



The Calcitropic Hormones

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Extracellular & Bone mineral Homeostasis

- A highly integrated and complex endocrine system maintains calcium, phosphate, and magnesium homeostasis in all vertebrates.
- It involves parathyroid hormone (PTH) and calcitonin (CT), 1,25-dihydroxycholecalciferol, $1,25(\text{OH})_2\text{D}_3$.
- Other hormones, such as insulin, cortisol, growth hormone (GH), thyroxine, epinephrine, estrogen, testosterone, somatomedin, and inorganic phosphate, together with some compounds not yet identified and certain physical phenomena, undoubtedly have roles in modifying and regulating organ response to PTH, CT, and $1,25(\text{OH})_2\text{D}_3$.
- PTH, CT, and $1,25(\text{OH})_2\text{D}_3$, regulate the flow of minerals into and out of the extracellular fluid compartment through their actions on intestine, kidney, and bone.

Role of Parathyroid Hormone Target Tissues

- Under normal circumstances, PTH prevents serum calcium from falling below physiologic concentrations by stimulating calcium movement from intestinal and renal tubular lumina and from the bone fluid compartment into the blood.
- Its effects on bone and kidney are direct, PTH acts indirectly on the intestine, through the mediation of Vitamin D.
- Stimulates the conversion of 25OHD_3 to $1,25(\text{OH})_2\text{D}_3$ in the kidney via a 25OHD_3 , 1α -hydroxylase in the mitochondria of the renal tubule.
- The $1,25(\text{OH})_2\text{D}_3$ thus formed stimulates intestinal calcium absorption. PTH also prevents serum phosphate levels from rising above normal physiologic concentrations by increasing renal tubular excretion of phosphate.

Role of Calcitonin

- Calcitonin prevents abnormal increase in both serum calcium and serum phosphate.
- It decreases the translocation of calcium from the renal tubule and bone fluid compartment into the blood and thus can be considered as a counter regulator of PTH.

Actions of major calcium-regulating hormones

	Bone	Kidney	Intestine
Parathyroid hormone (PTH)	Increases resorption of calcium and phosphate	Increases reabsorption of calcium, decreases reabsorption of phosphate; increases conversion of 25OHD3 to 1,25(OH)2D3; decreases resorption of bicarbonate.	No direct effects
Calcitonin (CT)	Decreases resorption of calcium and phosphate	Decreases reabsorption of calcium and phosphate. Questionable effect on vitamin D metabolism.	No direct effects.
Vitamin D	Maintains Ca ²⁺ transport system.	Decreases reabsorption of calcium	Increases absorption of calcium and phosphate.

Plasma Calcium & Phosphate

A. Calcium:

- Calcium is distributed in 3 major fractions: ionized, protein-bound, and complexed.
- The ionized fraction (Ca^{2+}), is the only biologically active form, constitutes 46-50% of the total calcium.
- The protein-bound fraction, roughly equivalent to the ionized fraction in amount, is biologically inert.
- However, the calcium bound to albumin (80%) and globulin (20%) is an important source of readily available Ca^{2+} , calcium can dissociate from its binding sites as a first line of defense against hypocalcemia.

$$\begin{aligned} \% \text{ protein-bound } \text{Ca}^{2+} &= 8 \times \text{albumin (g/dL)} \\ &+ 2 \times \text{globulin (g/dL)} + 3 \end{aligned}$$

Plasma Calcium & Phosphate

A. Phosphate:

- Only 15% of the plasma phosphate is bound to proteins in the blood.
- The rest is ultrafilterable and consists mainly of free HPO_4^{2-} and NaHPO_4^- (85%), with free H_2PO_4^- making up the remainder (15%).
- Phosphorus has a wider range of normal plasma values (2.5 – 4.5 mg/dL).
- Increases or decreases in dietary phosphorus are promptly reflected in corresponding increases or decreases in serum phosphorus and urinary phosphorus excretion.

Parathyroid Hormone

Structure & Biosynthesis

- PTH is an 84-amino-acid, linear polypeptide with a molecular weight of 9500.
- Preproparathyroid hormone (preproPTH).
- The hydrophobic 23-amino-acid "pre" sequence acts to bind the polyribosome-precursor complex to the endoplasmic reticulum, providing access to the cisternal space and, presumably, to the enzyme ("clipase") that removes the "pre" sequence, leaving the 90-amino-acid-proPTH structure.
- The proPTH is converted to PTH in the Golgi apparatus by proteolytic removal ("tryptic clipase") of the remaining 6-amino-terminal acid sequence.

Parathyroid Hormone

Structure & Biosynthesis

- Here, the 84-amino-acid polypeptide is readied for secretion either in a secretory granule or in its free form.
- Intracellular stores of PTH may be regulated by a degradative pathway that is stimulated by high and inhibited by low extracellular calcium.

Parathyroid Hormone

Control of Secretion

- PTH is rapidly released from the parathyroid gland in response to decreases in the plasma ionic calcium.
- It acts on kidney and bone and indirectly on intestine to restore the concentration of this cation to just above the normal set point, which in turn inhibits secretion of the hormone.
- The concentration of extracellular ionic calcium is the major regulatory of PTH secretion.
- Other factors influence secretion only indirectly through increasing or decreasing extracellular ionic calcium.
- Prolonged hypomagnesemia markedly inhibits secretion of PTH and may be associated with hypocalcemia.

