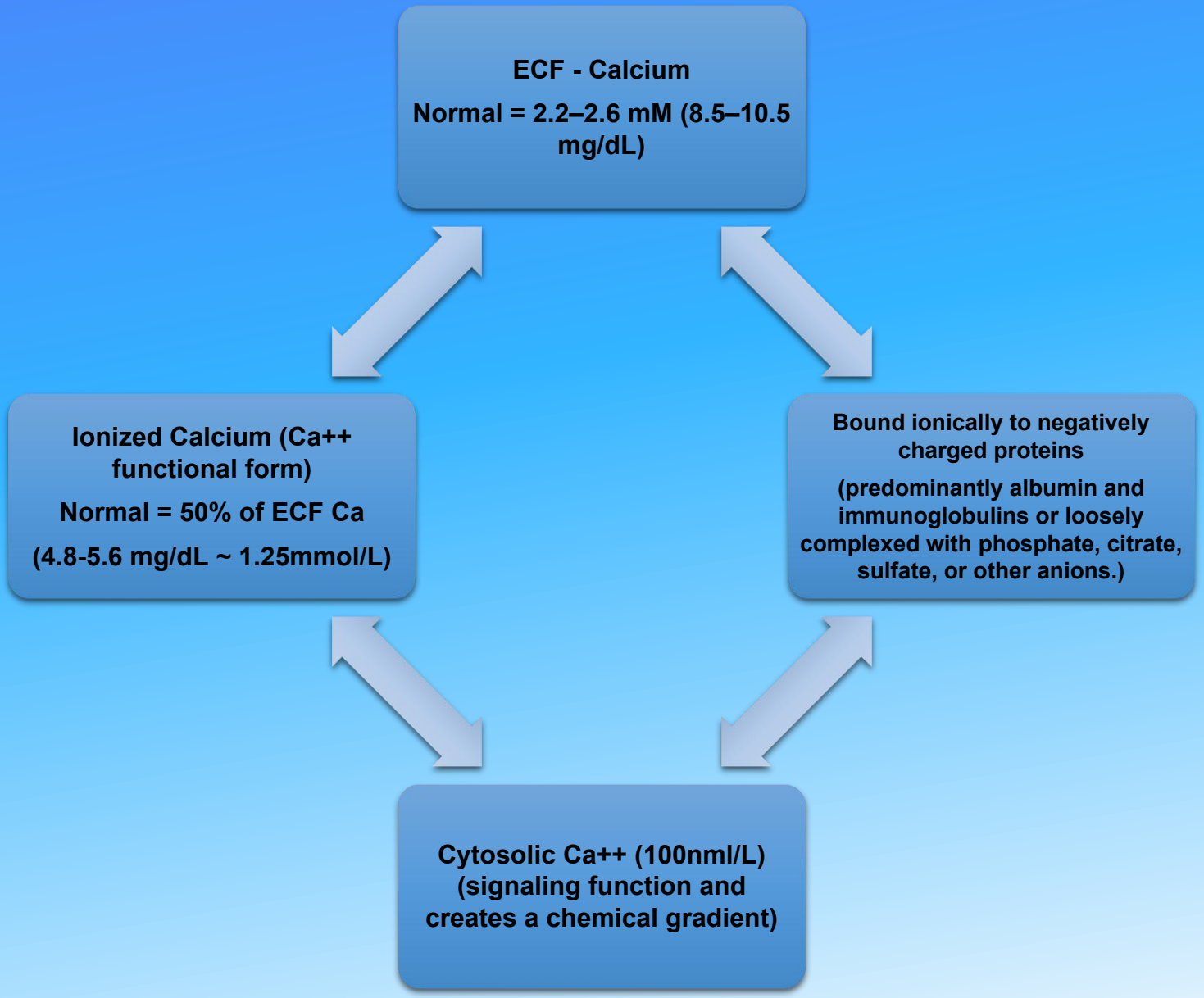
Parathyroid Adenoma and hypercalcemia

Objectives

- Calcium Homeostasis.
- PTH action on calcium homeostasis.
- Differential diagnosis of a case of hypercalcemia (algorithm).
- Parathyroid adenoma pathology (shape, location, consistency and functionality).
- PTHrp significance to rule out malignancy.
- Clinical manifestations of parathyroid adenomas (Signs and symptoms).
- Diagnosing parathyroid adenomas (PTH immunometric assays).
- Complications of parathyroid adenomas.
- Medical management of parathyroid adenomas.
- Surgical management of parathyroid adenomas.

Calcium Forms



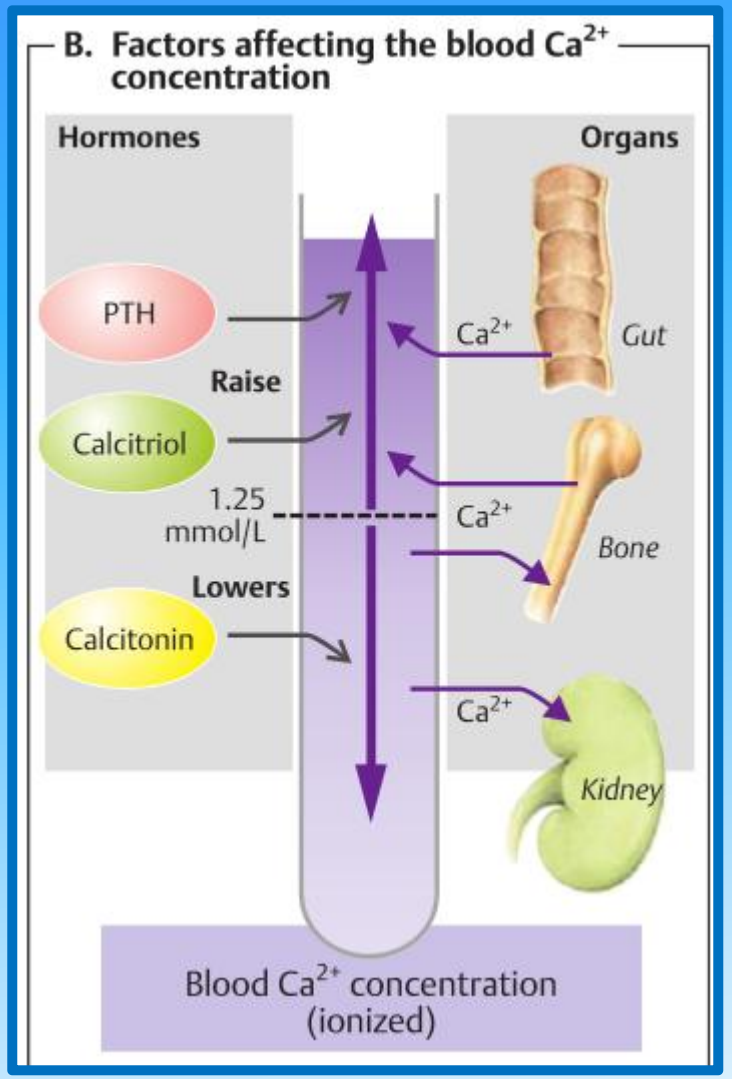
Calcium Homeostasis

=> Calcium homeostasis is a complex process involving the following 4 key components: **serum calcium**, **serum phosphate**, **1,25-dihydroxyvitamin D-3**, and **parathyroid hormone (PTH)**.

-> More than **99%** of the total body calcium is stored in bone in the form of **phosphate** and **hydroxide salts**, predominantly as **hydroxyapatite**.

-> Normally, a very small portion of this calcium is available for exchange in the serum (**total calcium = 8 - 10 mg/dL**, ionized (functional) = 4.8-5.6 mg/dL ~ 1.25mmol/L).

