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# Calcium Metabolism

M2 – Endocrine Sequence  
R. Grekin

Winter 2009



# CALCIUM IN SERUM

- Regulated within narrow limits; approx. 9.0-10.5 mg/dl
- Less than 50% is ionized. Majority of the rest is bound to albumin. Rule of thumb: 0.8 mg/dl Ca change for each 1 gm/dl change in albumin.
- Calcium and phosphate in serum are nearly saturated.
- Ionization decreases in alkaline pH

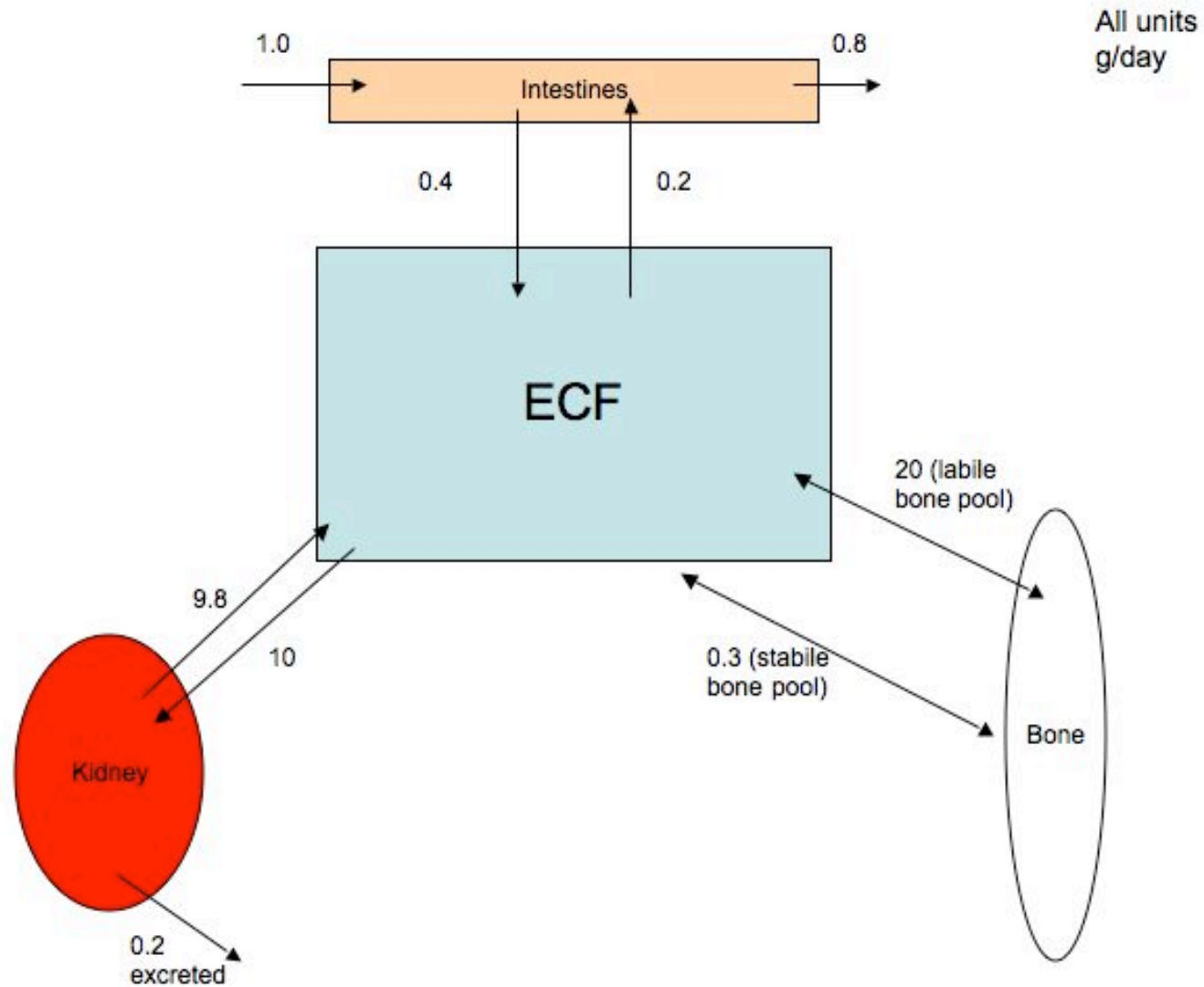
# GI ABSORPTION OF CALCIUM

- Average 1 gm intake but only 10 to 20%, absorbed - net
- Absorption is an active process which is vitamin D dependent

# RENAL EXCRETION OF CALCIUM

- **99% of filtered Ca is reabsorbed**
- **Reabsorption occurs in the proximal tubule linked to sodium reabsorption**
- **Reabsorption in the distal tubule is Pth dependent**