Parathyroid Hormone

Metabolism & Circulating Forms

- Circulating PTH is heterogeneous, consisting of the intact 84-amino-acid polypeptide and multiple fragments of the hormone.
- These fragments are biologically inert.

Parathyroid Hormone

Actions

- The major function of PTH is to correct hypocalcemia,
 1. conservation of calcium by the kidney,
 2. release of calcium from bone,
 3. enhanced absorption of calcium from the gut (indirectly via vitamin D), and
 4. reduction in plasma phosphate.

Parathyroid Hormone

A. Effects of PTH on Kidney:

1. To increase renal tubular reabsorption of calcium and magnesium, and
 2. To increase phosphate and bicarbonate excretion by inhibiting their proximal tubular resorption.
- Hormone: induced bicarbonaturia tends to produce acidosis, which decreases the ability of circulating albumin to bind calcium, thus increasing ionic calcium by physiochemical means.
 - Release of phosphate from bone, which occurs obligatory during hormone-induced calcium mobilization from bone, does not produce hyperphosphatemia.

Parathyroid Hormone

A. Effects of PTH on Kidney:

- PTH, either stimulates renal tubular 25OHD_3 , 1α -hydroxylase to convert the major circulating metabolite of cholecalciferol, 25OHD_3 , to its major biologically active metabolite, $1,25(\text{OH})_2\text{D}_3$.
- This latter compound acts directly on intestinal mucosal cells to increase calcium absorption and on bone to increase resorption.
- PTH increases urinary excretion of cAMP.

Parathyroid Hormone

B. Effects of PTH on Bone:

- PTH increases the net release of calcium and phosphate from bone into extracellular fluid.
- This is direct result of the hormone's effect on the differentiation of activities of bone cells (osteogenic precursors, osteoblasts, osteoclasts, and osteocytes).

Parathyroid Hormone

Mechanism of Action

- PTH binds to specific plasma membrane receptors of target cells.
- Activates membrane-bound adenylate cyclase to convert ATP to cAMP.
- Activates intracellular phosphorylations.

CALCITONIN

Structure & Biosynthesis

- Calcitonin (CT), a 32-amino-acid polypeptide with a molecular weight of 3700 and a disulfide bridge between residues 1 and 7 is biosynthesized and secreted (parafollicular, "C") cells.
- Human CT is cleaved from a high-molecular-weight precursor that also contains 2 other peptides, katacalcin and calcitonin gene-related peptide (CGRP).

CALCITONIN

Control of Secretion

- CT is rapidly released by the "C" cells in response to small increases in plasma ionic calcium.
- It acts on kidney and bone to restore the level of this cation to just below a normal set point, which in turn inhibits secretion of the hormone.
- CT thus is a physiologic antagonist of PTH.
- The hormones act in concert to maintain the normal concentration of ionic calcium in extracellular fluid.
- There is a positive correlation between plasma calcium and plasma immunoreactive CT (iCT) in normal subjects when plasma calcium is increased above the normal range.

CALCITONIN

Metabolism & Circulation Forms

- CT exists in several molecular forms both in ultimobranchial tissue and in plasma.
- Fragments consists of as many as 4 or 5 immunoreactive forms which molecular weights large than 32-amino-acid (CT.
- It is likely that some of these forms are polymers of CT with interchain disulfide molecular linkages.

- Actions

- Mechanisms of Action

VITAMIN D

- Vitamin D₃ (cholecalciferol) is primarily synthesized in the skin by ultraviolet irradiation of 7-dehydrocholesterol.
- Vitamin D₂ (ergocalciferol), which is used to fortify dairy products, is produced by ultraviolet irradiation of the plant sterol ergosterol.

VITAMIN D

A. Activation of Vitamin D.

1. 25-Hydroxylation
2. 1α -Hydroxylation

B. Concentrations of Vitamin D Metabolites:

- Normal individuals, $1,25(\text{OH})_2\text{D}_3$ is 30 pg/mL.
- 25OHD_3 circulates in concentrations 1000 times greater than $1,25(\text{OH})_2\text{D}_3$ suggests that 25OHD_3 may have intrinsic biologic importance as well.

C. Other Hydroxylation Pathways:

- 25OHD_3 to $24,25(\text{OH})_2\text{D}_3$ occurs mainly in the kidney .
- PTH stimulates production of $1,25(\text{OH})_2\text{D}_3$ but suppresses that of $24,25(\text{OH})_2\text{D}_3$.

VITAMIN D

Role of Vitamin D

- The principal physiological role of vitamin D is to increase plasma levels of calcium and phosphate and thus maintain conditions favorable for bone mineralization.
- Facilitate the absorption of calcium and phosphate by the intestine.
- Vitamin D acts as a classic steroid hormone.
- $1,25(\text{OH})_2\text{D}_3$ receptors have also been demonstrated in bone, parathyroid glands, pancreas, pituitary, placenta, and other tissues.

DISORDERS OF PARATHYROID FUNCTION

Hypoparathyroidism

- Deficient secretion of PTH is characterized clinically by symptoms of neuromuscular hyperactivity and biochemically by hypocalcemia, hyperphosphatemia, and diminished to absent circulating iPTH.

DISORDERS OF PARATHYROID FUNCTION

Etiology:

1. Surgical hypoparathyroidism:

- Most common type.
- After any surgical procedure including thyroidectomy, removal of abnormal parathyroid glands, and excision of malignant neck lesions.