-> Hormonal interactions are mediated by serum calcium (ionized) levels in blood as shown in this diagram.



PTH action on calcium homeostasis

The primary function of PTH Is to normalize Ca++ concentration in the blood :

This is accomplished as follows:
(1) PTH activates osteoclasts, resulting In bone breakdown and the release of ca++ (and phosphate) from the bone.

(2) PTH accelerates the final step
of calcitriol synthesis in the kidney, resulting in increased reabsorption of Ca++ from the gut.

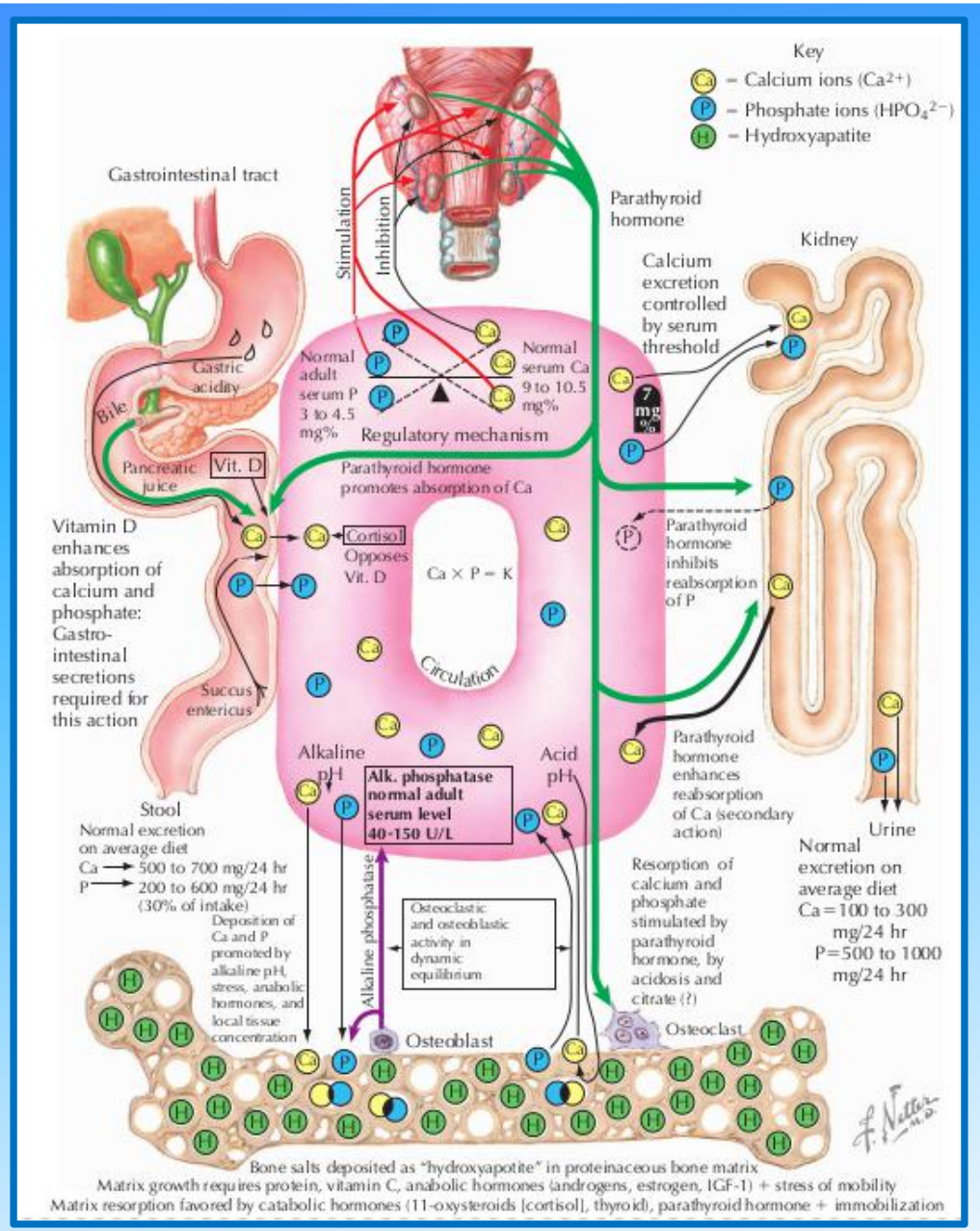
(3) In the kidney, PTH increases Ca++ reabsorption, which is particularly important due to the increased Ca++ supply resulting from actions (1) and (2).

Other secondary actions of PTH :

(1) PTH regulates Mg++ metabolism, mainly via
renal Mg++ excretion.

(2) PTH also **inhibits renal phosphate** reabsorption resulting in **hypophosphatemia**.

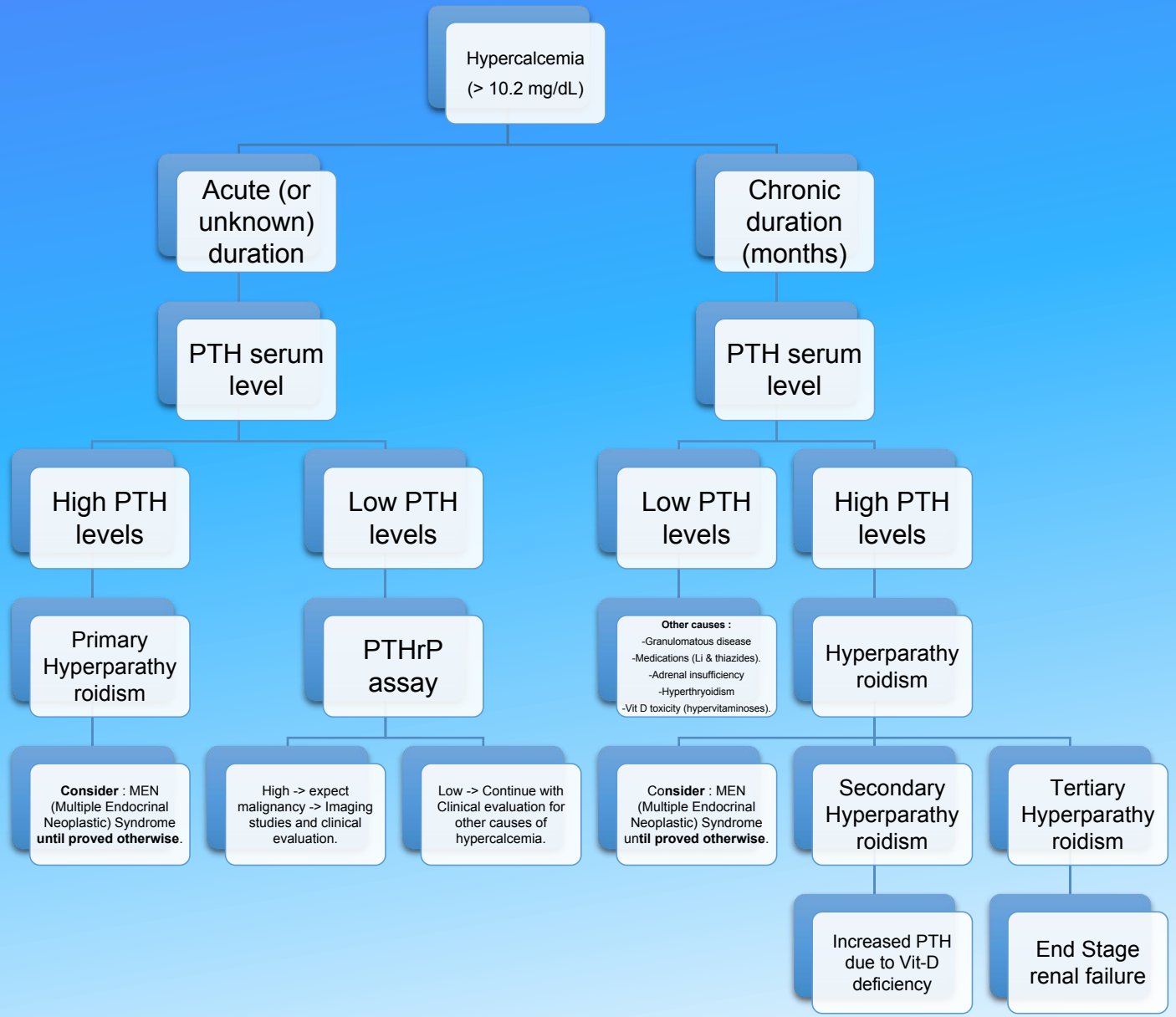
This, in turn, stimulates the release of Ca++ from the bone or prevents the precipitation of calcium phosphate in bone tissue to compensate the **hypophosphatemia**.