# Daily balance of calcium

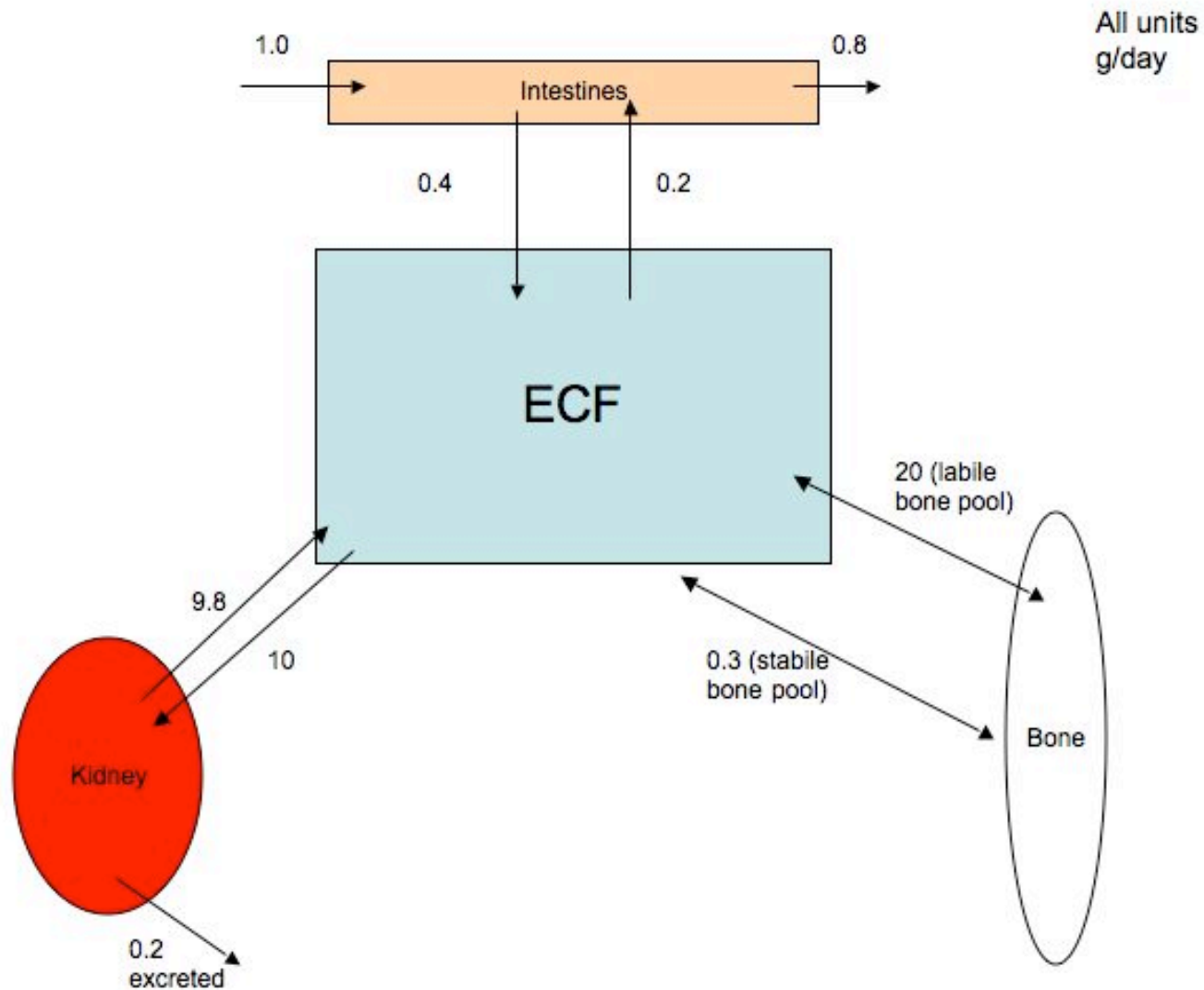


# PHOSPHORUS

- Present in skeleton as hydroxyapatite and widely distributed in macromolecules
- Normal serum levels 3.0-4.5 mg/dl in adults. Solubility product determines relationship between Ca and PO<sub>4</sub>
- G.I. absorption is efficient, primarily in jejunum. Vitamin D regulated
- Renal excretion is regulated by Pth



