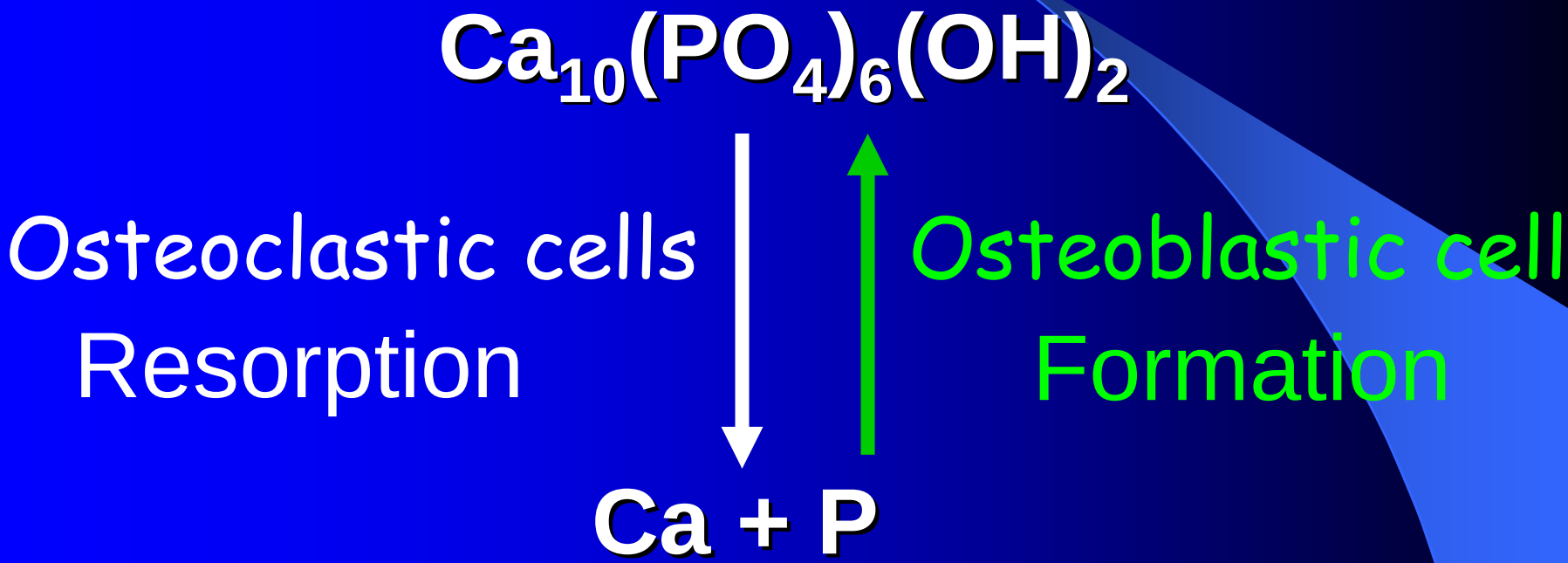


Osteoblasts: Formation of bone through ossification or osteogenesis

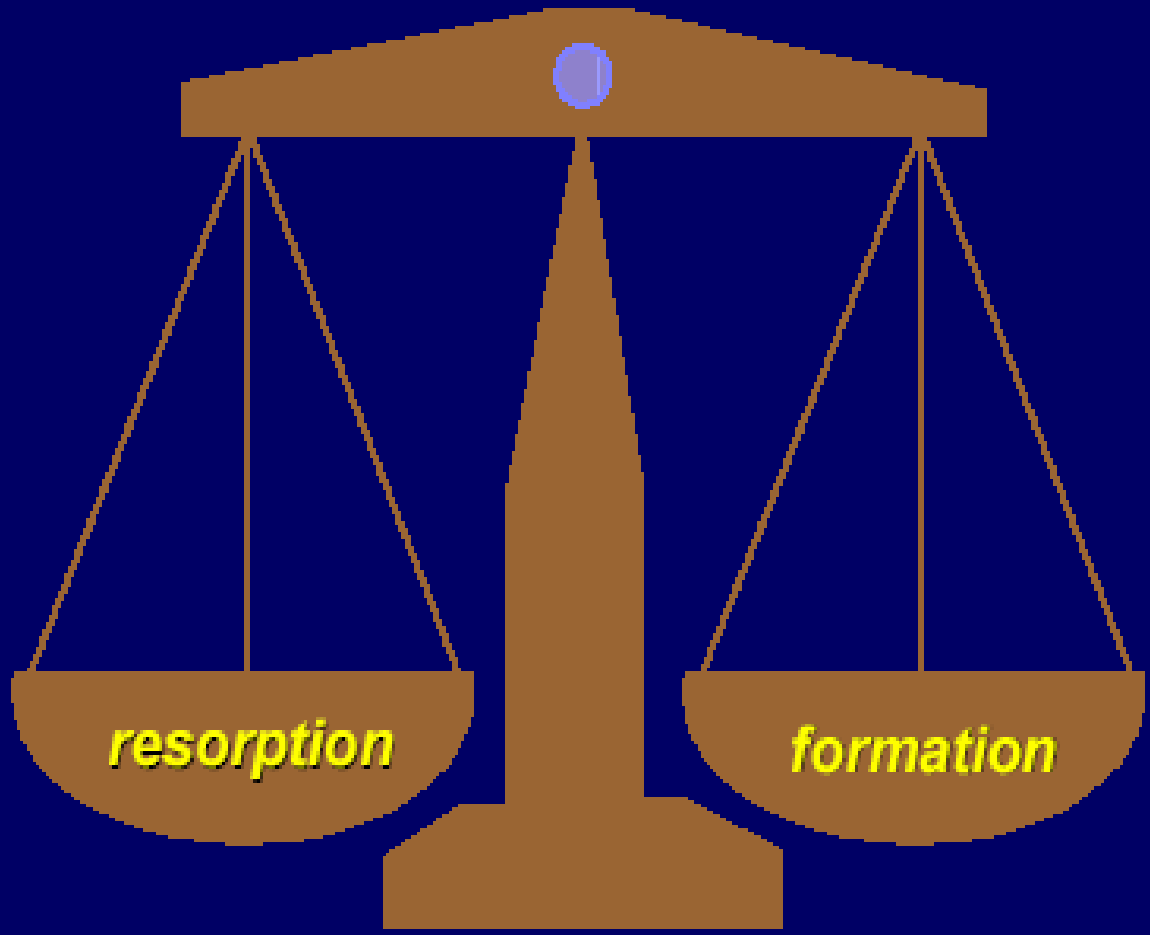
Osteocytes: Mature bone cells

Osteoclasts: Responsible for bone resorption or breakdown

Hydroxypartite

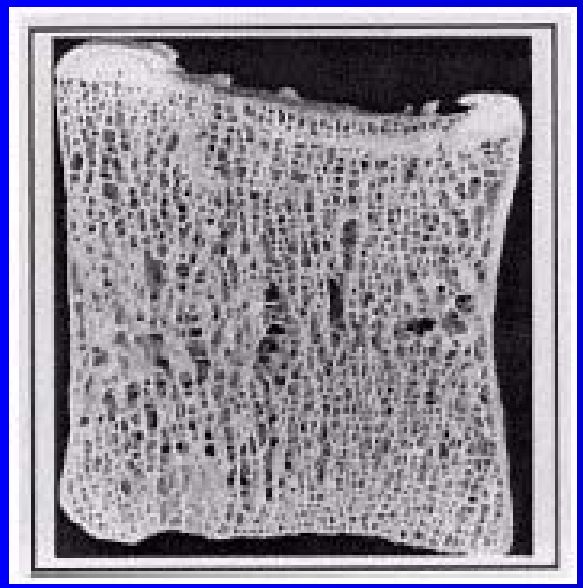


Bone is a Dynamic Tissue

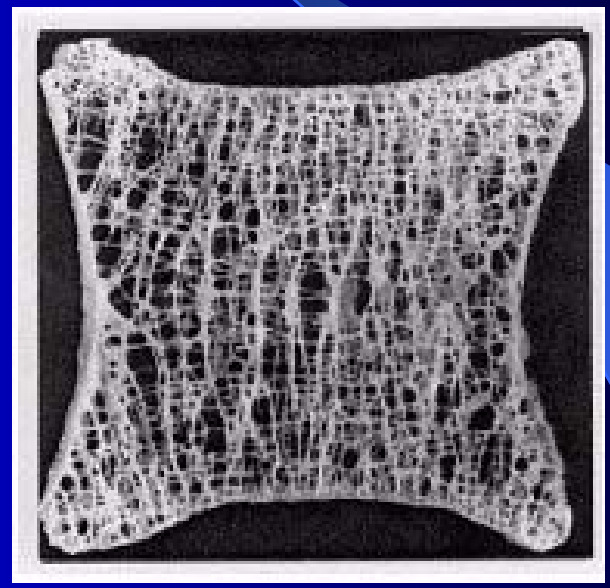


15% of bone mass turns over each year!