D.D algorithm of hypercalcemia

MEN (mulitple endocrinal neoplastic syndrome - autosomal dominant syndromes) :

- MEN-1 = Hyperparathyroidism + tumors of pituitary & pancreas + gastric hyperactivity & PUD.
- MEN-2A = Hyperparathyroidism + Pheochromocytoma + thyroid medullary carcinoma.
- MEN-2B = Lacks Hyperparathyroidism + multiple neuromas symptoms.
- Can be ruled out easily with family history.



Parathyroid Normal histology

It consists of 2 main cells :

- **Chief cells** : predominant, polygonal, has central round nuclei, cytoplasm is clear and light to dark pink in color. They are the main secretory cells of parathyroid hormone (Cells involved in adenomas and also known as principal cells.

- **Oxyphil cells** : slightly larger than chief cells, acidophilic cytoplasm with basal nuclei, also have secretory granules but they produce less PTH than chief cells.

- **Adipose tissue** : accumulates after puberty and makes up from 25-40% of total pt tissue in normal adults

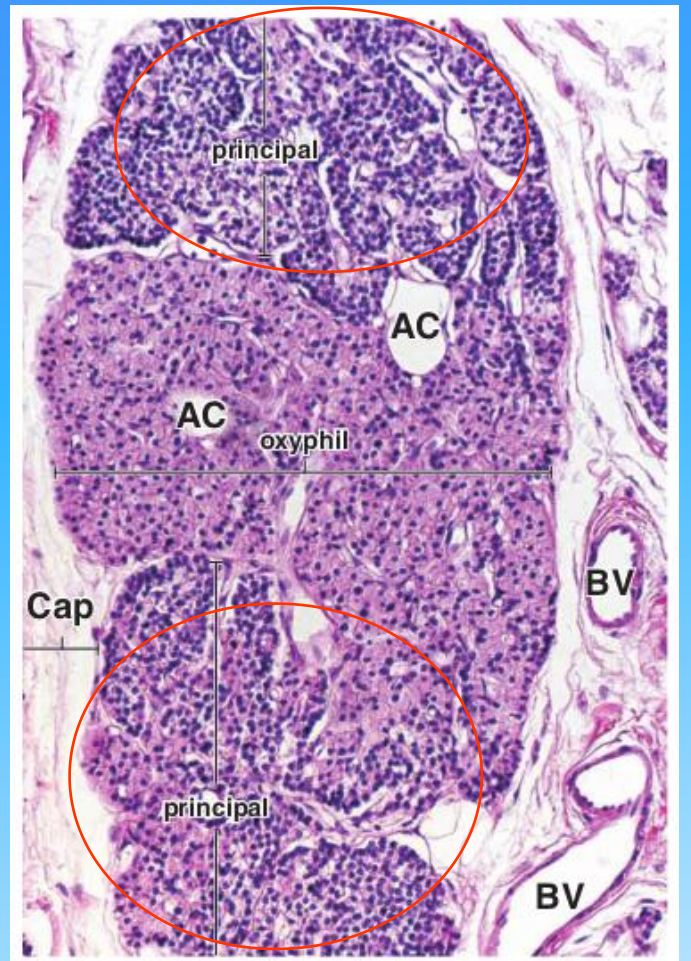


FIGURE 21.19 ▲ Photomicrograph of human parathyroid gland. This H&E–stained specimen shows the gland with part of its connective tissue capsule (*Cap*). The blood vessels (*BV*) are located in the connective tissue septum between lobes of the gland. The principal cells are arranged in two masses (*top* and *bottom*) and are separated by a large cluster of oxyphil cells (*center*). The oxyphil cells are the larger cell type with prominent eosinophilic cytoplasm. They may occur in small groups or in larger masses, as seen here. The principal cells are more numerous. They are smaller, having less cytoplasm, and consequently exhibit closer proximity of their nuclei. Adipose cells (*AC*) are present in variable, although limited, numbers. ×175.

Parathyroid pathology

Parathyroid Adenoma :

Histologically, there is usually a single mass, which is most often composed of chief cells.

Mostly shows monoclonal proliferation of one type of cells over the other.

adenomas are well demarcated, enclosed within a capsule that separates it from normal parathyroid gland.

The nodule usually lacks stromal adipose tissue.

The parenchymal cells are enlarged, with a slightly increased nucleus-to-cytoplasm ratio.

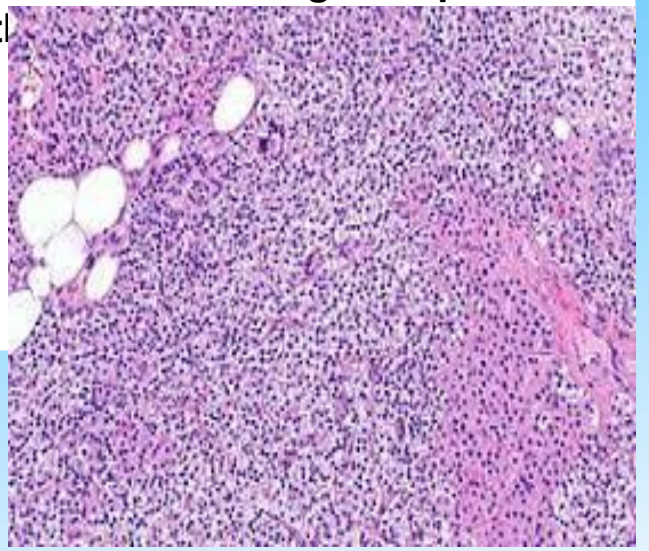
H&E stain is used.

Hyperplastic Parathyroid (multiglandular process) :

Affects more than one gland, usually the four glands.

The hyperplasiac tissue is mixed with chief cells & oxyphil cells with usual distribution ratio.