2. Idiopathic hypoparathyroidism:

- is a broad category of disorders undoubtedly with more than one cause.
- 2 subcategories:
 - occurring at an early age
 - Occuring late in life.

DISORDERS OF PARATHYROID FUNCTION

Etiology:

2. Idiopathic hypoparathyroidism:

- Congenital absence of the glands (as in DiGeorge's syndrome).
- Early age are of genetic origin, with an autosomal recessive mode of transmission.
- This type of hypoparathyroidism is "multiple endocrine deficiency-autoimmune-candidiasis (MEDAC) syndrome" or "juvenile familial endocrinopathy" or "hypoparathyroidism-Addison's disease-mucocutaneous candidiasis (HAM) syndrome"
- Circulating autoantibodies specific for parathyroid and adrenal tissue are frequently present.
- The late-onset form of idiopathic hypoparathyroidism occurs sporadically without circulating glandular autoantibodies.

DISORDERS OF PARATHYROID FUNCTION

Etiology:

3. Functional hypoparathyroidism:

- Occurs in patients who have undergone long periods of hypomagnesemia.
- Selective defects in gastrointestinal magnesium absorption, generalized gastrointestinal malabsorption, or alcoholism.
- Since magnesium is required for PTH release from the glands.
- Hypocalcemia is also present.
- Treatment with magnesium salts is followed within minutes by an increase in serum iPTH.

DISORDERS OF PARATHYROID FUNCTION

Pathology:

Pathologic Physiology:

1. Decrease bone resorption;
2. Decreased renal phosphate excretion, increased serum phosphate, decreased, $1,25(\text{OH})_2\text{D}_3$, and decreased intestinal absorption of calcium; and
3. Increased renal excretion of calcium for the prevailing serum concentration of calcium. There is hypocalcemia and usually hyperphosphatemia, if dietary phosphate intake has been normal. Urinary calcium is usually low unless eucalcemia has been restored with treatment. Hypocalcemia and alkalosis (due to decreased bicarbonate excretion), if sufficiently severe, cause increased neuromuscular excitability with consequent tetany and, rarely convulsions.

DISORDERS OF PARATHYROID FUNCTION

Clinical Features:

A. Neuromuscular Manifestations:

- Complications are most likely to occur within 1-2 days after parathyroidectomy, when serum calcium decreased acutely.
1. Paresthesias – Numbness and tingling may occur around the mouth, in the tips of the fingers, and sometimes in the feet.
 2. Tetany – An attack of tetany usually begins with prodromal paresthesias and is followed by spasms of the muscles of the extremities and face. The hands, forearms, and, less commonly, the feet become contorted in a characteristic way. First, the thumb is strongly adducted, followed by flexion of the metacarpophalangeal joints.

DISORDERS OF PARATHYROID FUNCTION

Clinical Features:

3. Hyperventilation – patients may hyperventilate and secrete increased amounts of epinephrine. Hyperventilation causes hypocapnia and alkalosis, which in turn worsen hypocalcemia by causing increased binding of ionic calcium to plasma proteins.
4. Adrenergic symptoms – Increased epinephrine secretion produces further anxiety, tachycardia, sweating, and peripheral and circumoral pallor.
5. Convulsions – Patients with hypoparathyroidism may have convulsions.

DISORDERS OF PARATHYROID FUNCTION

Clinical Features:

6. Signs of latent tetany – Chvostek's sign is elicited by tapping the facial nerve just anterior to the ear lobe. The response ranges from twitching of the lip at the corner of the mouth to twitching of all of the facial muscles on the stimulated side.

Trousseau's sign – should be sought with a sphygmomanometer cuff. The cuff is inflated to above systolic blood pressure for at least 2 minutes while the hand is observed carefully. A positive response consists of the development of typical carpal spasm, with relaxation occurring 5-10 seconds after the cuff is deflated.

7. Extraparamidal signs – classic parkinsonism.

DISORDERS OF PARATHYROID FUNCTION

Clinical Features:

B. Other Clinical Manifestations:

1. Posterior lenticular cataract.
2. Cardiac manifestations.
3. Dental manifestations.
4. Malabsorption syndrome.

DISORDERS OF PARATHYROID FUNCTION

Diagnosis:

- A. Serum calcium.
- B. Serum phosphours.
- C. Serum iPTH.

DISORDERS OF PARATHYROID FUNCTION

Treatment:

A. Therapeutic Difficulties:

- Theoretically, the most appropriate therapy for hypoparathyroidism would be physiologic replacement of PTH.
- Parenterally high cost.

B. Emergency Measures for Tetany:

- Intravenous calcium.
- This aim is to prevent laryngeal stridor and convulsions.

C. Severe Hypocalcemia ("Hungry Bone" Syndrome):

- As much as 10g of elemental calcium administered intravenously by infusion over 24 hours may be required to increase serum calcium above 7.5 mg/dl.

D. Severe Hypoparathyroidism:

- Long-term vitamin d treatment.