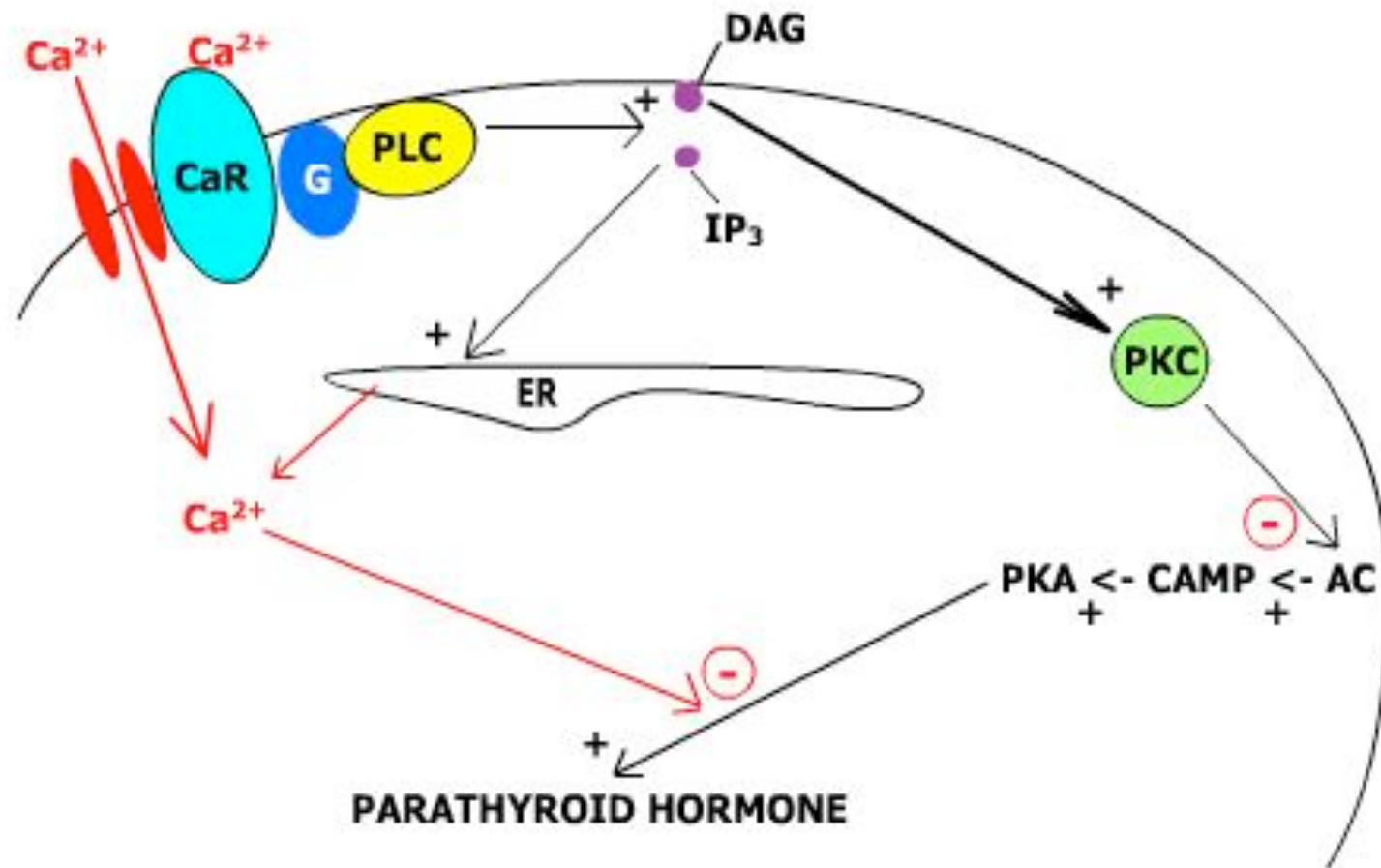
# Daily balance of phosphorus

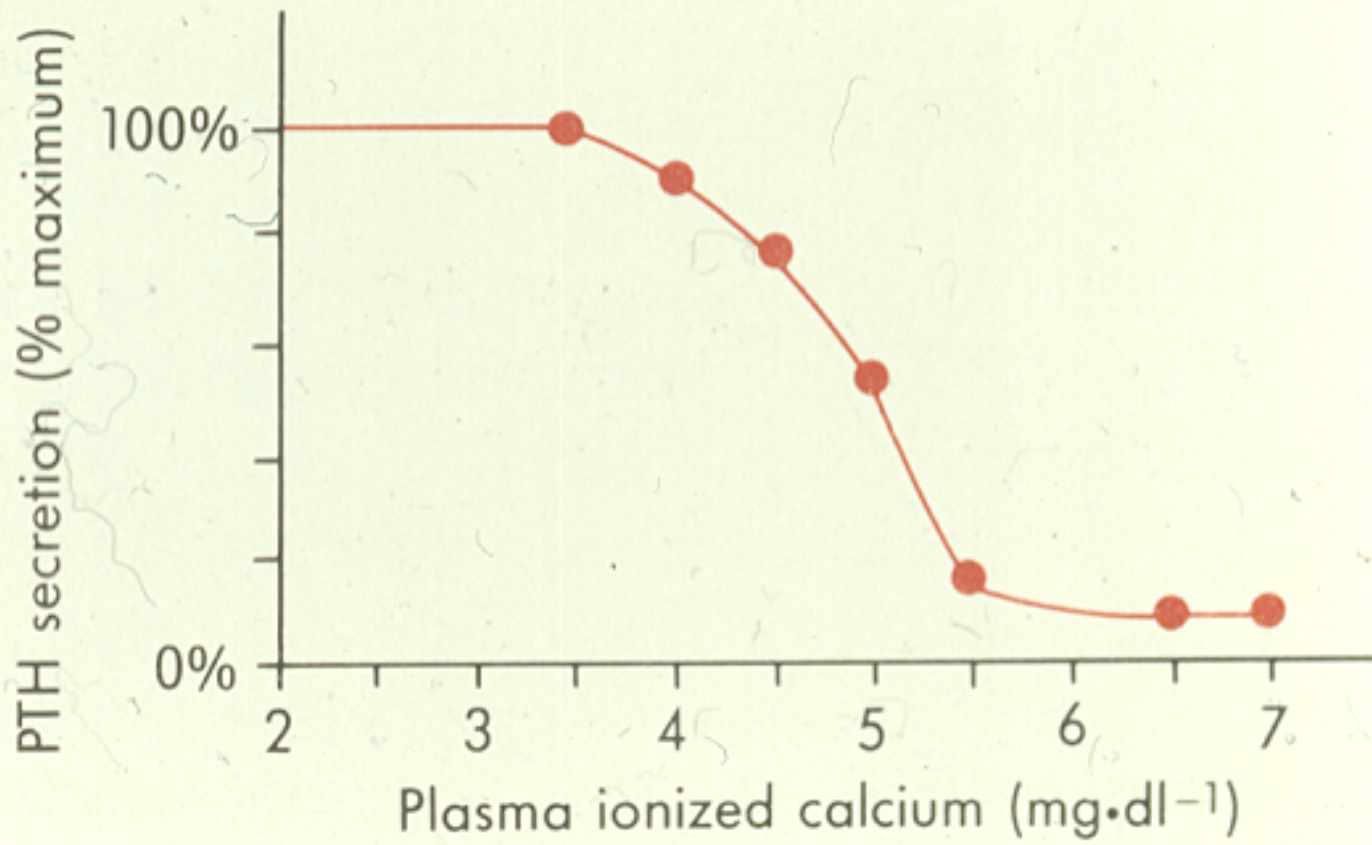


# **REGULATION OF PTH SECRETION**

- **Major factor is plasma level of ionized calcium.**
- **Chief cells have membrane bound Ca receptors that mediate the suppressive effects of Ca on Pth secretion**
- **1,25-dihydroxy vitamin D decreases the Pth secretory response to a given level of Ca<sup>++</sup>**