Follicle formation with colloid material might be present and can be mistaken for t



Parathyroid adenoma pathology

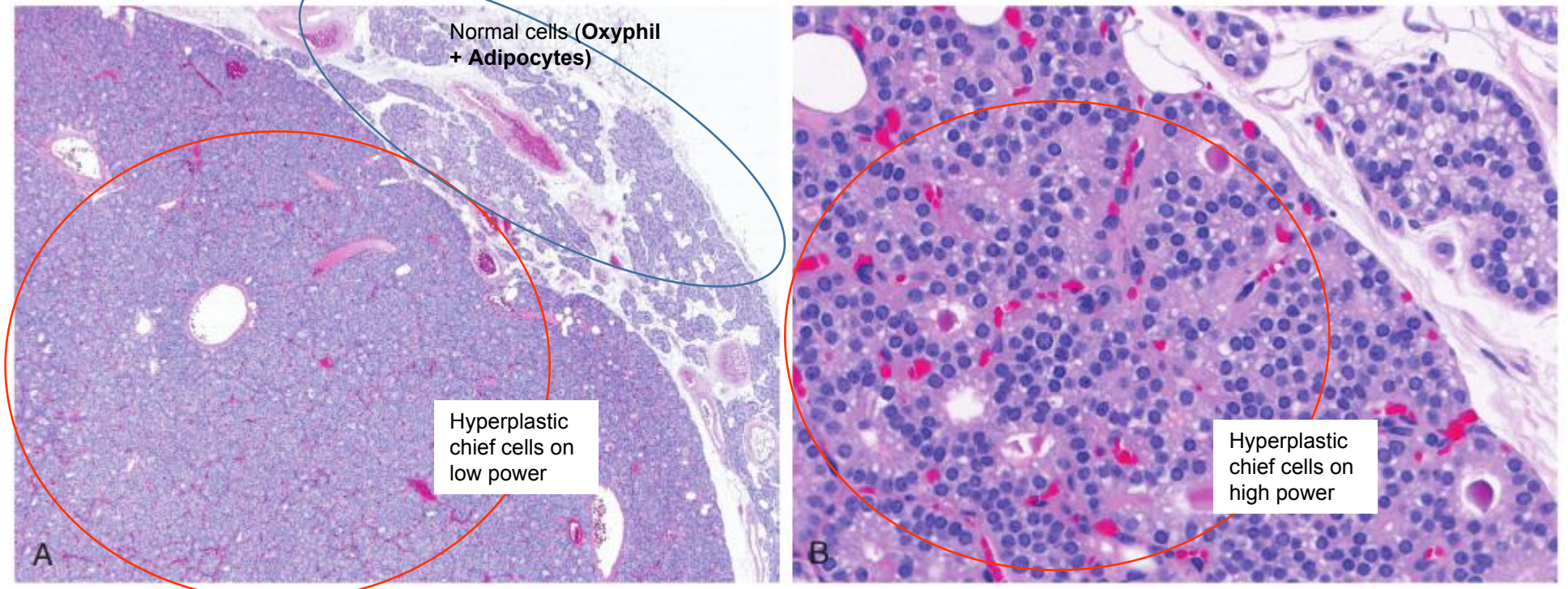


Fig. 20.20 Chief cell parathyroid adenoma. (A) In this low-power view, a solitary hypercellular adenoma is delineated from the residual normocellular gland on the upper right. (B) High-power detail shows minimal variation in nuclear size and occasional follicle formation. *(Courtesy of Dr. Nicole Cipriani, Department of Pathology, University of Chicago, Chicago, Illinois.)*

PTHrp significance

PTHrP significance :

PTHrP is responsible for most instances of humoral hypercalcemia of malignancy, a syndrome that resembles primary hyperparathyroidism but **without elevated PTH** levels (**@see Slide 5**).

PTHrP origin and function :

Most cell types normally produce PTHrP, including brain, pancreas, heart, lung, mammary tissue, placenta, endothelial cells, and smooth muscle.

Functions : PTHrP directs transplacental calcium transfer, plays an essential role in endochondral bone formation and in branching morphogenesis of the breast, and possibly in uterine contraction and other biologic functions, it's also secreted in milk (with unknown significance).

PTHrP Structure :

PTH and PTHrP, although products of different genes, exhibit considerable functional and structural homology, and have **evolved from a shared ancestral gene (same parent gene).**

PTHrP Action :

As a paracrine factor, PTHrP may be produced, act, and be destroyed locally within tissues.

In adults, PTHrP appears to have little influence on calcium homeostasis, except in disease states, when large tumors, especially of the squamous cell type as well as renal cell carcinomas, lead to massive overproduction of the hormone and hypercalcemia.

Both PTH and PTHrP bind to and activate the PTH/PTHrP receptor.

The PTH/PTHrP receptor (also known as the PTH-1 receptor, PTH1R) belongs to a subfamily of GPCRs,

The NET result of activating PTH/PTHrP receptors -> Activation of G-protein coupled receptors and PKA/C on three organs (Kidney, Bone, Intestine) (@see Slide 4) :

1) Inhibition of phosphate and bicarbonate transport (intestine).

2) Stimulation of calcium transport, and activation of renal 1α-hydroxylase in the kidney (intestine and kidney).

3) Effects on collagen synthesis, alkaline phosphatase, ornithine decarboxylase, citrate decarboxylase, and glucose-6-phosphate dehydrogenase activities; phospholipid synthesis; and calcium and phosphate transport (Bone resorption and inhibition of bone salts deposition).

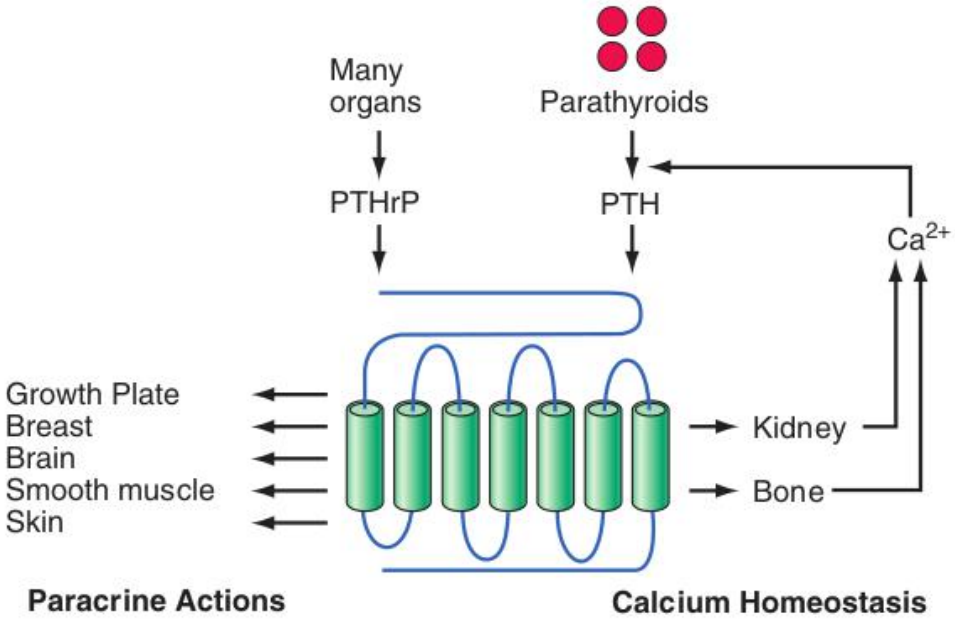


FIGURE 424-2 Dual role for the actions of the PTH/PTHrP receptor (PTH1R). Parathyroid hormone (PTH; endocrine-calcium homeostasis) and PTH-related peptide (PTHrP; paracrine–multiple tissue actions including growth plate cartilage in developing bone) use the single receptor for their disparate functions mediated by the amino-terminal 34 residues of either peptide. Other regions of both ligands interact with other receptors (not shown).