DISORDERS OF PARATHYROID FUNCTION

Treatment:

1. Errocalciferol (vitamin D₂).
2. Calcium.

D. Moderate Hypoparathyroidism.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

- Rare familial disorder characterized by target tissue resistance to PTH, hypocalcemia, increased parathyroid gland function, and a variety of congenital defects in the growth and development of the skeleton, including short stature and short metacarpal and metatarsal bones.
- Patients with pseudopseudohypoparathyroidism have the developmental defects without the biochemical abnormalities of pseudohypoparathyroidism.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

- There are also patients with pseudohypoparathyroidism who have target tissue resistance to the hormone but no developmental abnormalities, and others with developmental abnormalities who experience spontaneous cure of biochemical abnormalities.
- There are even patients who have developmental abnormalities and clinical hypoparathyroidism in the face of typical osteitis fibrosa cystica.
- This syndrome is known as pseudohypohyperparathyroidism.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

Etiology:

- Cannot be ascribed to a single underlying biochemical defect.
- It is likely that defects in any one of a number of limiting steps, from receptor binding of the hormone to final expression of the cellular action of PTH, could be involved.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

Genetic Basis of Pseudohypoparathyroidism:

- Pseudohypoparathyroidism is inherited.
- The 2:1 female:male ratio of occurrence suggests an X-linked dominant mechanism.
- 4 cases of male-to-male transmission of the developmental defects have been recorded.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

Incidence:

- Rare.

Pathologic Physiology:

- The biochemical findings in patients with surgical or idiopathic hypoparathyroidism.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

Clinical Features:

- Most of the symptoms and signs of pseudohypoparathyroidism are the same as those of surgical hypoparathyroidism and idiopathic hypoparathyroidism and are due almost entirely to chronic hypocalcemia.
- Certain unique developmental features.
- Mentally retarded, short and stocky, and obese with rounded faces.
- Many have one or more short metacarpal or metatarsal bones.
- There may be delayed dentition, defective enamel, and absence of teeth.

PSEUDOHYPOPARATHYROIDISM & PSEUDOPSEUDOHYPO-PARATHYROIDISM

Diagnosis:

- The diagnosis of pseudohypoparathyroidism is likely when the developmental abnormalities described above are present.
- Serum calcium and phosphorus are normal in such a patient.

Treatment:

- Identical to that for hypoparathyroidism.

PRIMARY HYPERPARATHYROIDISM

- Primary hyperparathyroidism represents an overlapping group of syndromes that are caused by excessive, secretion of PTH by one or more hyperfunctioning parathyroid glands.
- Hypercalcemia fails to inhibit gland activity in the normal manner.
- Nephrolithiasis, osteitis fibrosa cystica, and soft tissue calcification is rare today.

PRIMARY HYPERPARATHYROIDISM

Etiology:

- Genetic factor may be involved.
- Autosomal dominant trait.
- Thyroid carcinoma.

PRIMARY HYPERPARATHYROIDISM

Incidence:

- Serum calcium.
- The incidence of primary hyperparathyroidism increases dramatically in both men and women after age 50; it is 2-4 times more common in women.
- The age-adjusted incidence was estimated to be 42 per 100,000.
- Patients over 40 years of age have revealed as many as 1/1000 to 1/200 patients with the disease.

PRIMARY HYPERPARATHYROIDISM

Pathology:

A. Parathyroid Glands:

- Hyperplastic, adenomatous, or malignant.
- /subgke-gkabd ubvikvenebt ("adenoma") occurs in about 80% of patients with hyperparathyroidism and multiple-gland involvement ("hyperplasia") in about 20%.
- Less than 2% of hyperfunctioning glands are malignant.
- Familial primary hyperparathyroidism and the hyperparathyroidism associated with multiple endocrine neoplasia almost always involve multiple glands.

PRIMARY HYPERPARATHYROIDISM

Pathology:

A. Parathyroid Glands:

- Abnormal parathyroid glands usually weigh 0.2 – 2g (27-75 mg is normal) and have a characteristic yellow-red color and "bulging" appearance in situ.
- The severity of the clinical manifestations – especially the degree of hypercalcemia – is generally proportionate.

PRIMARY HYPERPARATHYROIDISM

Pathology:

B. Bone:

- Analysis of bone biopsies.
- Shows the effects of excess PTH on bone.
- Increased bone resorption surfaces, increased numbers of osteoclasts, osteocytic osteolysis, and , in moderate to severe cases, marrow fibrosis.

PRIMARY HYPERPARATHYROIDISM

Pathology:

C. Kidney:

- About 20-30% of patients have nephrolithiasis, which is frequently complicated by pyelonephritis.
- Gross nephrocalcinosis or calcification of the renal papillae is unusual.

PRIMARY HYPERPARATHYROIDISM

Pathology:

D. Other Organs:

- Calcification of other organs such as stomach, lung, and heart and blood vessels has been observed in patients with hyperparathyroid crisis (serum calcium > 15 mg/dl).

PRIMARY HYPERPARATHYROIDISM

Pathology:

E. Muscle:

- Myopathy is relatively common in primary hyperparathyroidism, and muscle biopsy may show neuropathic atrophy of both type I and type II muscle fibers.
- These histologic changes parallel clinical, neurologic, and neuromuscular dysfunction.

PRIMARY HYPERPARATHYROIDISM

Pathologic Physiology:

A. Hypercalcemia:

- Because the excess PTH stimulates the transport of calcium into the blood from the intestinal and renal tubular lumina as well as from bone.
- Many patients have decreased renal tubular reabsorption of phosphate, hyperphosphaturia, and hypophosphatemia.

PRIMARY HYPERPARATHYROIDISM

Pathologic Physiology:

B. Calcium in Soft Tissues:

- Deposition of calcium in soft tissues occurs because the normal solubility product of $\text{Ca}^{2+} \times \text{PO}_4^{3-}$ in serum (approximately 40) is exceeded.
- This may cause joint pain due to calcific tendinitis and chondrocalcinosis.