'The metabolic bone disease' reflects the disturbances in the organic matrix, the mineral phase, the cellular process of remodeling

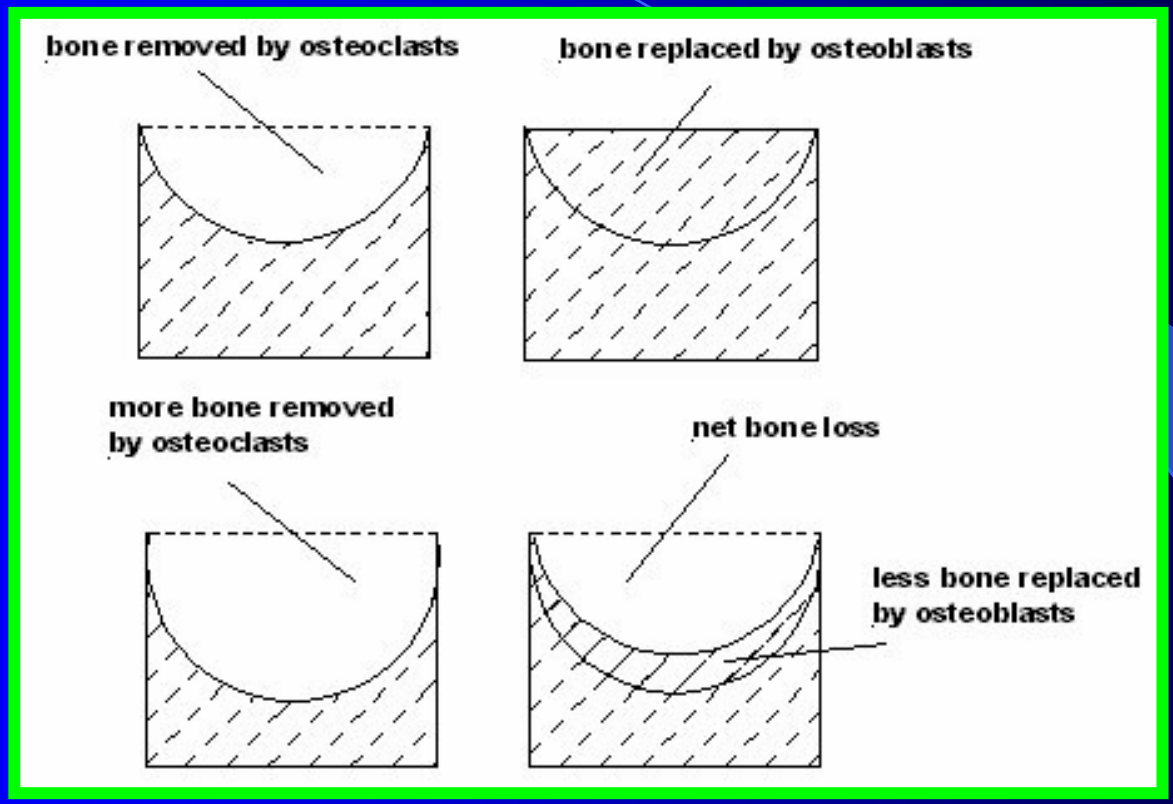


Normal cancellous bone



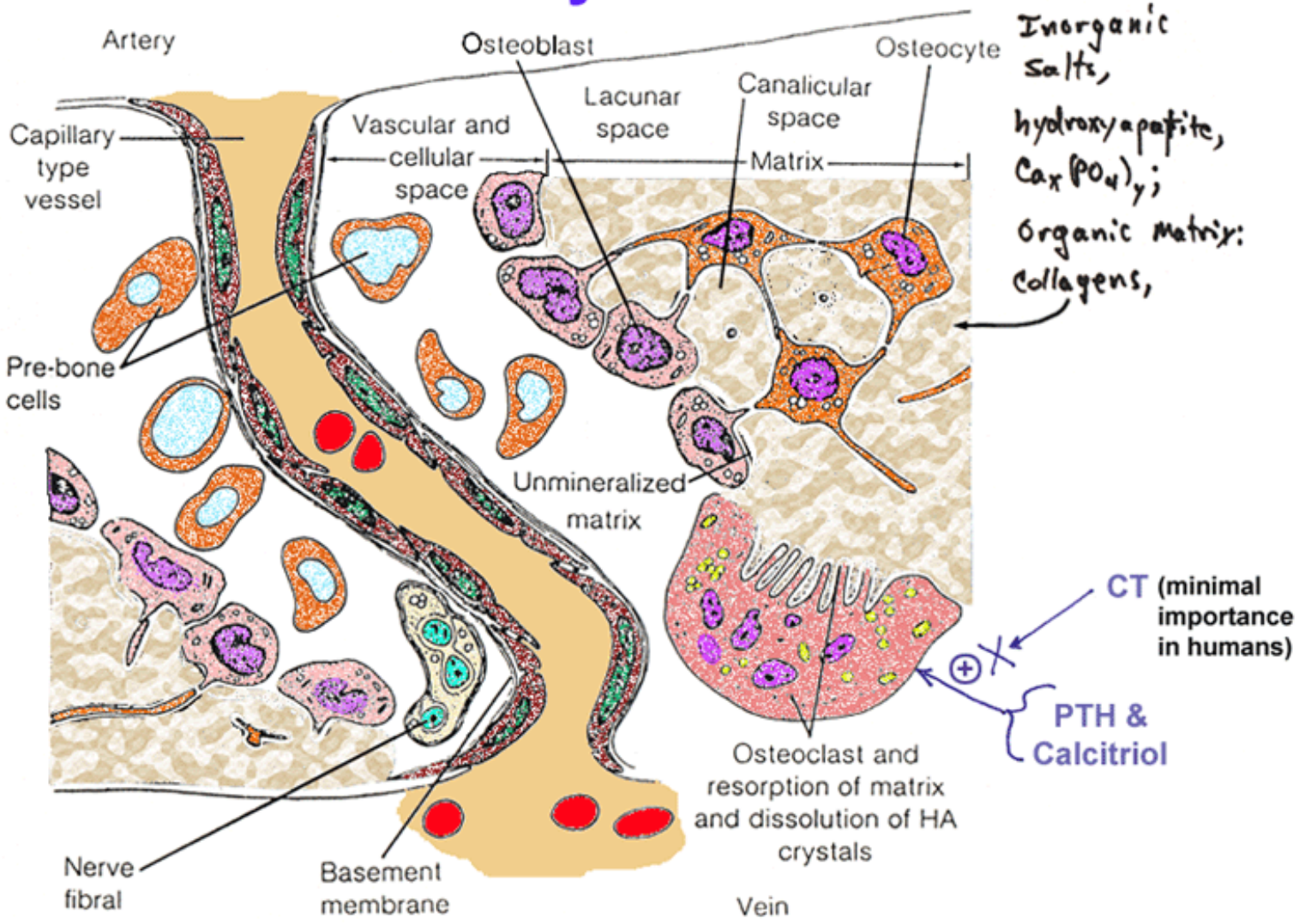
Osteoiporotic cancellous bone

Turnover and Remodeling of bone



Bone formation mediated by 'Osteoblast'
Bone resorption mediated by 'Osteoclast'

Cellular Anatomy of Bone



Modified from Paxton, *Endocrinology: Biological and Medical Perspectives,* W.C. Brown Publishers: Dubuque, IA, 1986.