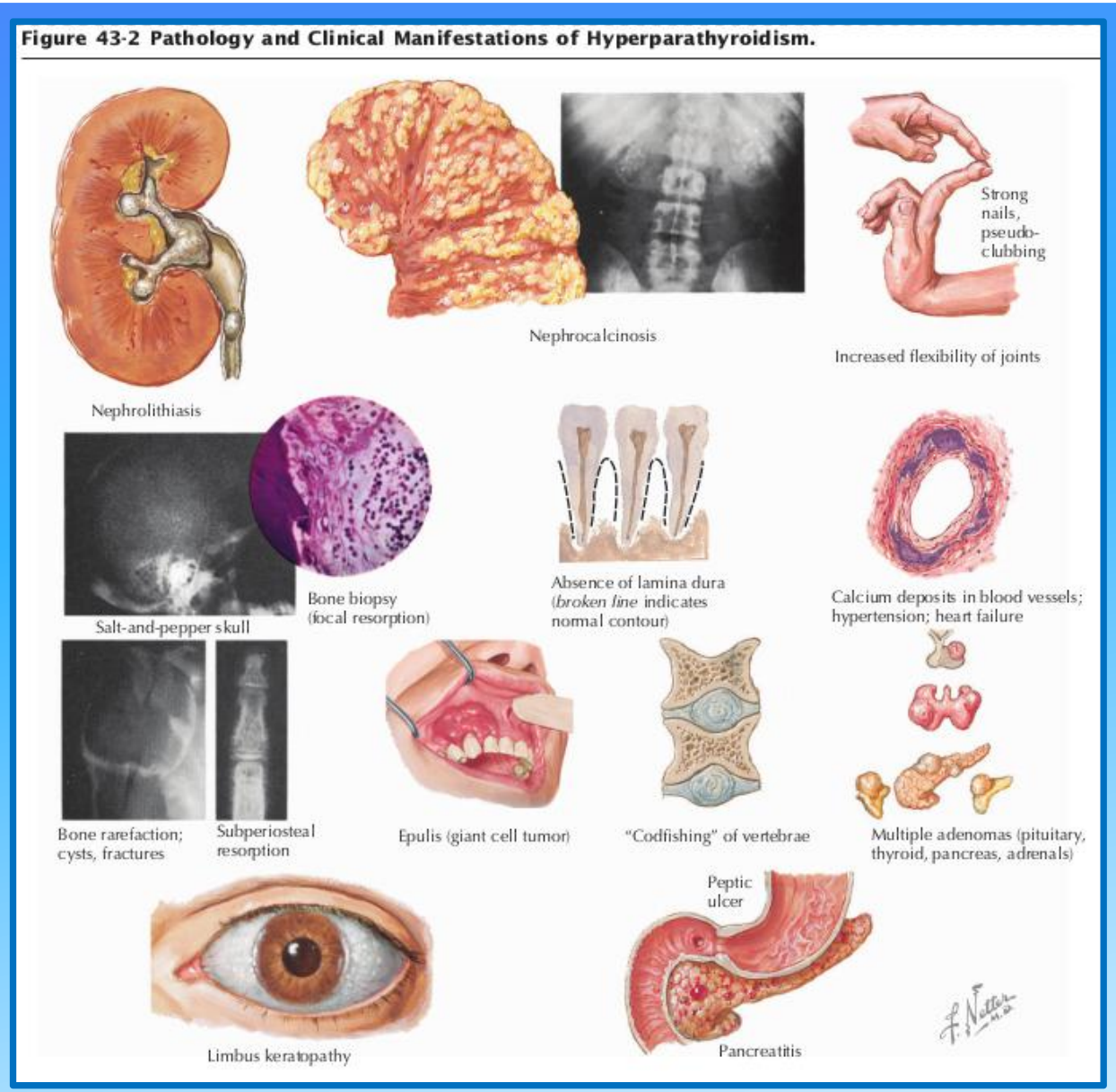
Clinical manifestations of parathyroid adenomas

Many people have no symptoms.

The condition is often discovered when blood tests are done for another medical reason.

Renal Symptoms	Skeletal Symptoms	Neurological Symptoms	Gastro-intestinal Symptoms
• Polyuria and polydipsia • Urinary stones • Renal insufficiency • Hypercalciuria	• Bone aches • Pathological fracture • Subperiosteal skeletal resorption	• Depression • Confusion • Fatigue • psychosis	• Vomiting • Constipation • Peptic ulcer

Clinical manifestations of parathyroid adenomas



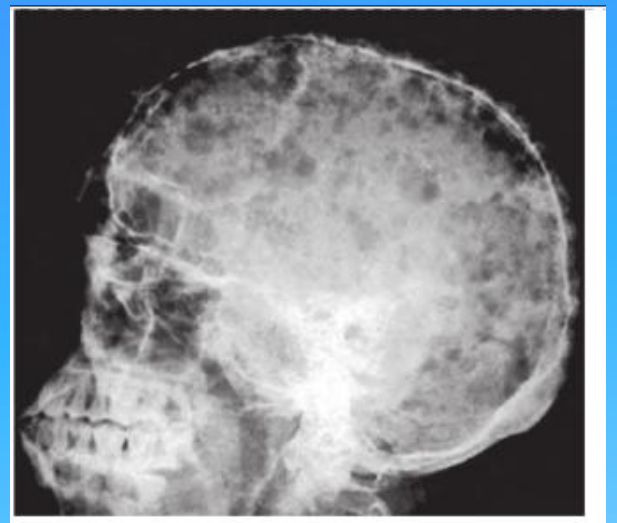
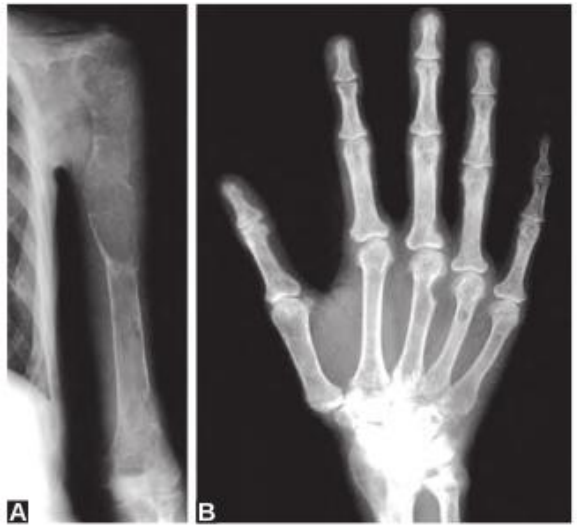
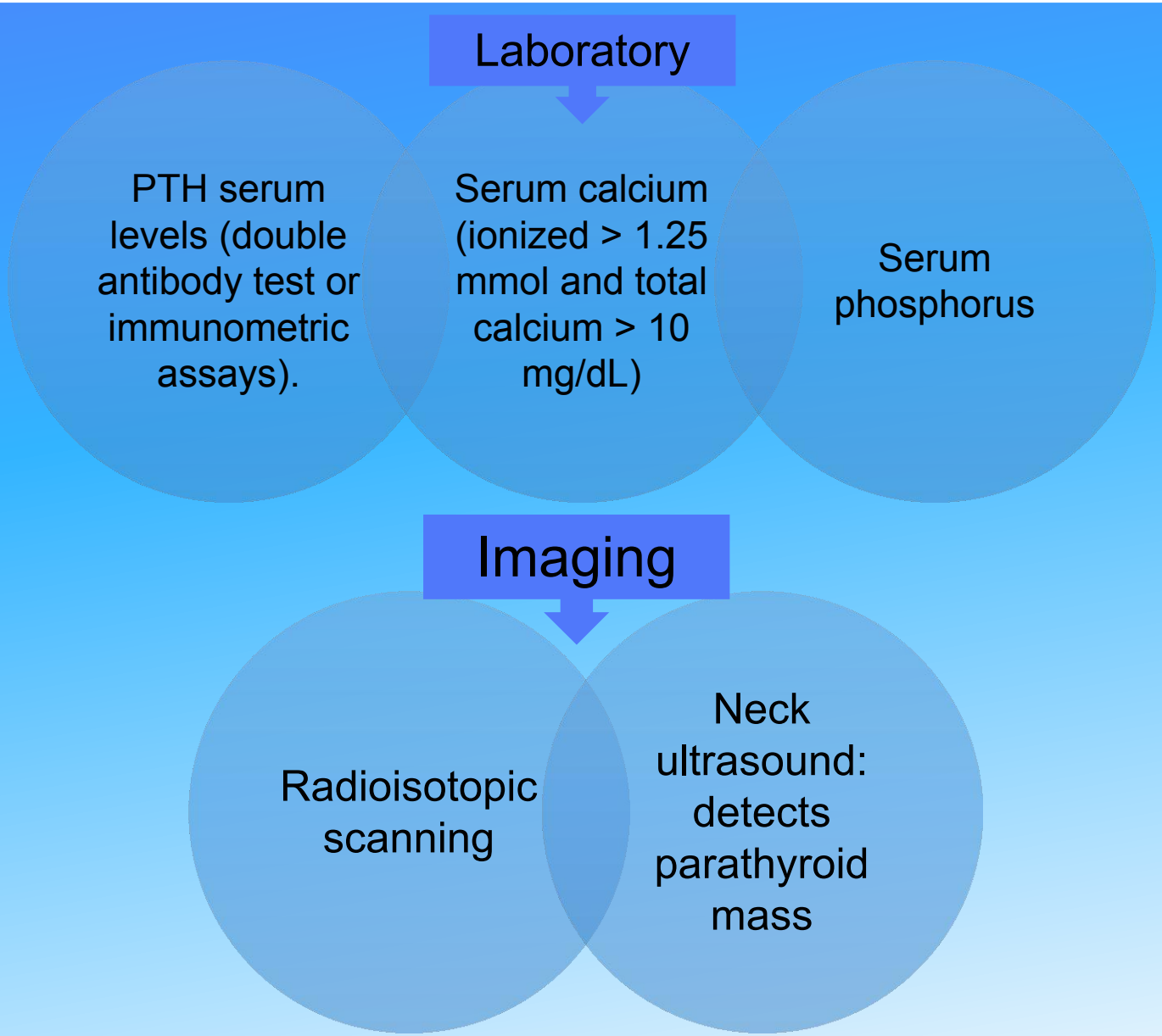