- **Marked hyperphosphatemia can also stimulate Pth secretion**

## PTH regulation by Ca in parathyroid chief cell





# RENAL ACTIONS OF PTH

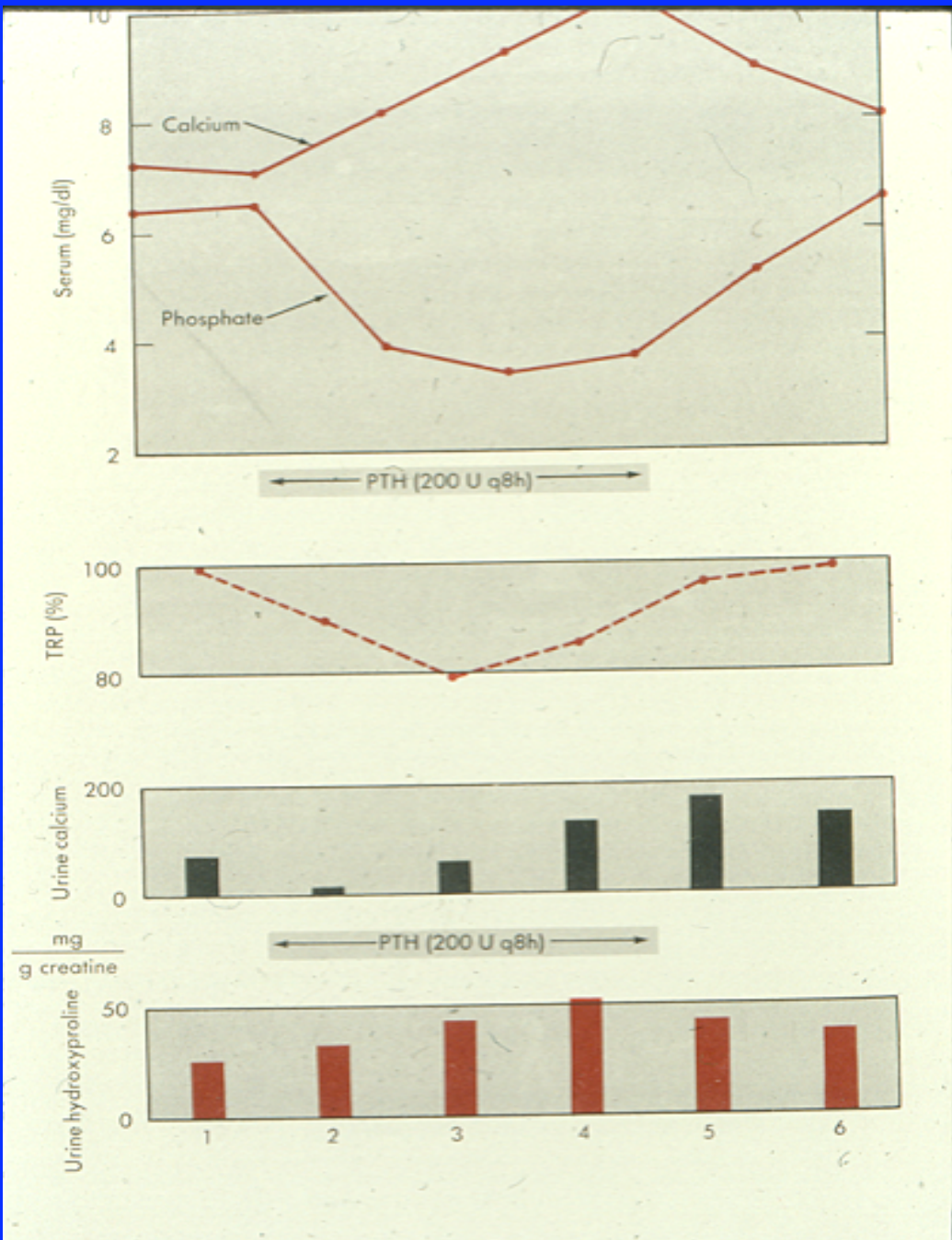
- **Decreases proximal tubular reabsorption of phosphate**
- **Increases calcium reabsorption in the distal tubule**
- **Increases 1-alpha hydroxylation of vitamin D**
- **Effects are mediated through cAMP**