PRIMARY HYPERPARATHYROIDISM

Pathologic Physiology:

C. Vitamin D Deficiency:

- Adaptive mechanism is the development of vitamin D deficiency which may render patients with even severe hyperparathyroidism eucalcemic or nearly so.

PRIMARY HYPERPARATHYROIDISM

Pathologic Physiology:

D. Increased Degradation of PTH.

- A final adaptive mechanism may be a hypercalcemia-induced increase in the degradation of biologically active forms of PTH peripherally (eg, in the liver and possibly the kidney) and in parathyroid tissue itself.

PRIMARY HYPERPARATHYROIDISM

Pathologic Physiology:

E. Hyperchloremic Acidosis:

- Patients with primary hyperparathyroidism generally have mild to moderate hyperchloremic acidosis.
- This is due chiefly to excess PTH, which decreases the urinary concentration of hydrogen ion and increases urinary bicarbonate excretion.

PRIMARY HYPERPARATHYROIDISM

Pathologic Physiology:

F. Increased Urinary cAMP:

- Urinary cAMP is increased in as many as 80% of patients with primary hyperparathyroidism.

G. Osteitis Fibrosa Cystica:

PRIMARY HYPERPARATHYROIDISM

Clinical Features:

A. Symptoms:

1. Hypercalcemia and associated hypercalciuria.
2. Osteitis fibrosa cystica:
 - Diffuse bone pain.
 - Pathologic fracture through a bone cyst.

PRIMARY HYPERPARATHYROIDISM

Clinical Features:

B. Signs:

- Most patients show no signs of the disorder.
- Neurologic abnormalities are nonspecific and include impaired mentation, mental depression, psychosis, hypoactive deep tendon reflexes, joint hyperextensibility, sensory loss for perception of pain and vibration, proximal muscle weakness, abnormal tongue movements, lingual atrophy, ataxic gait, and abnormally strong (hard) fingernails.

PRIMARY HYPERPARATHYROIDISM

Clinical Features:

B. Signs:

1. Soft tissue calcification.
2. Enlarged glands.
3. Bone tenderness and deformities.

C. X-Ray Findings:

PRIMARY HYPERPARATHYROIDISM

Table: Differential Diagnosis of Hypercalcemia

Due to increased serum PTH:

- Primary and "tertiary" hyperparathyroidism
- Some nonhematologic malignant diseases

Not due to increased serum PTH:

- Drug-induced hypercalcemia (thiazides, furosemide, vitamin D, calcium, vitamin A, lithium).
- Granulomatous diseases (sarcoidosis, tuberculosis, berylliosis).
- Genetic diseases (familial hypocalciuric hypercalcemia)
- Immobilization
- "Idiopathic" hypercalcemia.
- Some nonhematologic malignant diseases
- Malignant hematologic diseases
- Nonparathyroid endocrine diseases (Addison's disease, hyper- and hypothyroidism).

PRIMARY HYPERPARATHYROIDISM

Diagnosis:

A. Review of History of Present Illness:

1. Nephrolithiasis and body weight.
2. Thiazide drugs.
3. Lithium.
4. Vitamin D intake.
5. Calcium intake.
6. Family History.

PRIMARY HYPERPARATHYROIDISM

Diagnosis:

B. Radioimmunoassay of Parathyroid Hormones:

- iPTH in primary hyperparathyroidism.
- iPTH in hypercalcemia of cancer.

C. Serum and Urine Biochemistry.

D. Nephrogenous cAMP.

SECONDARY HYPERPARATHYROIDISM OF CHRONIC RENAL FAILURE

- An increase in PTH secretion that is adaptive and unrelated to intrinsic disease of the parathyroid glands is called secondary hyperparathyroidism.
- The disorder is associated with prolonged stimulation of the parathyroid glands by chronic decreases in the concentration of ionic calcium in the blood.

DISORDERS OF CALCITONIN (CT) SECRETION

- No clinical disorder has been reported in which hypocalcitoninemia plays a definitive role.
- However, there are a number of conditions in which hypercalcitoninemia is found – most notably medullary carcinoma of the thyroid gland.

MEDULLARY CARCINOMA OF THE THYROID GLAND

- Medullary carcinoma is a malignant tumor of the parafollicular cells of the thyroid gland.
- It occurs so radically but may also be inherited as an autosomal dominant trait as part of the type II multiple endocrine neoplasia (MEN) syndrome.
- There are 2 variants of the syndrome: type IIa and type IIb. Patients with MEN type IIa have a normal appearance but a high incidence of hyperparathyroidism, most frequently due to enlargement of multiple parathyroid glands.
- Patients with MEN type IIb have a striking appearance due to labial and mucosal ganglioneuromas, a marfanoid habitus, and other somatic abnormalities.
- Hyperparathyroidism is unusual in this variant.

MEDULLARY CARCINOMA OF THE THYROID GLAND

Incidence:

- Medullary carcinoma constitutes 1-3% of all thyroid cancers.
- The sex incidence is almost equal (male:female ratio of 1.3:1 in sporadic cases and 1:1 in familial cases).
- In general, familial cases present at a younger age than do sporadic ones.

MEDULLARY CARCINOMA OF THE THYROID GLAND

Pathology:

- Medullary carcinoma appears as a solid, often hard mass confined to but not encapsulated in the thyroid gland.

