

**By the Name of ALLAH the Most Gracious the Most Merciful**



# Parathyroid Gland

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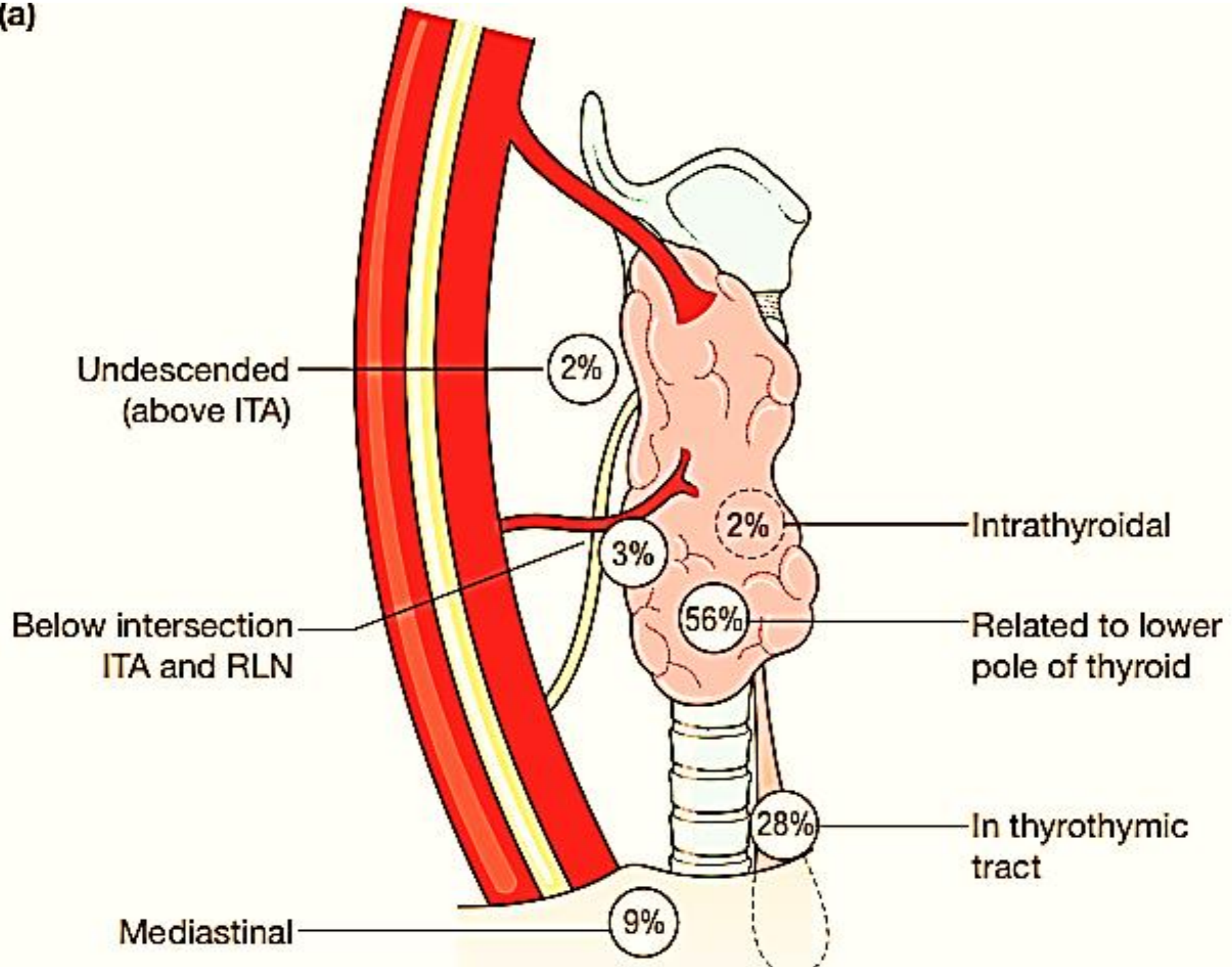
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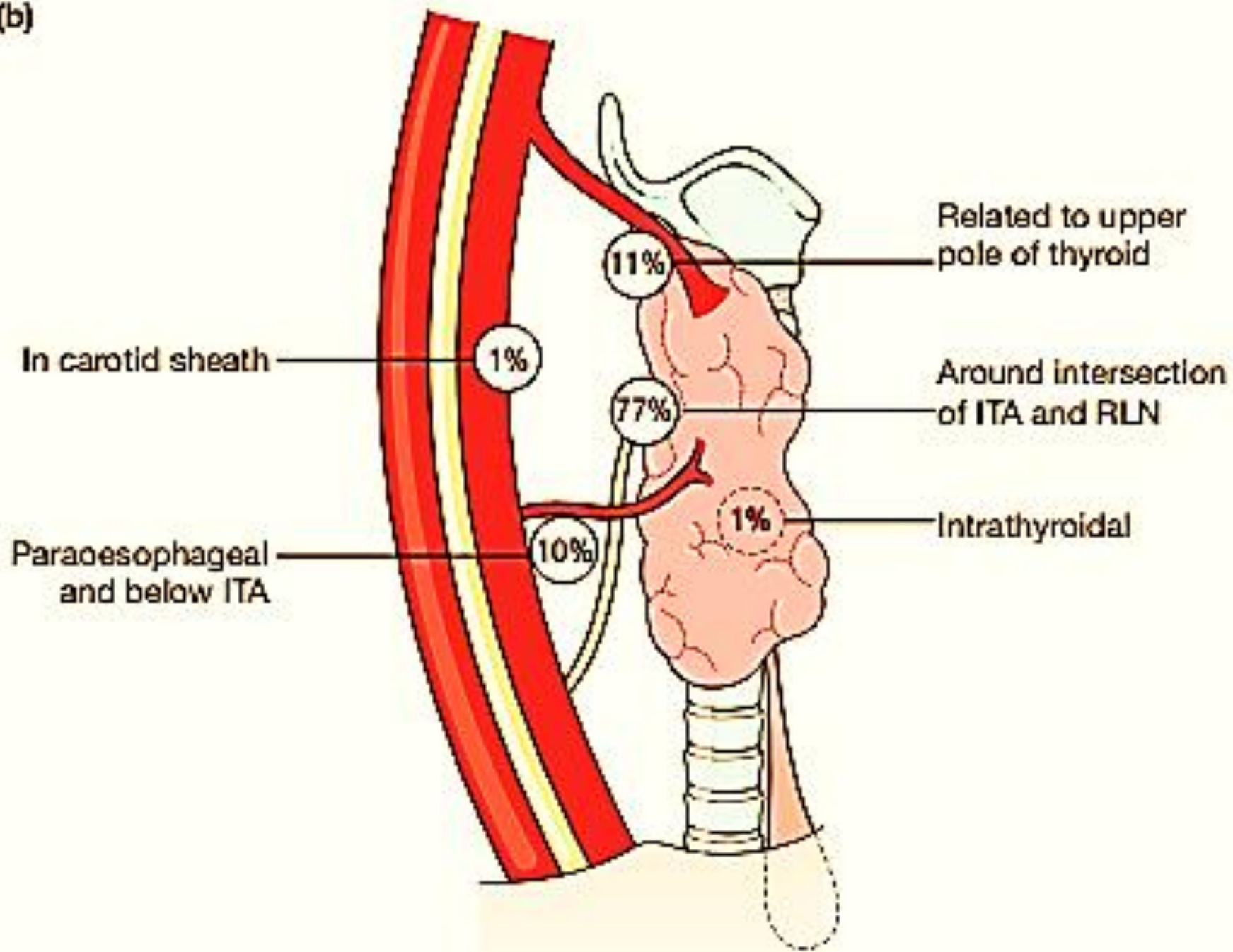
# Parathyroid Gland