Fig. 7.2: Plain X-ray skull. Note the characteristic salt-pepper appearance of the skull bone.



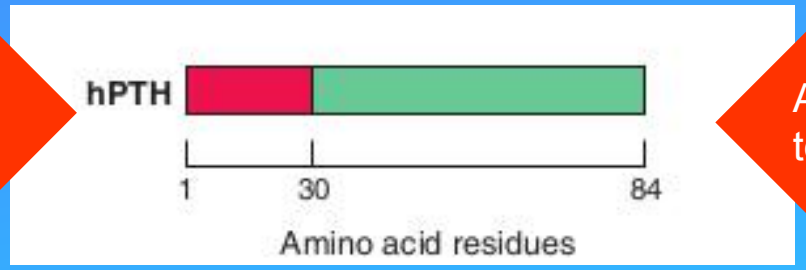
igs 7.3A and B: X-ray of humerus bone and hand bones showing bone features—**brown tumour**—osteitis fibrosa cystica.

Diagnosing parathyroid adenomas



PTH Assays

Antibody against N-terminus

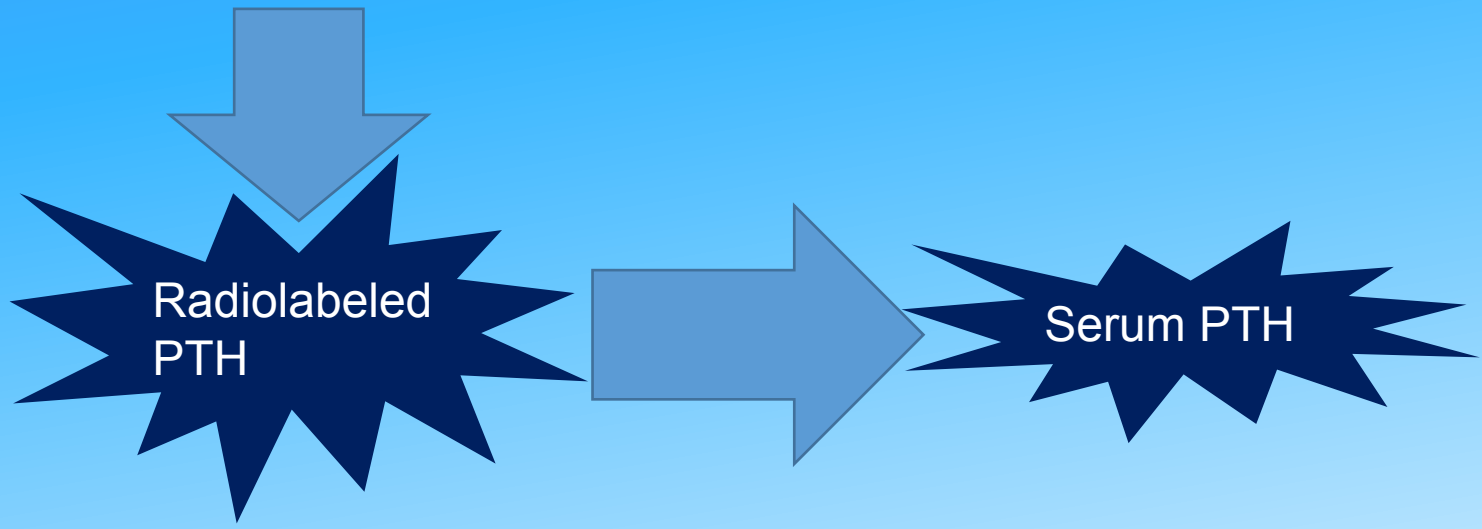


Antibody against C-terminus

Double Antibody Assays :

Two radiolabeled antibodies are directed against the carboxyl terminal of intact PTH (C-terminus) and the other against the amino terminal (N-terminus).

These tests have been now the most specific tests to diagnose hyperparathyroidism in conjunction with simultaneous blood Ca measurements.



Complications parathyroid adenomas

Complications of hyperparathyroidism are mainly related to the long-term effect of too little calcium in your bones and too much calcium in your bloodstream.

Osteoporosis

- Osteoporosis and the increased risk for bone fractures is the most common concern.

Nephrocalcinosis

- Too much serum calcium may lead to too much urine calcium, which can cause small, hard renal deposits of calcium.
- A kidney stone usually causes major pain as it passes through the urinary tract.
- calcium deposits in the kidneys can reduce kidney function by time.

Osteitis fibrosa cystica

- Softened, weak areas in the bones

Cardiovascular disease

- Although the exact cause and effect link is unclear, high calcium levels are associated with cardiovascular conditions, such as **high blood pressure** and brady arrhythmias (as Ca++ ions sustains the cardiac contractility).

Medical management

The guidelines for recommending surgical intervention, if feasible , as well as for monitoring patients with asymptomatic hyperparathyroidism who elect not to undergo parathyroidectomy.

Tightened guidelines favoring surgery include **lowering the recommended level of serum calcium elevation**, **more careful attention to skeletal integrity through reference to peak skeletal mass at baseline (T scores) rather than age adjusted bone density (Z scores)**, as well as the presence of any fragility fracture.

The other changes noted in the two guidelines (**Tables 424-2 and 424-3**) reflect accumulated experience and practical consideration, such as a difficulty in quantity of urine collections.

Despite the usefulness of the guidelines, the importance of individual patient and physician judgment and preference is clear in all recommendations.
- There is no long-term experience regarding specific clinical outcomes such as fracture prevention, but it has been established that **bisphosphonates** increase **bone mineral density significantly** without **changing serum calcium (**as does estrogen, but the latter is not favored because of reported adverse effects in other organ systems).