Action of PTH on Kidney

Immediate action

- If PTH increases : Ca reabsorption, P excretion
- IF PTH decreases : Ca excretion, P reabsorption

Stimulate vit. D activation

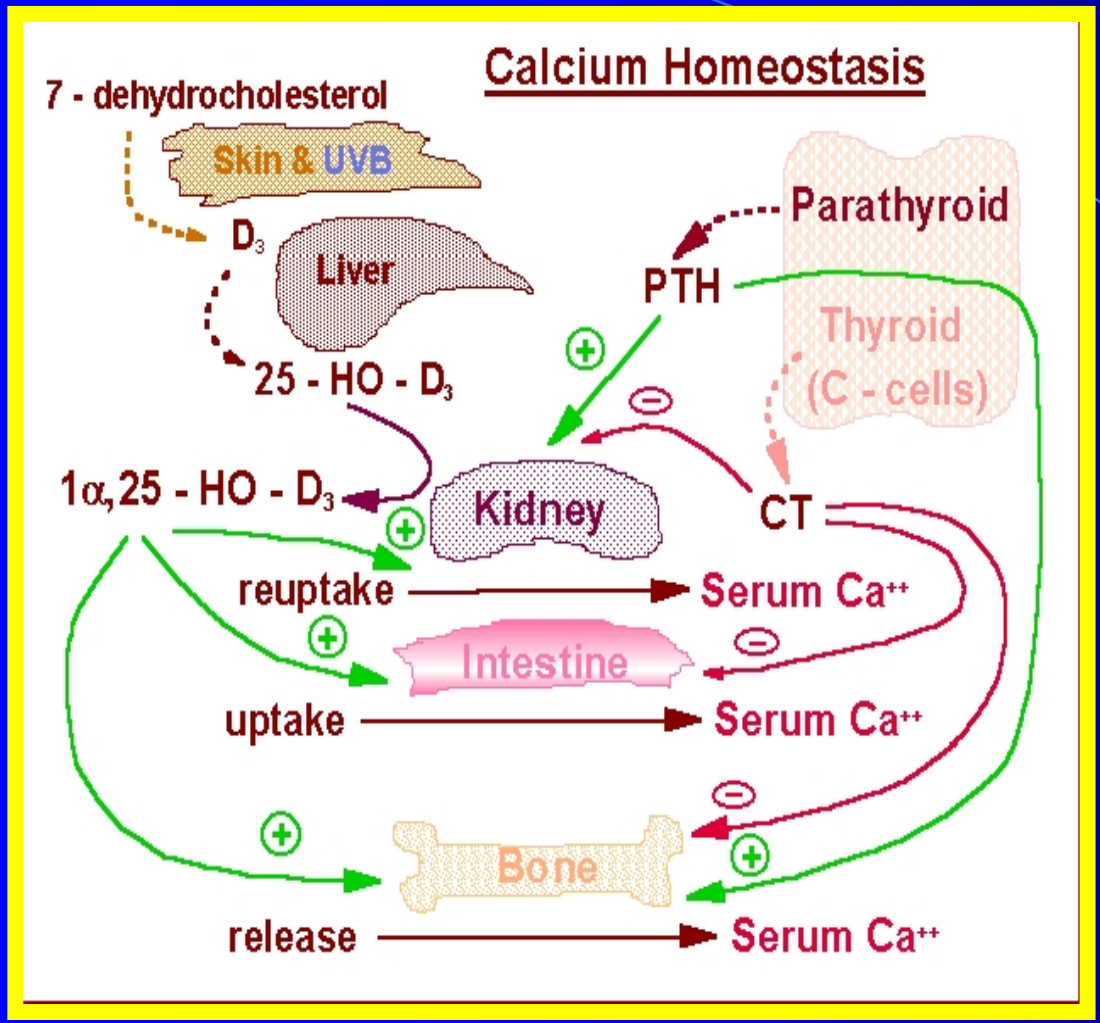
Normally P was excreted about 700-800 mg/day as micromoles of cAMP

Action of PTH on Intestine

- Increase Ca absorption with aids of vitamin D

Vit. D (Cholcalciferol)
(at liver) *25-Hydroxylase*
25-OH vit.D
(at kidney) *1-Hydroxylase*
1,25-di OH vit.D

Action Mechanisms of PTH



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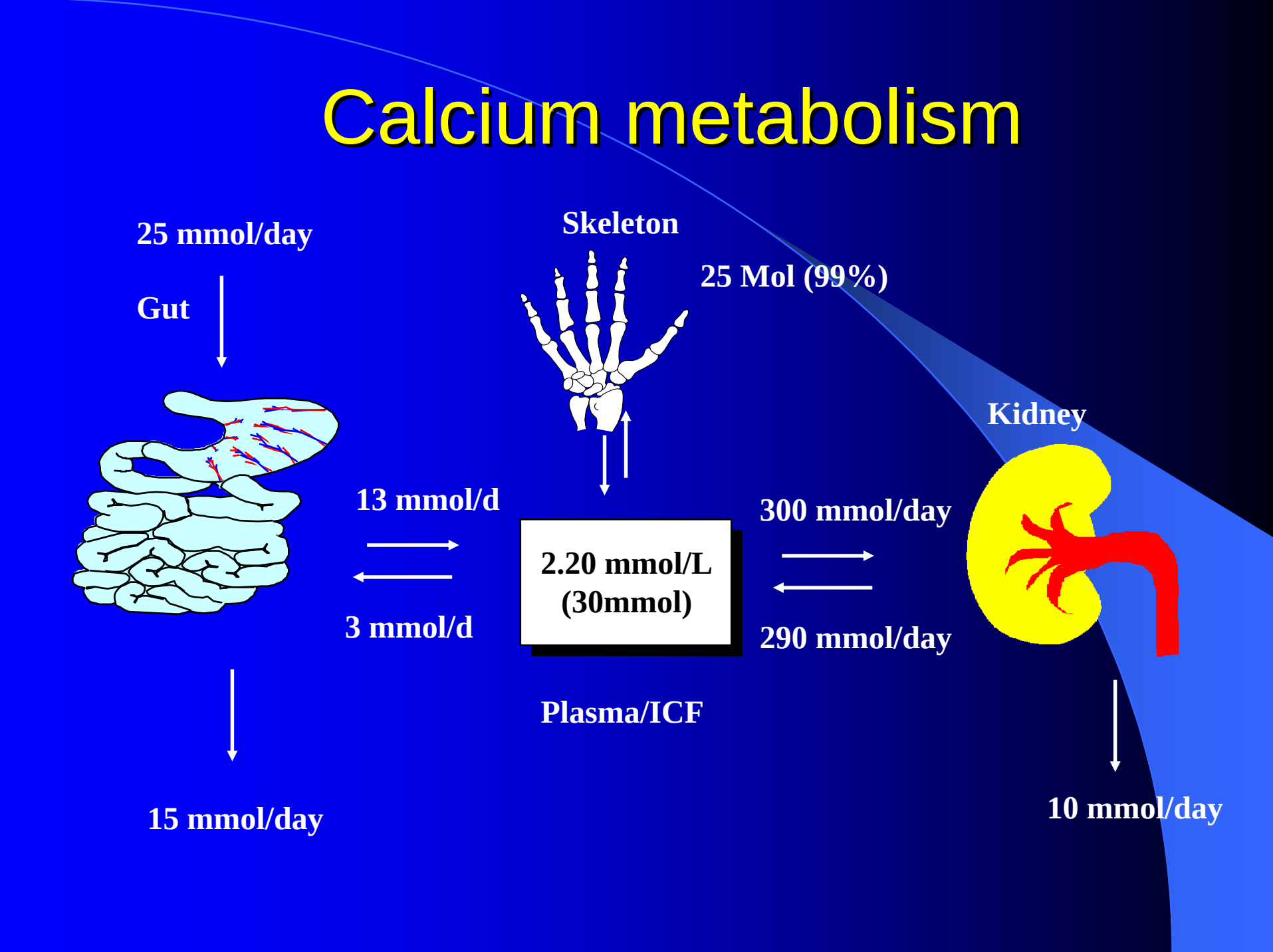
Calcium metabolism