- CLINICAL ANATOMY.
- CALCIUM AND PARATHYROID HORMONE REGULATION
- PRIMARY HYPERPARATHYROIDISM .
- SECONDARY HYPERPARATHYROIDISM .
- TERTIARY HYPERPARATHYROIDISM.
- PARATHYROID CARCINOMA .
- PERSISTENT HYPERPARATHYROIDISM
- RECURRENT HYPERPARATHYROIDISM.

(a)



(b)



# CALCIUM AND PARATHYROID HORMONE REGULATION

Low serum calcium or high serum magnesium levels.

84-amino-acid peptide

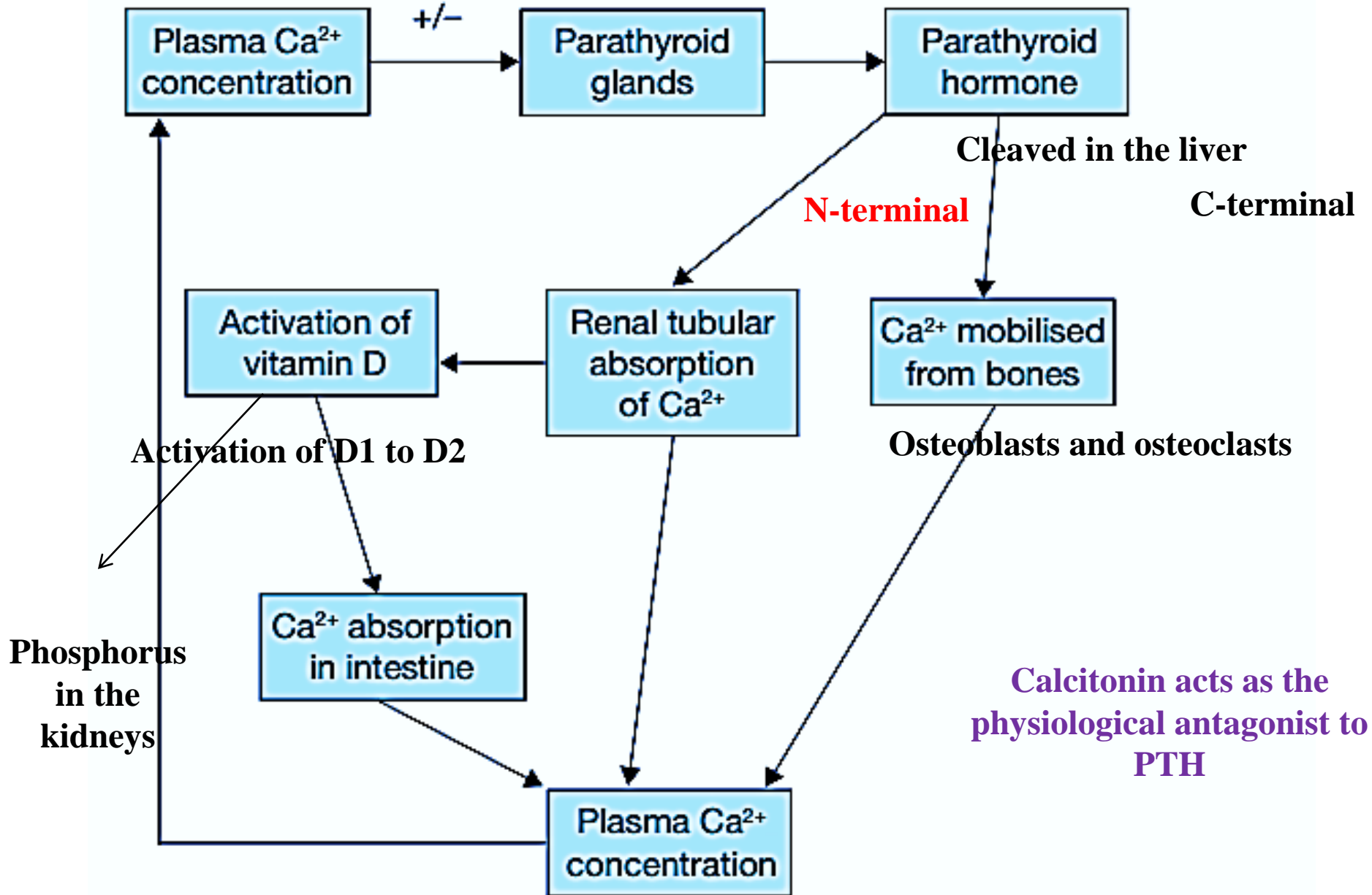


Figure 56.2 The actions of parathyroid hormone.

# PRIMARY HYPERPARATHYROIDISM

- Hypercalcaemic crisis.
- Pathology.
- Diagnosis.
- Localisation studies.
- Ultrasonography.
- Nuclear medicine-based studies (sestamibi scanning).
- Four-dimensional computed tomography scanning/positron emission tomography– computed tomography.
- Magnetic Resonance Imaging,
- Parathyroid angiography and venous sampling for parathyroid hormone.
- Management strategies ( Surgical & medical ).
- Special cases (Lithium, Familial syndromes ).

# PRIMARY HYPERPARATHYROIDISM

Hypercalcaemia in the presence of an unsuppressed and therefore relatively, or absolutely, elevated PTH level.



- Presentation is now typically asymptomatic rather than the classical ‘bones, stones, abdominal groans and psychiatric overtones’
- The diagnosis of PHPT is a biochemical one
  - ( an elevated ionised calcium with an inappropriately elevated/not suppressed PTH level )
- Sestamibi and focused neck ultrasonography are the first-line radiological investigations

- 85% of cases are due to a single adenoma
- Minimally invasive parathyroidectomy is a safe and acceptable  
alternative to a four-gland exploration in the presence of localised disease
- Familial syndromes and disease that is not localised require a formal four-gland exploration and three-and-a-half-gland parathyroidectomy

- The early descriptions of patients with PHPT were dominated by those with osteitis fibrosa cystica. Brown tumours of the long bones and associated subperiosteal bone reabsorption, distal tapering of the clavicles and the classical ‘salt and pepper’ erosions of the skull were typical findings.
- Over 80% of patients had associated renal stones, significant neuromuscular dysfunction and muscle weakness. This led to the traditional mnemonic that patients with PHPT presented with ‘bones, stones, abdominal groans and psychiatric overtones’.