# **ACTIONS OF PTH ON BONE**

- **Increases osteocytic and osteoclastic osteolysis, leads to increased release of Ca and PO<sub>4</sub>**
- **Probably plays a role in bone remodeling**
- **Intermittent administration increases trabecular bone density and reduces fracture risk**

# GI ACTIONS OF PTH

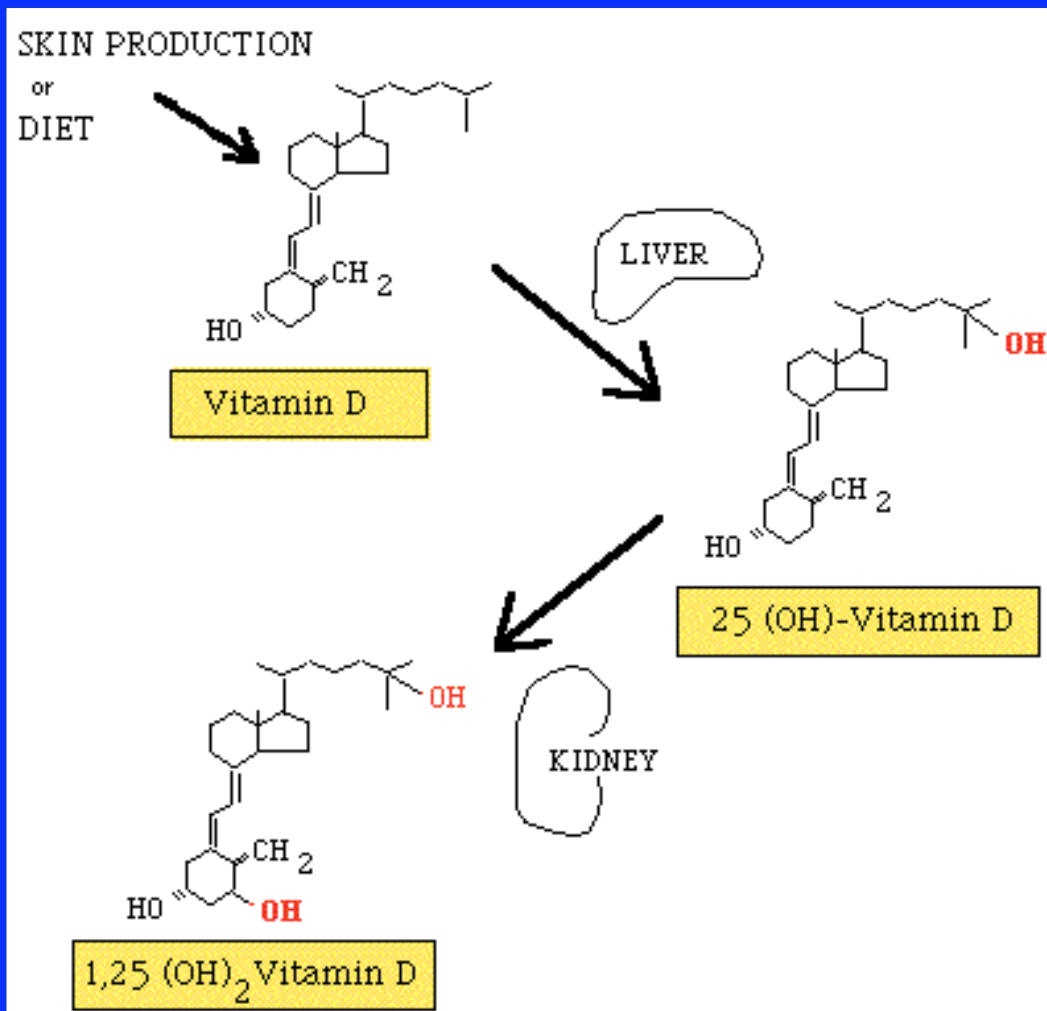
- **Promote absorption of  $\text{Ca}^{++}$**
- **Effect is primarily mediated through increased levels of 1,25-dihydroxycholecalciferol**





# SOURCES OF VITAMIN D

- **7-dehydrocholesterol stored in skin in large amounts**
- **Vitamin D added to milk, cereal, etc**



# REGULATION OF VITAMIN D METABOLISM

- **1 alpha-hydroxylase is the regulated step**
- **Pth and hypophosphatemia both increase 1-alpha hydroxylase activity**
- **1,25 dihydroxy D inhibits activity**

# ACTIONS OF VITAMIN D

- **Gut - stimulate calcium and phosphate absorption**
- **Bone - in higher doses, stimulate resorption. Allows effect of Pth.**
- **Parathyroid gland – suppress Pth secretion**

# CALCITONIN

- **32 amino acid peptide produced in the C cells of the thyroid**
- **Inhibits osteoclastic activity.**
- **No known disorders of calcium metabolism relate to alterations in calcitonin secretion**

# CALCITONIN

- **Elevated calcitonin levels are an important marker for medullary carcinoma of the thyroid**
- **Calcitonin is used therapeutically in hypercalcemia, Paget's disease, and osteoporosis**

A 55 year old man was admitted to the hospital with excruciating left flank pain of two hours duration. He also gave a history of two years of increasing anorexia, nausea, constipation, and a 15 pound weight loss. He complained of increased fatigue and weakness, and had suffered intermittent rib pain for the past five months.