TAblE 424-3 Guidelines foR moniToRing in ASymPTomATiC PRimARy HyPERPARATHyRoiDiSm[a]

Parameter	Guideline
Serum calcium	Annually
24-h urinary calcium	Recommended
Creatinine clearance	Recommended
Serum creatinine[b]	Annually
Bone density	Annually (3 sites)[a]

Medical management of hypercalcemia

TABLE 424-4 THERAPIES FOR SEVERE HYPERCALCEMIA

Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
Most Useful Therapies				
Hydration with saline	Hours	During infusion	Rehydration invariably needed	Volume overload
Forced diuresis; saline plus loop diuretic	Hours	During treatment	Rapid action	Volume overload, cardiac decompensation, intensive monitoring, electrolyte disturbance, inconvenience
Pamidronate	1–2 days	10–14 days to weeks	High potency; intermediate onset of action	Fever in 20%, hypophosphatemia, hypocalcemia, hypomagnesemia, rarely jaw necrosis
Zoledronate	1–2 days	>3 weeks	Same as for pamidronate (may last longer)	Same as pamidronate above
Calcitonin	Hours	1–2 days	Rapid onset of action; useful as adjunct in severe hypercalcemia	Rapid tachyphylaxis
Special Use Therapies				
Phosphate oral	24 h	During use	Chronic management (with hypophosphatemia); low toxicity if phosphate <4 mg/dL	Limited use except as adjuvant or chronic therapy
Glucocorticoids	Days	Days, weeks	Oral therapy, antitumor agent	Active only in certain malignancies, vitamin D excess and sarcoidosis; glucocorticoid side effects
Dialysis	Hours	During use and 24–48 h afterward	Useful in renal failure; onset of effect in hours; can immediately reverse life-threatening hypercalcemia	Complex procedure, reserved for extreme or special circumstances

Surgical management

The definitive treatment is to remove the enlarged gland (or glands).

This surgery cures the problem up to 98% of the time.
In patient who are unfit to have surgery, medication may be the only option.

Indications :
- Symptomatic HPT
- Asymptomatic HPT with—Criteria (2002) for surgical intervention are:

- Raise in serum calcium level more than 1 mg/dl of upper limit of the normal calcium range;
- 24 hour urinary calcium if more than 400 mg; creatinine clear ance when reduced more than 30%.
- Bone density greater than 2.5 standard deviations below peak bone mass in lumbar spine/hip/lower end of radius.
- Age below 50 years;
- When medical therapy is not possible.

Preoperative assesment

Laboratory Assesment :

1. Tc-sestamibi (radioisotope scanning).
2. Serum calcium levels and intact parathyroid hormone (iPTH)
3. Serum value of 25-hydroxy vitamin D
4. Serum creatinine concentration (kideny function test).
5. 24-hour urinary calcium concentration and creatinine values
6. Serum thyroid-stimulating hormone (TSH) and thyroxine levels

Surgical Assesment :

1. Vocal cords should be assessed by preoperative indirect laryngoscopy.
2. High calcium levels preoperatively may require **treatment with hydration**; diuresis; **steroids (prednisolone 20 mg TID for 5 days before surgery);** 100 mmol **phosphate infusion** in 6 hours; 200 units; **calcitonin subcutaneous injection** for 5 days twice daily before surgery; **diphosphanate—etiodronate disodium 7.5 mg/kg daily as slow IV infusion** for 3 days; mithramycin 25 μg/kg as single dose.

Imaging of parathyroid adenomas

Sestamibi scan of right lower parathyroid adenoma.

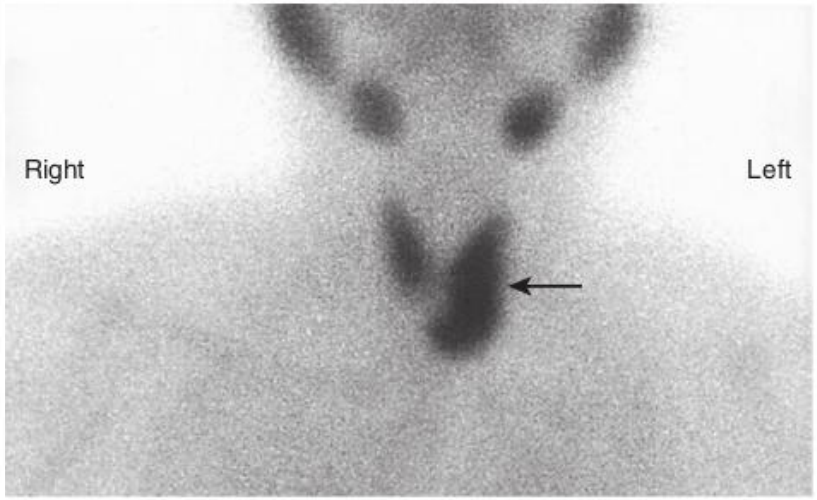
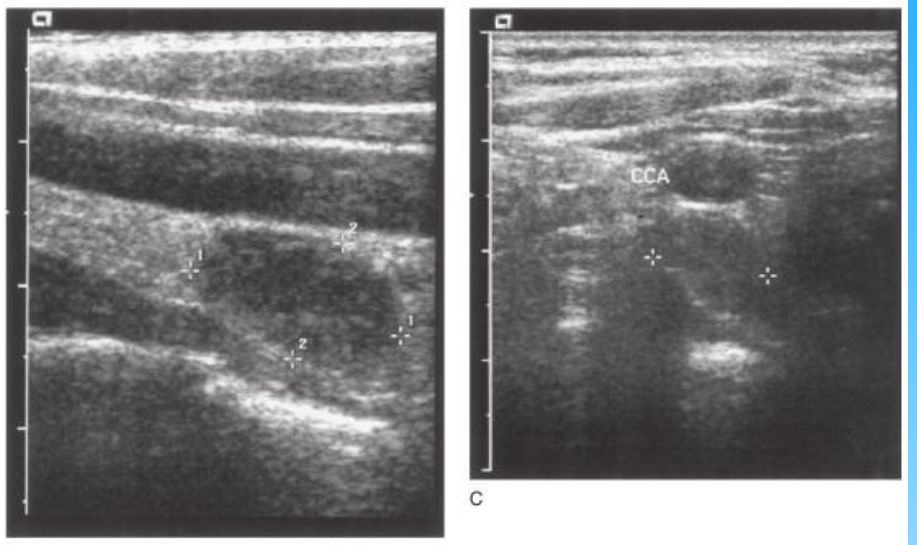


Fig. 20.19 Technetium-99 radionuclide scan demonstrates an area of increased uptake corresponding to the left inferior parathyroid gland *(arrow)*. This proved to be a parathyroid adenoma. Preoperative scintigraphy is useful in localizing and distinguishing adenomas from parathyroid hyperplasia, in which more than one gland will demonstrate increased uptake.



B: Longitudinal ultra-
sound scan of left lower parathyroid adenoma.

C: Transverse ultrasound scan of left lower parathyroid adenoma.

Surgery Steps

1. A small incision is made in the front of the neck under general anesthesia (same as thyroidectomy).
2. All 4 parathyroid glands are inspected during surgery. The surgeon takes out the abnormal parathyroid. If 1 or 2 abnormal parathyroid glands are found, they are removed and the remaining normal parathyroid gland can maintain normal calcium level.
3. If all 4 parathyroid glands are abnormal, then 3½ of the glands are removed. Some parathyroid tissue needs to be left in the body to maintain normal calcium levels
4. Intraoperative parathyroid hormone levels are checked during surgery. If the diseased parathyroid gland(s) have all been removed, then the parathyroid hormone level before removal should drop at least 50% after removal. Parathyroid glands removed during surgery will be checked by a pathologist (frozen evaluation) for confirmation that the parathyroid gland was indeed hyperactive

Fig. 6.66: Kocher's thyroid incision for thyroidectomy.