- What is the recommended daily intake?
  - 1000mg
- What is the plasma concentration?
  - 2.2-2.6mmol/L
- How is calcium excreted?
  - Kidneys - 2.5-10mmol/24 hrs
- How are calcium levels regulated?
  - PTH and vitamin D (+others)

Calcium metabolism



Functions of Calcium

- Structural role: Combination of calcium, phosphorus, and OH to make "**hydroxypatite**" or $Ca_{10}(PO_4)_6(OH)_2$ in bone.
- Activator (effector or coupling factor) : Activation of enzymes via cAMP.
- Blood coagulation: Calcium (factor 5) is essential produce thrombin from prothrombin.
- Skeletal Muscle Contraction: Calcium activates the reaction of actinomycin and ATP.
- Cardiac Muscle Contraction: Impulse.

Functions of Calcium

- Nerve impulse transmission: Coupling factor of the neurotransmitter release.
- Regulation of membrane transport and Membrane stability: Maintaining rigidity of plasma membrane and importance for membrane permeability.
  - Low Ca^{2+} will increase sodium permeability and excitability.
- Milk production.
- Cellular secretion: Increase exocytosis of amylase and insulin from secretory vesicles.

Serum Forms of Calcium

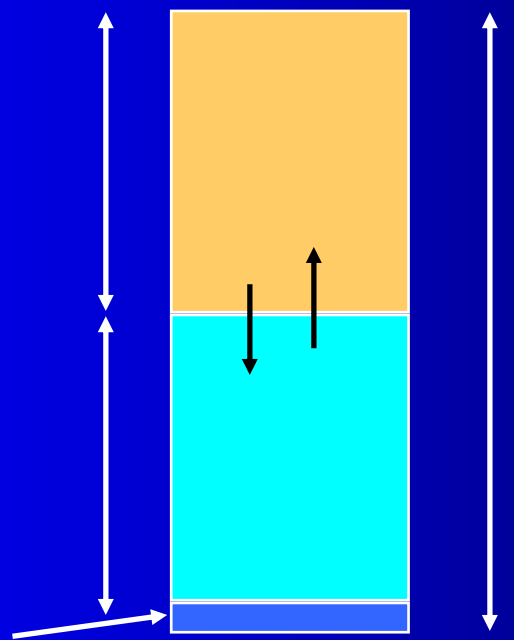
- Ionized or Free Calcium (45-50%) is the only **biologically active** form because it can diffuse freely.
- Complexed Calcium (5-10%): sulfate, citrate, lactate, and phosphate.
- Protein bound (40-50%):
  - Albumin (80%)
  - Globulin

Calcium Distribution in Plasma

Ionized Calcium
~1.0 mmol/L

Bound Calcium
~0.95 mmol/L

Complexed Calcium
~0.05 mmol/L



Total Calcium
~2.0 mmol/L

Protein and pH Effects on [total calcium]

1) Protein Effects: normal albumin is 4.5 g/dL.

- Normal serum albumin (albumin 1 g/Ca^{2+} 0.8 g).
- Hyperalbuminemia

Adjusted calcium (mg/dL)=total calcium (mg/dL) – 0.8 [albumin (g/dL) – 4]

- Hypoalbuminemia

Adjusted calcium (mg/dL)=total calcium (mg/dL) + 0.8 [4 - albumin (g/dL)]

2) pH Effects:

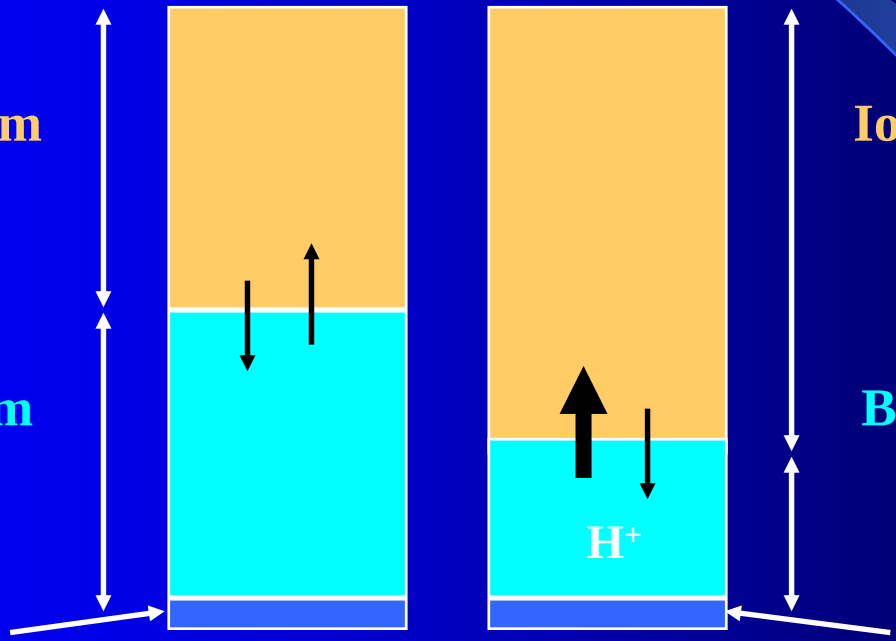
- Acidosis will increase free (ionized) Ca^{2+} in serum because H^+ will compete for albumin.
- Alkalosis will decrease free (ionized) Ca^{2+} in serum.