On physical examination, blood pressure was 150/105, pulse 85 and temperature 37°C. He was obviously very uncomfortable, and had marked tenderness in the left costovertebral angle, the left flank, and left lower quadrant of the abdomen. The rest of the exam was negative.



On urinalysis, he had 20-30 RBC and 2-5 WBC per hi power; Serum Ca = 14.2 mg/dl (8.5-10.5); PO4 = 1.7 mg/dl (3.0-4.5); Alkaline phosphatase = 205 units/ml (nl 100). Chest film showed decreased bone mineralization, and CT demonstrated a left ureteral stone.

He was treated with narcotics and bed rest, and on the third hospital day he spontaneously passed a calcium oxalate stone. Subsequent evaluation showed a 24 hour urine calcium of 348 mg/24<sup>o</sup> (150-250) and a serum parathyroid hormone level of 123 pg/ml (10-65).

One month later he underwent neck exploration, and a 1 x 1 cm parathyroid adenoma was removed. Postoperatively, serum calcium fell to 7.6 mg/dl and he had symptoms of tetany. He was treated with calcium infusions, and by ten days post op his calcium was 8.4 mg/dl. Two weeks after discharge his calcium was 8.9 mg/dl and he felt better than he had during the past two to three years.

# **PRIMARY HYPERPARATHYROIDISM**

**The clinical syndrome that results from  
primary overproduction of parathyroid  
hormone**

# **PRIMARY HYPERPARATHYROIDISM**

- **Common disorder occurs more commonly in women and in older individuals**
- **Most commonly due to a single benign adenoma. Less often due to hyperplasia**

# **PRIMARY HYPERPARATHYROIDISM**

## **CLINICAL MANIFESTATIONS**

- **Most people are asymptomatic**
- **Renal - Kidney stones, hyposthenuria, renal failure**
- **Bone - Pain, pathologic fractures**
- **GI - Anorexia, nausea, vomiting, constipation**
- **Neurologic - Lethargy, weakness, depression**

# **PRIMARY HYPERPARATHYROIDISM LABORATORY ABNORMALITIES**

- **Increased calcium**
- **Decreased phosphate**
- **Increased alkaline phosphatase**
- **Increased serum parathyroid hormone**

# **PRIMARY HYPERPARATHYROIDISM DIAGNOSIS**

- **Increased serum calcium**
- **Elevated Pth level**
- **Normal or elevated urine calcium**



# **PRIMARY HYPERPARATHYROIDISM THERAPY**

- **Parathyroidectomy for severe or symptomatic cases**
- **Older asymptomatic patients may not need therapy**
- **Calcium receptor agonist therapy has been shown to be effective (cinacalcet)**

# **PARATHYROID HORMONE RELATED PEPTIDE (PTHrP)**

- **Some homology with PTH, binds to PTH receptors, and mimics all known actions of PTH**
- **Levels are commonly elevated in patients with squamous cell carcinoma of lung and head and neck**
- **Many other tumors may also overproduce PTHrP**

# **CYTOKINE MEDIATED HYPERCALCEMIA**

- **Occurs most commonly in patients with multiple myeloma and lymphoma**
- **Breast cancer may activate both local and systemic mechanisms**

# **HYPERCALCEMIA OF MALIGNANCY**

- **Because of the rapid onset, CNS and GI symptoms tend to predominate**
- **With mild to moderate hypercalcemia, symptoms are similar to those of hyperparathyroidism**
- **With severe hypercalcemia (>15 mg/dl) patients may develop obtundation, disorientation, coma**
- **Volume depletion is uniformly present and serves to worsen hypercalcemia**

# **THERAPY OF SEVERE HYPERCALCEMIA**

- **Hydration with saline**
- **Intravenous Pamidronate or Zoledronic acid**
- **Other therapies**
  - **Gallium nitrate**
  - **Calcitonin**
  - **Loop diuretics**

A 64 year old philanthropist has had increasing nausea, vomiting, anorexia and constipation for 8 months. During the last 4 weeks his physicians have noticed lethargy, disorientation and decreasing mental status. His attending physicians have found the serum calcium to be elevated, and asked for consultation by an endocrinologist.

On physical exam, his blood pressure was 140/100, pulse was 84. He was disoriented and unable to give a coherent history. No bowel sounds were heard on abdominal examination. Neurologic exam showed markedly decreased mental status, but he could move all extremities and was responsive to pain. He was able to follow simple commands.

Ca = 16.4 mg/dl (8.5-10.5), PO<sub>4</sub> = 4.8 mg/dl (3.0-4.5), Albumin = 4.1 gm/ dl (3.5-4.5).



A brief survey of his medicine chest disclosed large amounts of vitamin preparations. He was treated with intravenous saline and glucocorticoids with rapid fall of his calcium to 11.4 mg/dl. He woke up within 36 hours, and his mental status returned to its usual alert state.