MEDULLARY CARCINOMA OF THE THYROID GLAND

Pathophysiology:

- Medullary carcinomas secrete large quantities of CT and respond to provocative stimuli such as intravenous pentagastrin or hypercalcemia induced by intravenous calcium.
- Medullary carcinomas may secrete many other bioactive substances in addition to CT, each with the potential of causing symptoms.
- These include biogenic amines, ACTH and corticotropin-releasing hormone, prostaglandins, nerve growth factor, and possibly a prolactin-releasing hormone.

MEDULLARY CARCINOMA OF THE THYROID GLAND

Clinical Features:

- Asymptomatic thyroid mass.
- Patients with MEN type IIb may complain of neuromas and their marfanoid appearance.
- Hypertension may reflect the presence of pheochromocytoma, which may be more immediately life-threatening than medullary carcinoma.
- Paraneoplastic syndromes (eg. Cushing's syndrome) as well as intractable diarrhea and flushing should alert the physician to the possible existence of medullary carcinoma.
- Medullary cancers occasionally calcify.

MEDULLARY CARCINOMA OF THE THYROID GLAND

Diagnosis:

- Plasma, increased serum level of iCT in patients with a thyroid mass, a family history of medullary carcinoma, or pheochromocytoma virtually established the diagnosis.

MEDULLARY CARCINOMA OF THE THYROID GLAND

Treatment:

- In patients with medullary carcinoma, pheochromocytoma must be excluded or treated first.
- Medullary carcinoma is then treated by total thyroidectomy.
- Total thyroidectomy is especially important in patients with MEN type IIa or IIb, because medullary carcinoma is almost always bilateral and polycentric.

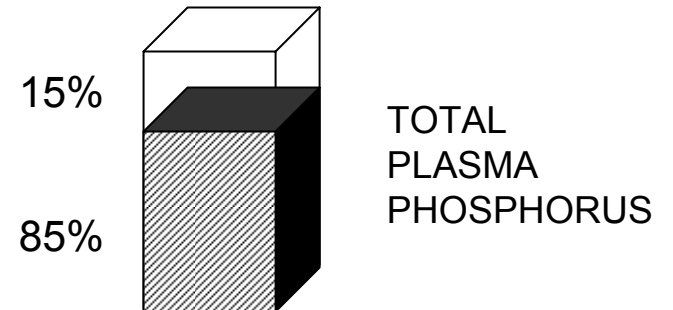
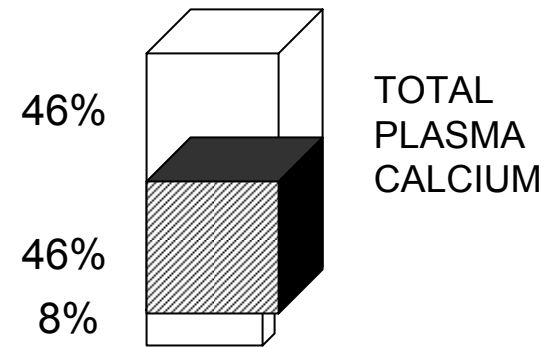
MEDULLARY CARCINOMA OF THE THYROID GLAND

Prognosis:

- Patients with sporadic medullary carcinoma have the least favorable prognosis because metastases are usually present at the time of diagnosis; only 46% of these patients survive for 10 years.
- Patients with MEN type IIa appear to fare better.

Normal Ranges

	MG/DL	MMOL/L
TOTAL PROTEIN	8.9-10.1	2.2-2.5
<u>IODIZED</u>	4.1-4.7	1.0-1.2
COMPLEXED	0.7-0.8	0.18-0.2
TOTAL PROTEIN BOUND	2.5-4.5	0.8-1.4
<u>FREE</u>	0.4-0.7	0.12-0.2
	2.1-3.8	0.68-1.2