Effects of pH Changes :
Acidosis

Total Calcium
~2.0 mmol/L

Ionized Calcium
~1.0 mmol/L

Bound Calcium
~0.95 mmol/L



Total Calcium
~2.00 mmol/L

Ionized Calcium
~1.40 mmol/L

Bound Calcium
~0.55 mmol/L

Complexed Calcium
~0.05 mmol/L

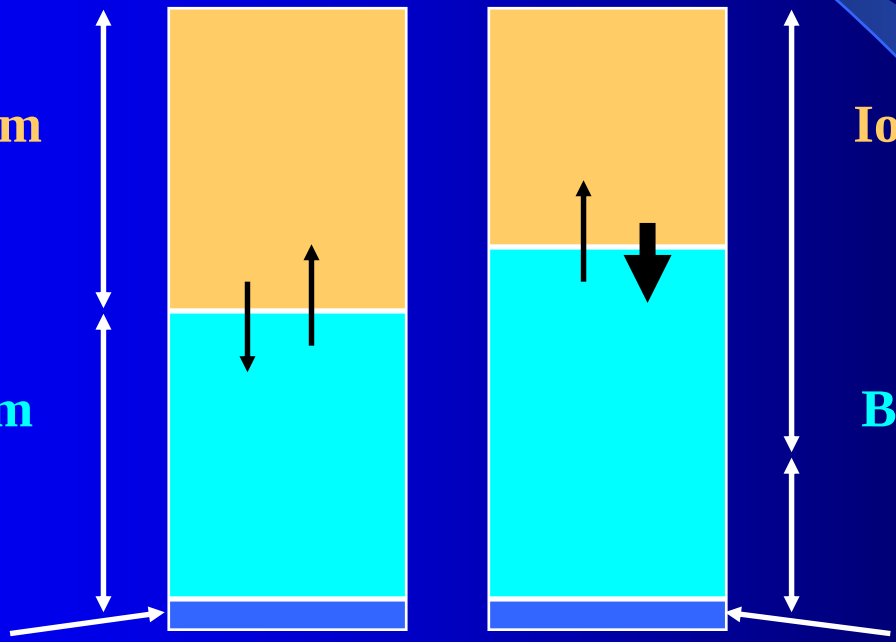
Complexed Calcium
~0.05 mmol/L

Effects of pH Changes :
Alkalosis

Total Calcium
~2.0 mmol/L

Ionized Calcium
~1.0 mmol/L

Bound Calcium
~0.95 mmol/L



Total Calcium
~2.00 mmol/L

Ionized Calcium
~0.60 mmol/L

Bound Calcium
~1.35 mmol/L

Complexed Calcium
~0.05 mmol/L

Complexed Calcium
~0.05 mmol/L

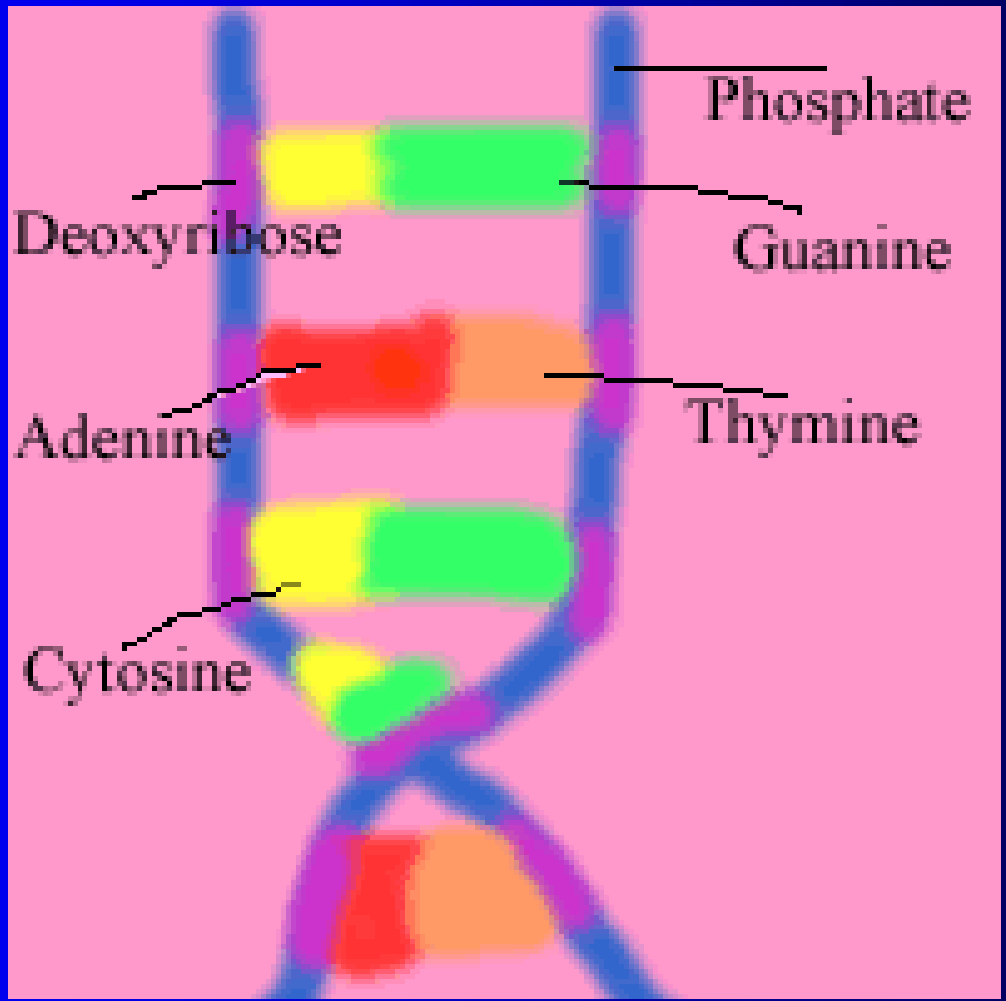
Phosphate metabolism

- Normal plasma concentration?
  - 0.9-1.3 mmol/L
- Absorption and excretion?
  - Gut and kidneys
- Regulation
  - Not as closely regulated as calcium but PTH most important

Functions of Phosphorus

- Structural roles:
  - Combination of calcium, phosphorus, and OH to make hydroxypatite or $Ca_{10}(PO_4)_6(OH)_2$ in bone.
  - Organic phosphate in phospholipids and phosphoproteins in cell membranes.
  - Genetic materials such as nucleic acids.
- Carbohydrate metabolism: Production of hexose phosphate and triose phosphate.
- Stored energy:
  - Purine nucleotides such as ATP.
  - Creatine phosphate in muscle.
- Regulatory functions: cAMP controls phosphorylation of enzyames.
- Buffering system of urine and blood: Inorganic phosphates ($HPO_4^=$ and $H_2PO_4^-$). At pH 7.4, the ration is 4:1.