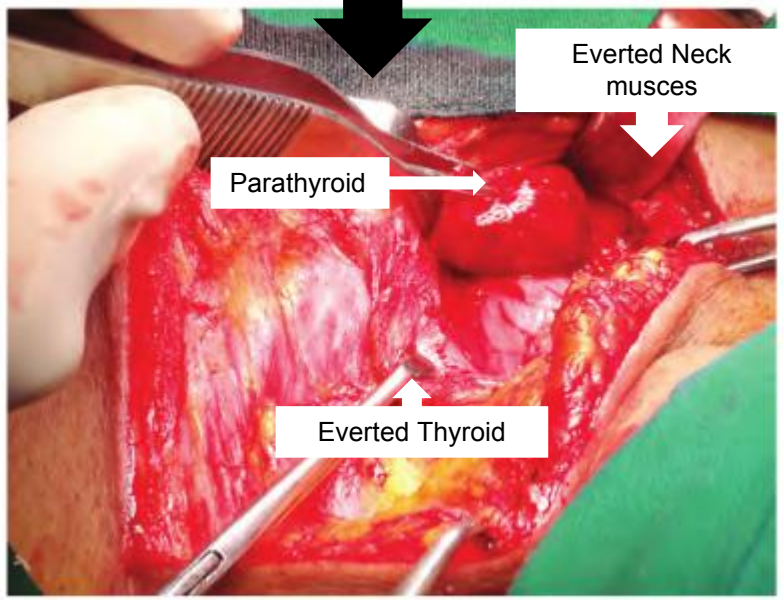


Fig. 7.4: On table look of parathyroid adenoma of inferior parathyroid gland (left sided).

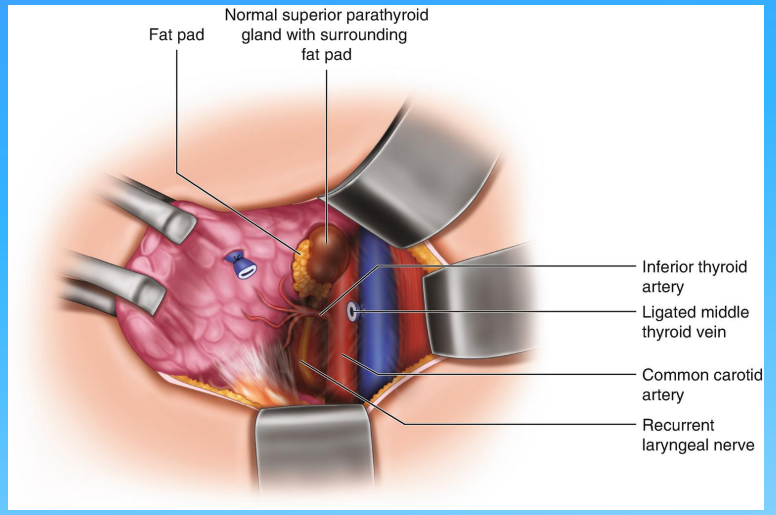
Complications of surgery

1. Short-term or permanent **low calcium levels** in the blood (**hypocalcemia**). These can manifest as **numbness/tingling** in the fingers and around the **mouth** and **muscle cramps**.

2. Patients who have **3 or more** parathyroid glands removed will definitely experience **low calcium symptoms** in the **first week after surgery**.

3. Injury to the recurrent laryngeal nerve.

Tips : To reduce these risks all patients will be on **calcium** and **vitamin D supplements** for the **first 2 weeks** after surgery. A patient who had 3½ glands removed may be instructed to take even more calcium pills.



Types of surgical approaches

1) **Bilateral neck exploration (also standard, open, conventional parathyroidectomy) :**

A traditional surgical approach for the treatment of PHPT.

Due to the development of less invasive procedures, its application is decreasing.

During the operation, the surgeon exposes **all four parathyroid glands** using a **large incision** and the **diseased glands are removed**, therefore precise preoperative localization is not required (but it may be helpful).

Fig. 6.66: Kocher's thyroid incision for thyroidectomy.

Types of surgical approaches

2) Minimally Invasive :

It is a procedure with **minimal dissection** (excision of the adenoma without the removal of non-pathological parathyroid glands) and a wound smaller than 2.5 cm.

It includes the following procedures:

1) Directed parathyroidectomy:

- Accurate preoperative localization (with neck ultrasound, sestamibi scan) is critical to the success of this type of surgery. this procedure is recommended for patients with solitary adenoma.

Types of surgical approaches

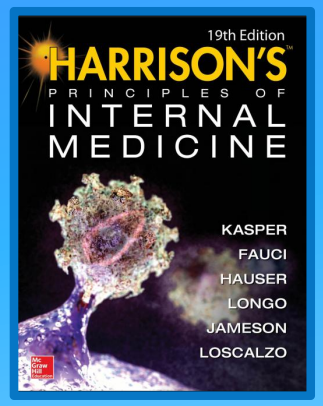
2) Endoscopic parathyroidectomy (total endoscopic, video-assisted and robotic parathyroidectomy) :

- Endoscopic parathyroidectomy is a surgical technique using an endoscope. It is divided into two types, depending on the course: **total endoscopic** and **video-assisted parathyroidectomy**, which is a combination of **endoscopic intervention** and **open surgical approach**.

3) Isotope-guided parathyroidectomy:

- Radioguided parathyroidectomy is a type of minimally invasive surgery, during which the gamma probe is used to guide the surgeon towards the location of the pathological parathyroid gland.

Resources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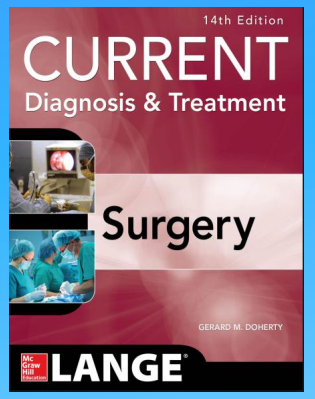
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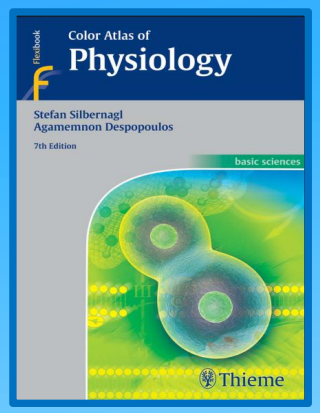
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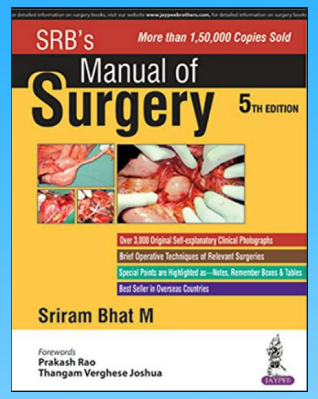
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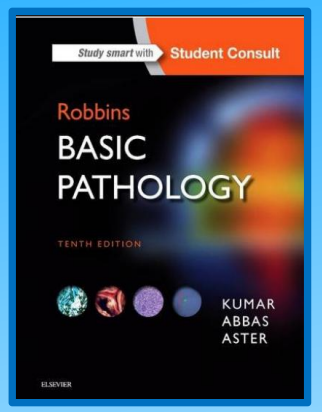
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