85% = $\text{HPO}_4^{2-} + \text{NaHPO}_4^-$

15% = H_2PO_4^-

DISTRIBUTION AND NORMAL RANGES OF CALCIUM AND PHOSPHORUS IN THE PLASMA

Calcium Pools At Balance

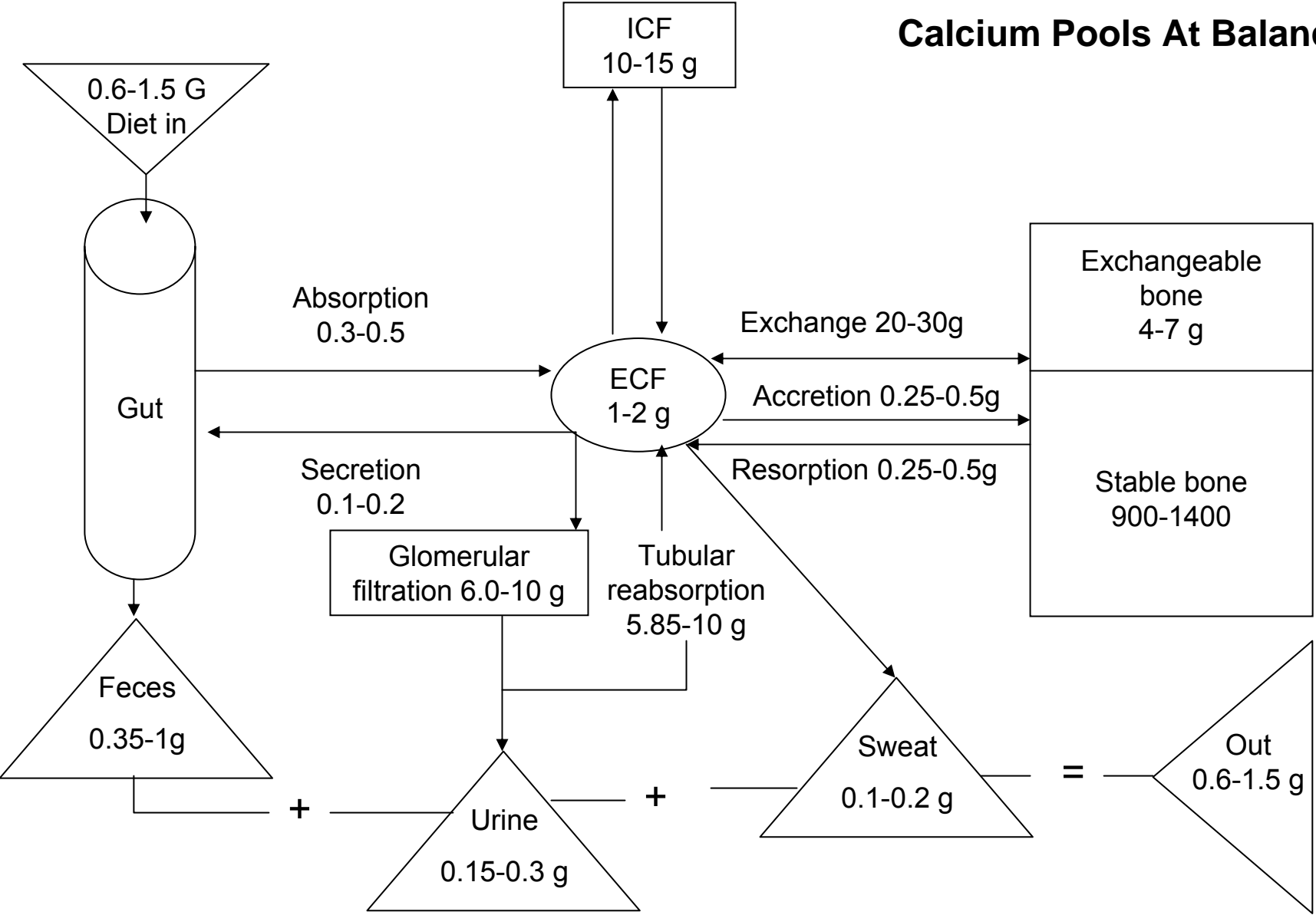


Figure: Normal distribution of calcium in the body.
ICF = intracellular fluid, ECF= extracellular fluid