DNA Structure



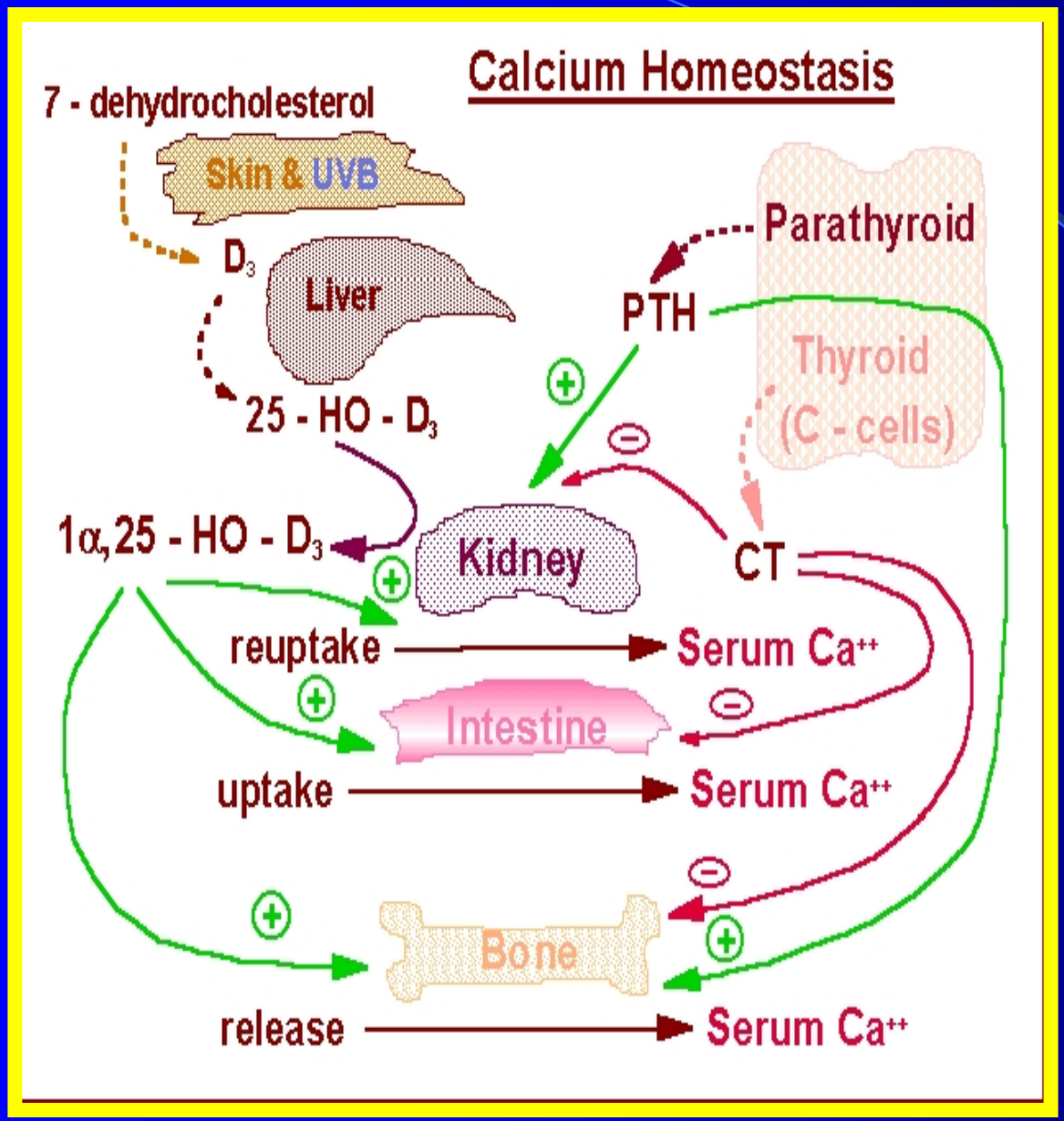
Regulatory Mechanisms for Ca and P

- PTH
- Calcitonin (CT)
- Vitamin D
- Other factors such as glucocorticoids, androgen, estrogens, and growth hormones.

Role of PTH, Vit.D, Calcitonin

	Bone	Kidney	Intestine
PTH	+ Ca res. + P res	+ Ca reabs. - P reabs.	+Ca abs.(Indirect) + P abs. (Indirect)
Vit. D	+ Ca res. + P res	+ Ca reabs. + P reabs.	+Ca abs.(Direct) + P abs.
Calcitonin	-Ca res. - P res.	-Ca reabs. - P reabs. - vit.D activation	None

Res.=resorption, reabs.=reabsorption, abs.=absorption



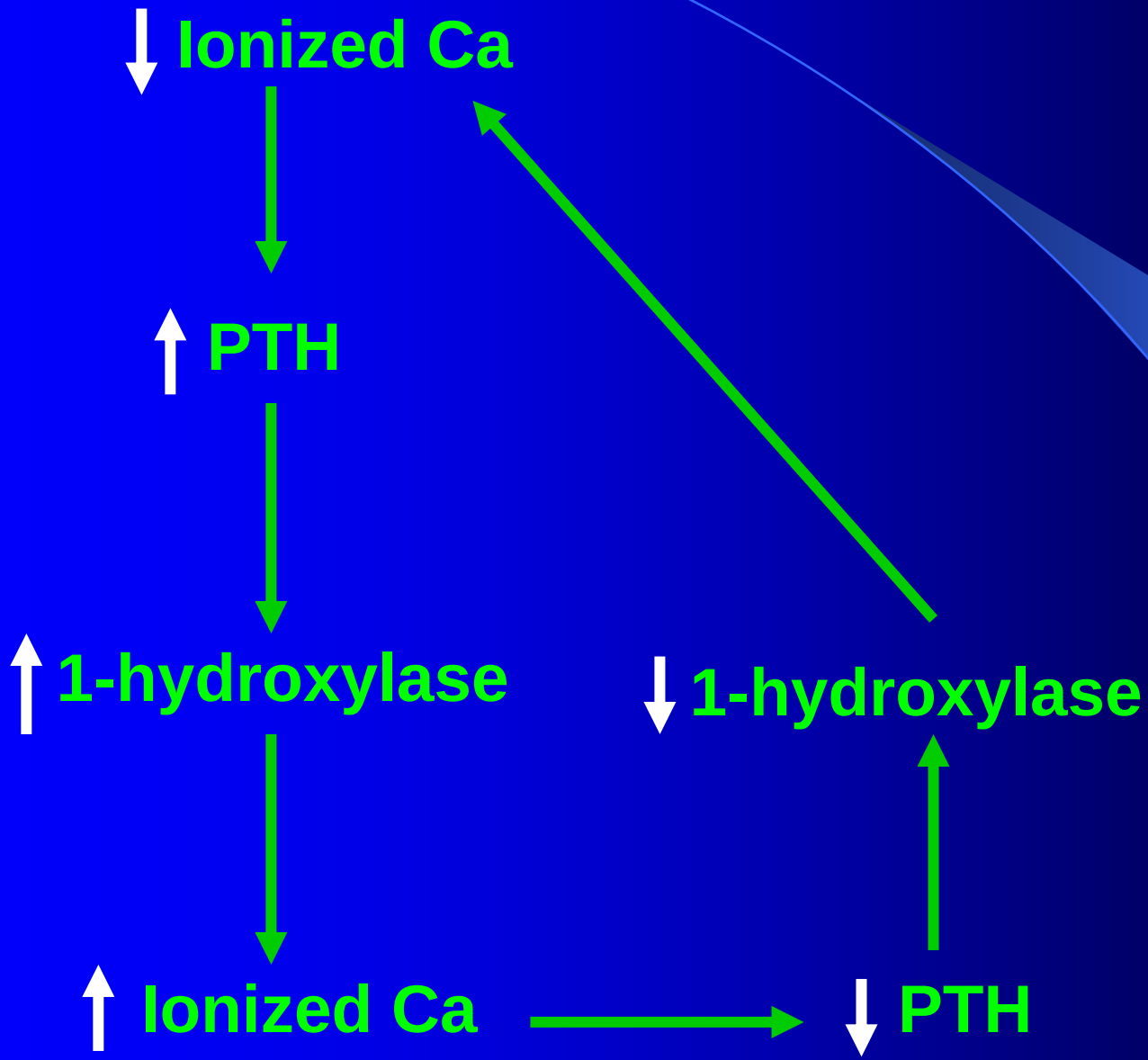
Calcitonin (CT)

- Actions on bone and kidney.
- To decrease serum calcium.
- Against PTH and 1, 25-HO-D_3.