# **HYPERVITAMINOSIS D**

- **Granulomatous diseases**
- **Lymphoma**
- **Inadvertent overdosage in hypoparathyroidism or renal failure**
- **Associated with megavitamin therapy**

# **HYPERVITAMINOSIS D PATHOGENESIS**

- **Macrophages and lymphocytes have 1-alpha hydroxylase activity**
- **When there is a marked increase in macrophages, increased 1, 25 dihydroxy D is secreted**

# **HYPERVITAMINOSIS D PATHOGENESIS**

- **Modest overdosage causes no abnormalities.**
- **Massive doses result in enough active vitamin D generation to cause increased calcium absorption.**
- **When 1,25 dihydroxy D is used in therapy, modest overdoses are more likely to cause abnormalities**

# **HYPERVITAMINOSIS D PATHOGENESIS**

- **With moderate hyperabsorption of calcium, Pth levels are suppressed and hypercalciuria occurs, maintaining normal serum calcium**
- **With severe hyperabsorption, renal excretory capacity is exceeded, and hypercalcemia ensues**

# **HYPERVITAMINOSIS D**

## **SYMPTOMS**

- **Symptoms are secondary to hypercalcemia and hypercalciuria**
  - **Renal disease and stones**
  - **GI symptoms**
  - **CNS dysfunction**
  - **No bone disease or symptoms**

# **HYPERVITAMINOSIS D TREATMENT**

- **Treat granulomatous disease or remove vitamin D excess**
- **Saline infusion to enhance calcium excretion**
- **Glucocorticoids to decrease GI calcium absorption**

A 21 year old woman was seen in neurology clinic for evaluation of a convulsive disorder. Despite taking phenytoin and phenobarbital she had continued to have convulsions several times a year for the past several years. In addition, she had intermittent muscle twitching.



On physical exam she had positive Chvostek and Trousseau signs. Her serum Ca = 7.2 mg/dl (8.5-10.5), PO<sub>4</sub> = 6.5 mg/dl (3.0-4.5), Albumin = 4.1 gm/dl (3.5-4.5), BUN - 10 mg/dl (6-20), creat - 1.0 mg/dl (<1.2). 72° fecal fat measurement was less than 5 gm. Serum parathyroid hormone level was 158 pg/ml (10-65).

She was treated with high dose vitamin D therapy and calcium tablets. Serum calcium was maintained in the 7.9-8.8 mg/dl range. Anticonvulsant medication was discontinued, and all symptoms abated.

# **HYPOPARATHYROIDISM AND PSEUDOHYPOPARATHYROIDISM**

- **Symptoms: increased neuromuscular irritability, twitching, tetany, convulsions**
- **Laboratory abnormalities**
  - **Low serum calcium**
  - **High phosphate**
  - **If hypoparathyroidism, serum Pth is low**
  - **If pseudohypoparathyroidism (end organ resistance) serum Pth is high**

A 47 year old man had resection of 15 feet of small intestine 10 years earlier for inflammatory bowel disease. He was admitted for evaluation of recurrent fractures; four in the past 18 months. Two of the fractures were not associated with any apparent trauma.

On physical exam he was 5'10", 124 lbs. He had generalized bone tenderness.

Ca = 8.6 mg/dl (8.5-10.5), PO<sub>4</sub> = 1.2mg/dl (3.0-4.5), Albumin = 3.7 gm/dl ( 3.5-4.5), Hgb = 9.7 gm/dl (13-15), Carotene = 37 mg/dl (100-200), cholesterol = 107 gm/dl (160-250), Alkaline phosphatase = 382 (under 100).

A 72 hour fecal fat was 28 gm (under 5). Serum parathyroid hormone was 385 pg/ml (10-65). Serum 25 hydroxycholecalciferol levels were unmeasurable. Bone biopsy showed increased osteoid seams.

He was treated with high dose vitamin D and calcium tablets with some improvement in bone pain. No further fractures were seen over the following year.



# **VITAMIN D DEFICIENCY ETIOLOGY**

- **Inadequate intake and sunlight**
- **Malabsorption**
- **Severe liver disease**
- **Renal failure**

# **VITAMIN D DEFICIENCY PATHOGENESIS**

- **Decreased absorption of calcium by the GI tract.**
- **As serum calcium starts to fall, secondary hyperparathyroidism occurs.**
- **Elevated Pth levels may maintain serum calcium in the normal range, but at the cost of phosphaturia, hypophosphatemia and increased bone reabsorption**

# **VITAMIN D DEFICIENCY PATHOGENESIS**

- **Low serum phosphate results in inadequate bone mineralization and osteopenia**
- **In severe cases, secondary hyperparathyroidism is not adequate to maintain serum calcium levels, and hypocalcemia occurs**

# **VITAMIN D DEFICIENCY CLINICAL MANIFESTATIONS**

- **Bone pain and pathologic fractures**
- **Decreased bone density**
- **Hypophosphatemia, increase in alkaline phosphatase and serum PTH levels**
- **Late hypocalcemia**

# VITAMIN D DEFICIENCY TREATMENT

- **Vitamin D replacement**
- **Patients with renal failure need 1,25 dihydroxycholecalciferol**
- **Patients with malabsorption may need high doses**

A 35 year old diabetic man presented with chronic renal failure. He had weakness, anorexia, vomiting, dyspnea and pleuritic chest pain. He also complained of several months of diffuse bone pain.