Phosphorus Pools At Balance

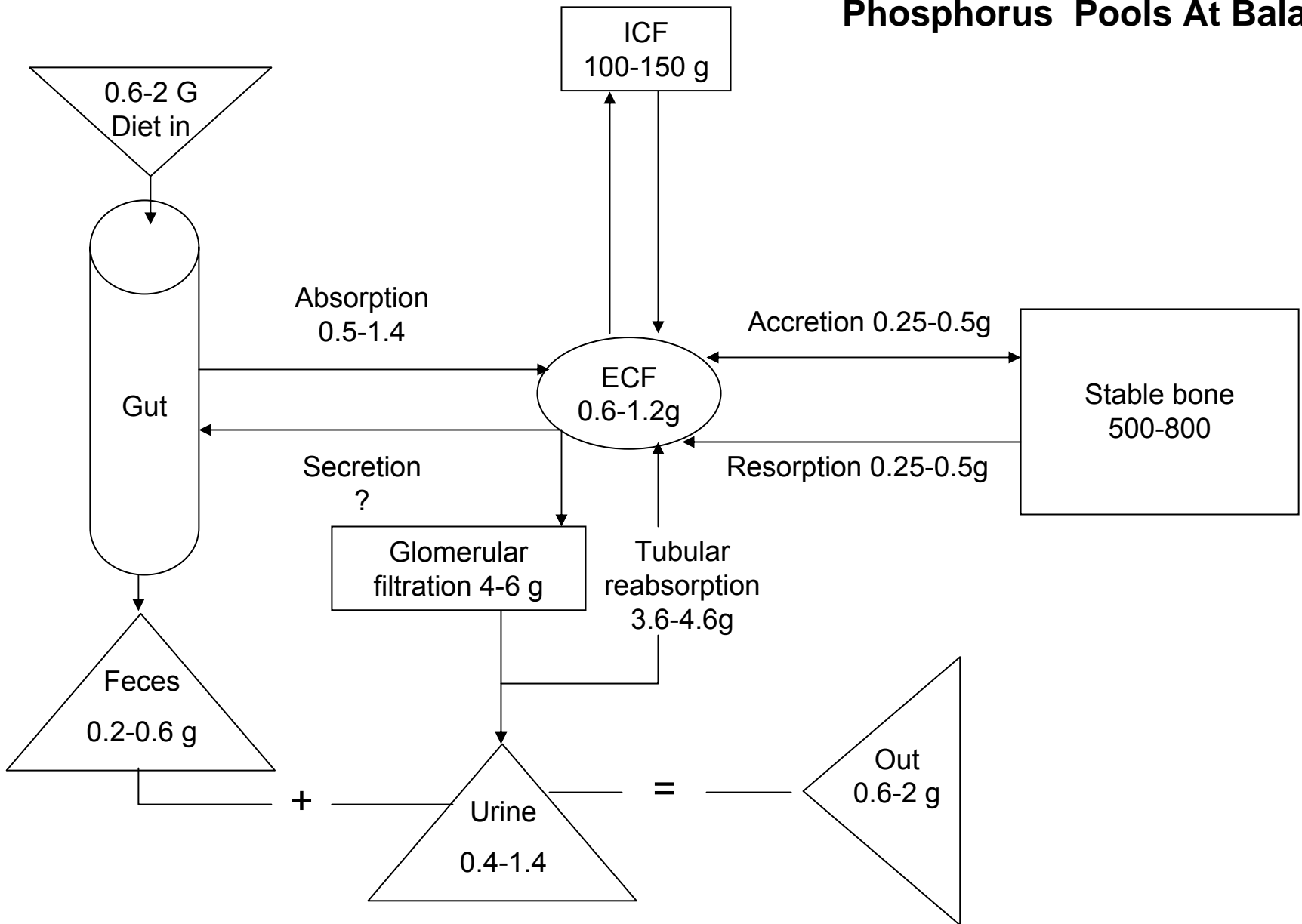


Figure: Normal distribution of phosphorus in the body.
ICF = intracellular fluid, ECF= extracellular fluid

A.S.Warsy

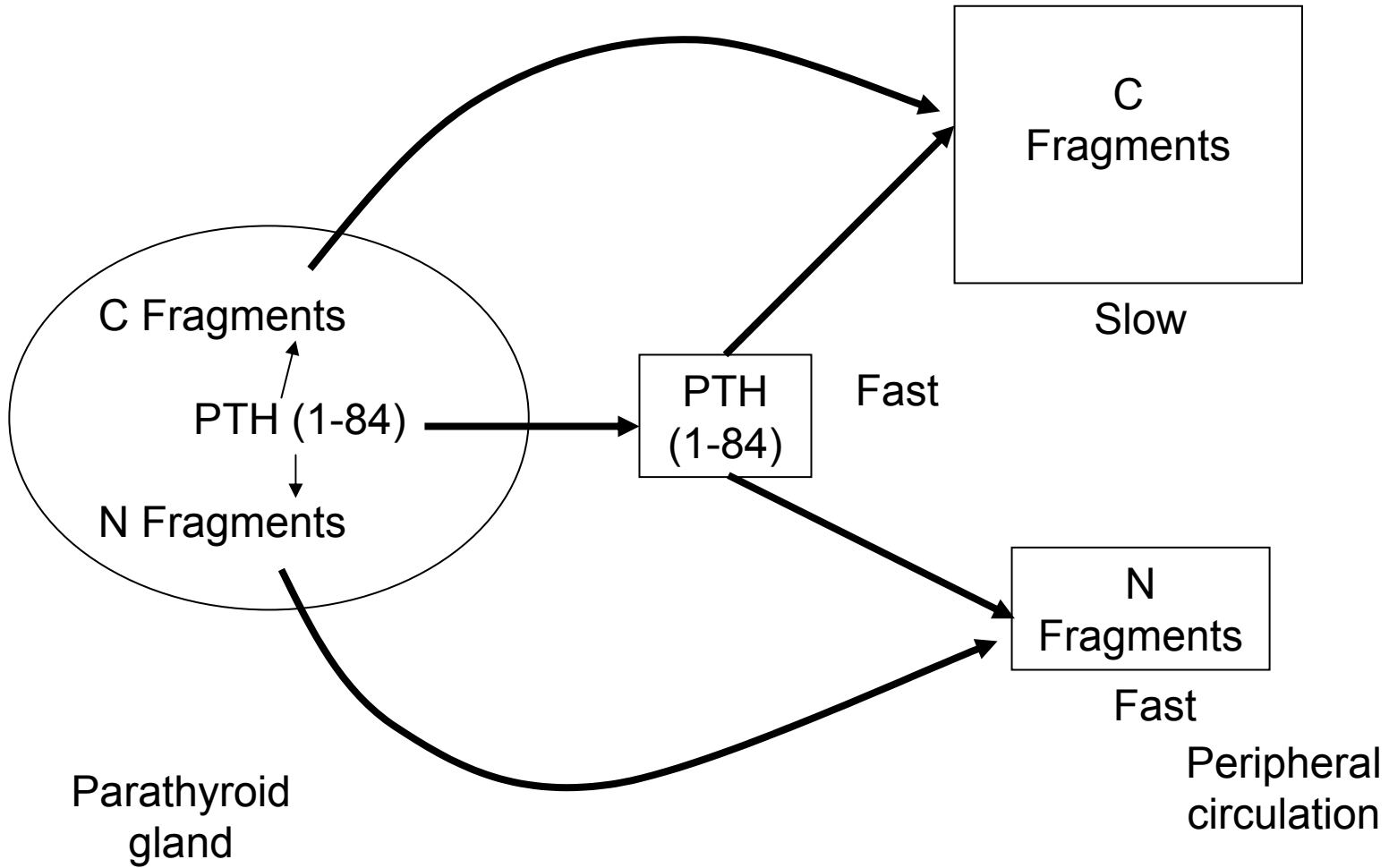


Figure: Metabolic alterations in PTH (1-84) that result in its immunoheterogeneity.