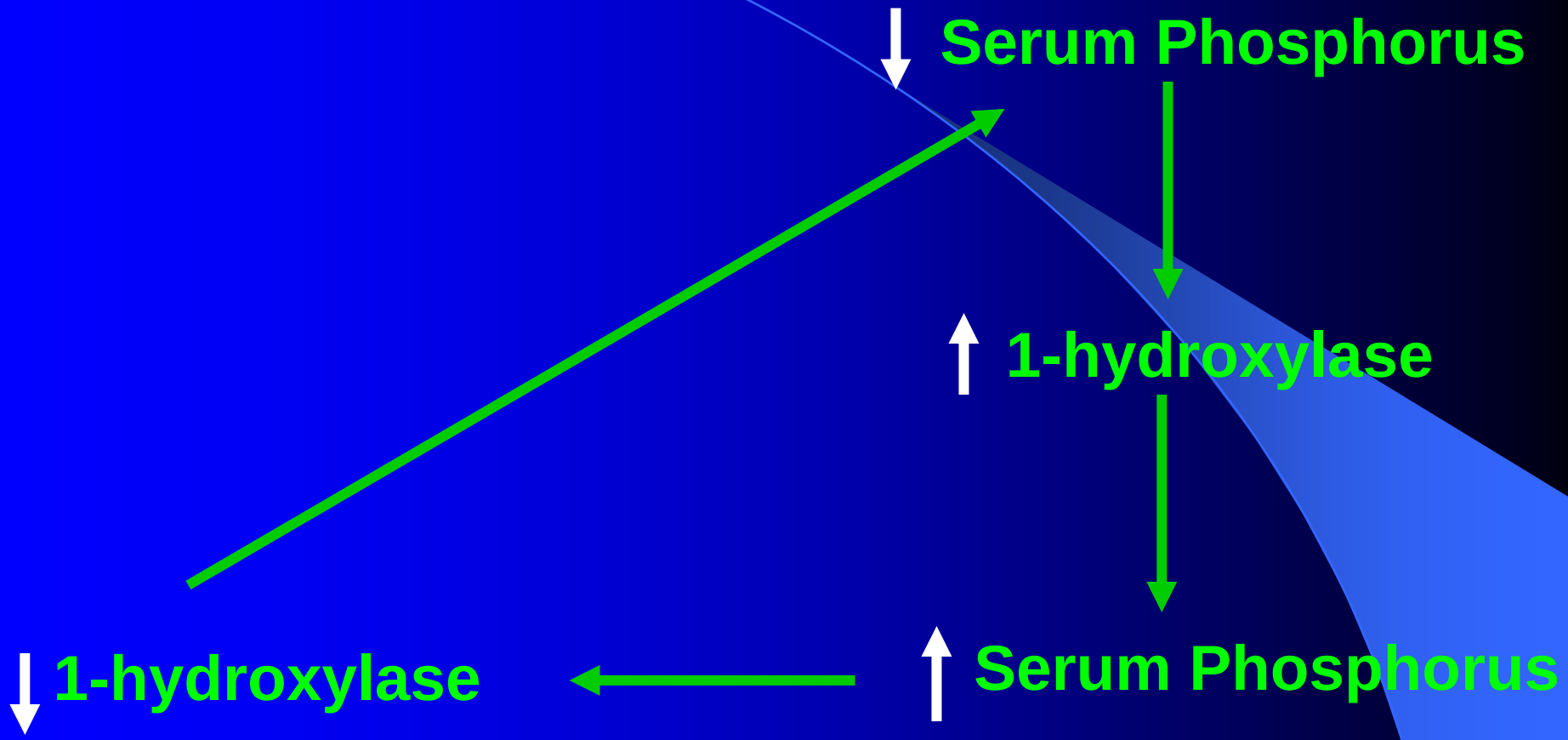
Feedback Mechanisms

- Controls the formation of activated vitamin D.
- 1-hydroxylase.
- Ionized Ca sends signal to PTH.
- Serum P will not send via PTH.

Feedback Mechanisms



Feedback Mechanisms



Laboratory Tests

1. Serum PTH - RIA, Immunochemistry
   - Intact molecule
   - C-terminal
   - N-terminal
2. Ca, P, Alakaline phosphatase in serum
3. Ca, P in urine
4. Hydroxyproline, hydroxylysine in serum & urine
5. cAMP in serum & urine
6. Others - X-ray
   - Bone density, etc.

Clinical Applications

- Serum Calcium is lower than 8.5 mg/dL

Causes of Hypocalcemia

- **hypoparathyroidism** เช่น ความเสียหายจากการผ่าตัด **thyroid gland**
- **pseudohypoparathyroidism** มี **PTH** เพิ่มขึ้น แต่ผิดปกติที่ **target organs**
- **Chronic renal failure (renal osteodystrophy)** ไตสร้าง **activated vit. D** ได้น้อยลง
- **vit. D deficiency** การขาด **Ca** และ **P** จนไม่สร้าง **bone mineralization (Rickets** ในเด็ก **Osteomalacia** ในผู้ใหญ่)

- **Serum Calcium is higher than 10.5 mg/dL**

Causes of Hypercalcemia

- **Primary hyperparathyroidism**
- **Metastasis CA of bone**
- **PTH-like substance from Tumor (bronchogenic CA, lung CA, etc.)**
- **Milk-alkali syndrome (toxicity)**
- **Thiazide-induced hypercalcemia**
- **Adrenocortical insufficiency --> increased vit. D action**

Treatment of Hypercalcemia

- Subtotal surgery
- Autotransplantation at upper arms

.

Hyperparathyroidism

Primary : rare disease, about 1/1000

age : <20 yrs., post-menopause

sex : F > M ~ 2-3 times

Cause : Gland hyperfunction

~ 0.1% Asymptomatic hypercalcemia

~ 5% - Nephrocalcinosis was also found

Incidence : ~ 80% Single gland - Chief cell adenoma

~ 2% CA gland may accompanied with multiple neoplasm of pancreas, pituitary, thyroid, adrenal glands

1º Hyperparathyroidism

Symptom : Hypercalcemia

Bone - back pain, joint pain, bone fracture

fibrous deposit at gum - brown pigment

pseudoclubbing

Kidney - Polyuria, polydipsia

- U/A - Ca-oxalate, Ca-phosphate

---> easily infected

- Nephrocalcinosis

GI - Anorexia, nausea, vomit, weak

- constipation, peptic ulcer, obstruction

bleed --> anemia, weight loss

- high BP, psychosis

1º Hyperparathyroidism

Lab. Test :

- Serum Ca -ionized increased
  - total normal or high
- Alk. P-ase increase ~ 1/4 of patients
- decrease P -- ~ 3 mg/dL or less
- Urinary hydroxyproline, Ca - increase / normal
- X-ray - subperiosteal resorption
  - osteoporosis at skull
- PTH - increase / normal
  depend on principle of test, form of PTH