BUN = 238 mg/dl (6-20), Creat = 14.4 mg/dl (1.2), Hgb = 5.1 gm/dl (13-15), Glucose 274 mg/dl, Ca = 6.0 mg/dl (8.5-10.5), PO4 = 10.1 mg/dl (3.0-4.5), Albumin = 2.5 gm/dl (3.5-4.5) PTH 498 pg/ml (10-65)

Treatment was instituted with hemodialysis, phosphate binding agents and 1,25 dihydroxycholecalciferol.

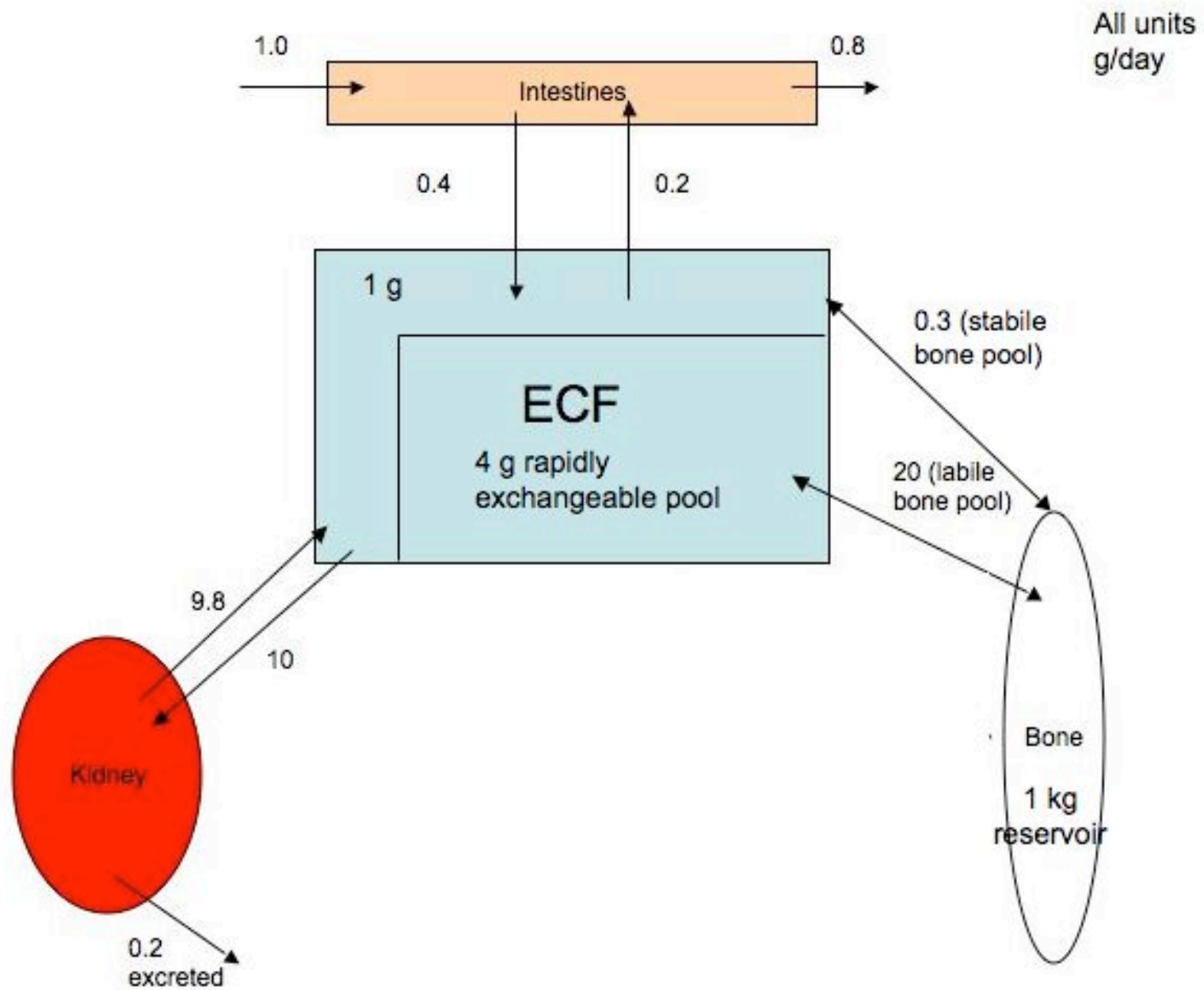


# **SECONDARY HYPERPARATHYROIDISM**

- **Increased parathyroid hormone secretion in response to decreased plasma calcium level**
- **Commonly occurs in renal failure and vitamin D deficiency**
- **Serum calcium may be low or normal, prolonged Pth secretion may result in bone resorption**

# **SECONDARY HYPERPARATHYROIDISM TREATMENT**

- **Treat underlying cause**
- **Phosphate binders for renal failure**
- **Calcitriol**
- **Paracalcitol**
- **Cinacalcet**
- **Parathyroidectomy**



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Slide 18: Society for Bone & Mineral Research

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