Hyperparathyroidism

Secondary : rare disease, about 1/1000

age : <20 yrs., post-menopause

sex : F > M ~ 2-3 times

Cause : Gland hyperfunction

~ 0.1% Asymptomatic hypercalcemia

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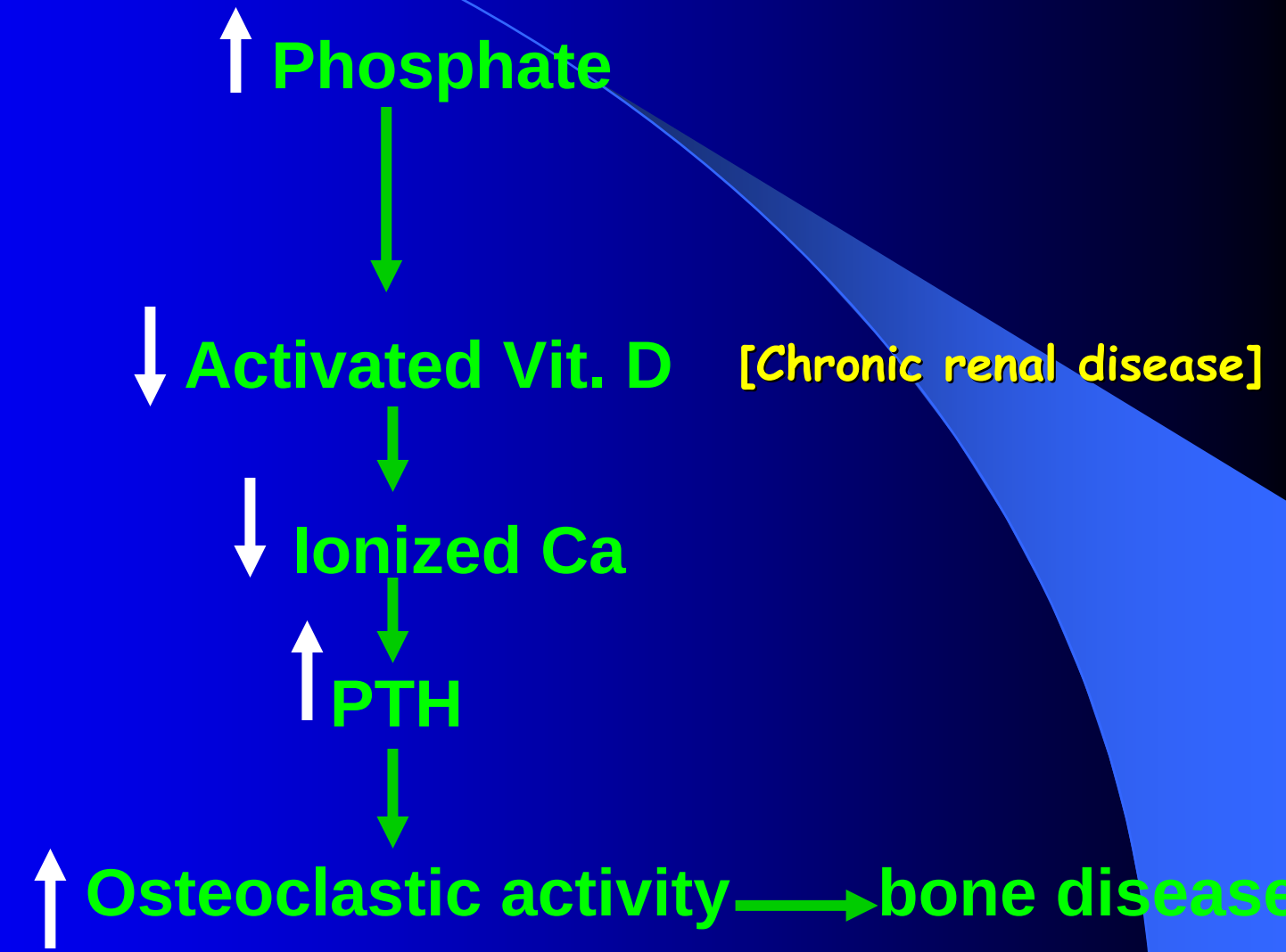
Incidence : ~ 80% Single gland - Chief cell adenoma

~ 2% CA gland may accompanied with multiple neoplasm of pancreas, pituitary, thyroid, adrenal glands

2º Hyperparathyroidism



2º Hyperparathyroidism

Usually 4 glands involved

Underlying disease :

- Chronic renal failure - P retention,
  - vit. D inactivation
- Osteomalacia, rickets
- Steatorrhea
- Chronic malabsorptive syndrome
- Prolonged hemodialysis

2º Hyperparathyroidism

Lab. Test :

- Serum Ca - ionized increased/normal
  - total normal or low
- Alk. P-ase increase
- increase P

.

3º Hyperparathyroidism

Chronic Renal failure/ or other 2º causes

↓

Lower blood Ca

↓

PT gland hypertrophy & hyperplasia

↓

Autonomy

↓

Tertiary hyperparathyroidism

Hypoparathyroidism

Cause : Thyroidectomy
Surgery at area of Neck
Pseudohypoparathyroidism (No response of target orgen)

<u>Ellsworth-Howard test for Pseudohypoparathyroid :</u>

Inject PTH ---> Observe urinary P excretion
Increase - hypoparathyroidism
No change - Pseudohypoparathyroidism

Hypoparathyroidism

Symptom : Hypocalcemia

- Numb -----> spasm ----> tetany (laryngo, broncho-) ----> convulsion

- Chvostek's sign of Chronic hypocalcemia : tapping at facial nerve ---> spasm at lip of the the same side

  Touniquet > systolic BP for 2-3 min. ---> Hand spasm

- Scaly eruption, เล็บมีสัน ลิ้นเหี่ยว ผมบาง

Hypoparathyroidism

- **Lab tests :**

- Blood Ca < 9 mg/dL
- Alk. P-ase - normal
- Urine Ca, P - Low
- X-ray - Calcification of basal ganglia

Metabolic Bone Diseases

1. **Rickets / Osteomalacia**

=> Long Bone softening

Matrix - OK, **Calcification - poor**

Cause : vit. D, Ca, P, protein intake / Abnormal

Renal disease

GI :- malabsorptive syndrome

Lab :

- Low serum Ca --- --- --- > Tetany
- High P -- in case of PT uncompensation
- Alk. P-ase increase
- X-ray - pseudofracture, flatening of skull (child)

Treat : Oral/IV - Vit. D, Ca, P

Metabolic Bone Diseases

2. **Osteoporosis** (Porosity of bone)
   => decrease Bone density
   Matrix - low, Calcification - normal

Cause :↓1º Old age, post-menopause, senile
2º Catabolic hormone
Anabolic hormone
No exercise, weightless
Low Ca intake and/or High P intake
PTH/ Calcitonin imbalance

Metabolic Bone Diseases

Osteoporosis (Porosity of bone)

Lab : ↓ Serum Ca, ↑ Urine Ca
Alk. P-ase - Normal

Bone size and density - decrease

Treat : Oral Ca, vit. D
Estrogen, androgen
Fluoride

Non-Metabolic Bone Diseases

1. **Polyostotic fibrous dysplasia**
   (Oseitis fibrosa diseminata or Albright's syndrome or Osteogenesis imperfecta)

   => Fibrous tissue Bone - brittle bone syndrome
   no bone or cartilage

Cause : Congenital dysplasia

Sign : - swollen bone, mostly skull, leg bones
- finger bones, ribs without pain,
- one point or distributed with thin or porous
- brown skin at the defected area
- sexual precocity in female

Non-Metabolic Bone Diseases

Lab : Normal serum Ca, P

Normal Alk. P-ase

Hydroxyproline - increase

X-ray - thin and hyperostotic especially at middle of skull fractures or deformities my be seen

Non-Metabolic Bone Diseases

2. Paget's disease (Osteitis deformans)

Cause : Unknown

Inclusion bodies were found - Virus ?

Character

- increase osteoclastic activity --> bone resorption rapidly
- increase osteoblastic activity --> bone formation rapidly but laid down in disorganized way
- bone pain especially in severe case

Non-Metabolic Bone Diseases

Lab : - Serum Ca, P vary with the disease status

- Alk. P-ase **very high** - (heat labile)
- Serum & urine hydroxyproline **- very high**
- Urine Ca - very high at disease onset
- X-ray - Multiple fissure fracture in long bone.

Non-Metabolic Bone Diseases

Complications :

- Deaf, Blindness
- Nephrocalcinosis (high Ca intake)
- Depressed nerve at spinal canal -- -- --> Osteosarcoma
- Multiple arteriovenous fistula (due to high blood supply) --> cardiac failure

Treat :

- Protein, vit. C, vit. D
- Anabolic hormone
- Calcitonin as needed (reduce osteoclast activity)

Bone Turnover Markers

Formation markers:

- Serum osteocalcin
- Serum total alkaline phosphatase
- Serum bone specific alkaline phosphatase
- Serum procollagen I carboxyterminal propeptide
- N-terminal propeotide

Bone Turnover Markers

Resorption markers:

- Urinary hydroxyproline
- Urinary total pyridinoline
- Urinary total deoxypyridinoline
- Urinary free pyridinoline
- Urinary free deoxypyridinoline
- Urinary collagen type I cross-linked
  - N-telopeptide
  - C-telopeptide
- Serum carboxyterminal telopeptide of type I collagen