- Prevalence is 0.2–0.5% .
- The majority of PHPT is sporadic in nature.
- Familial disease can occur in multiple endocrine neoplasia (MEN) type 1 or type 2A or as a familial cluster. Patients usually present in the fifth or sixth decades and there is a female predominance with a ratio of 3:1.

**TABLE 56.1** Causes of hypercalcaemia.

Endocrine	<ul style="list-style-type: none"><li>• Primary hyperparathyroidism</li><li>• Thyrotoxicosis</li><li>• Pheochromocytoma</li></ul>
Renal failure	<ul style="list-style-type: none"><li>• Secondary hyperparathyroidism</li><li>• Tertiary hyperparathyroidism</li></ul>
Malignant disease	<ul style="list-style-type: none"><li>• Skeletal metastatic disease</li><li>• Multiple myeloma, lymphoma, leukaemia</li><li>• Solid tumours (PTH-related peptide mediated): lung, renal, squamous cell carcinoma of the head and neck, oesophagus, genital tract</li></ul>
Nutritional	<ul style="list-style-type: none"><li>• Excessive vitamin D ingestion</li><li>• Vitamin A intoxication</li><li>• Milk-alkali syndrome</li><li>• Aluminium intoxication</li></ul>
Granulomatous	<ul style="list-style-type: none"><li>• Sarcoidosis</li><li>• Tuberculosis</li></ul>
Inherited disease	<ul style="list-style-type: none"><li>• Hypercalciuric hypercalcaemia</li></ul>
Immobilisation	
Paget's disease	
Drug related	<ul style="list-style-type: none"><li>• Lithium</li></ul>

- Presentation
- Patients are typically identified incidentally with an elevated total calcium or following routine assessment of bone densitometry (DEXA scan).
- Most patients will, however, have some vague constitutional symptoms, such as fatigue, muscle weakness, depression or some mild memory impairment on questioning.
- Renal stones remains the most common clinical manifestation of symptomatic PHPT. Between 15% and 20% of patients will have nephrolithiasis and over 40% of patients will have hypercalciuria.

- Increasingly, postmenopausal osteopenia or osteoporosis in the distal one-third of the radius with a minimal reduction in the lumbar spine, which prompts further investigation. This distribution arises as PTH appears to be catabolic at cortical sites (distal one-third of the radius) and anabolic at cancellous sites (lumbar spine).
- It may present with pancreatitis, although it is rarely seen in patients with milder forms of the disease.
- Hypertension and peptic ulcer disease, are often encountered.

- Clinical examination is usually normal.
- Band keratopathy, pathognomonic of the disease and due to deposition of calcium phosphate crystals in the cornea, is now rarely identified.
- The differential diagnosis includes other causes of hypercalcaemia, which are usually readily distinguishable (**Table**).
- Widespread malignancy has to be excluded, in which patients will typically have other symptoms. The exception to this rule is multiple myeloma, in which hypercalcaemia can be the presenting complaint.



- Improvements in the immunoradiometric and immunochemiluminometric assays for PTH can help to distinguish these conditions, as in malignancy PTH levels are typically suppressed.

# Hypercalcaemic crisis

## Presentation and Management

- Hypercalcaemia is documented in 0.5% of the general population and in up to 5% of hospitalised patients. The vast majority are asymptomatic with a mild to moderate elevation of serum calcium (<3 mmol/L and 3–3.5 mmol/L, respectively) and respond to treatment of the underlying aetiology with associated dietary modification. A small proportion of patients will present symptomatically with a total calcium of >3.5 mmol/L. This is referred to as a hypercalcaemic crisis and requires aggressive medical management.
- **Although symptoms** can be varied, the typical presentation is of acute confusion, abdominal pain, vomiting, dehydration and anuria. Prolongation of the PR interval with a shortened QT interval can be identified on an electrocardiogram (ECG) prior to potentially lethal cardiac arrhythmias. Where the calcium is >4.5 mmol/L, coma and cardiac arrest can occur.

- **Treatment revolves** around increasing renal excretion of calcium, reducing skeletal release of calcium and treatment of the underlying cause. Aggressive rehydration plays a pivotal role.
- Typically, 200–500 mL/h of normal saline is given to maintain a urine output  $>100$  mL/h, with the caveat that this may be modified to account for associated patient comorbidities.
- Once intravascular volume has been adequately restored, loop diuretics, such as furosemide, can be used to enhance the renal excretion of calcium. The majority of patients will have normalisation of their calcium with these simple measures.

- In patients with **advanced malignancy** and a serum calcium level  $>3$  mmol/L, agents that blunt the release of calcium from skeletal stores may be required.
- First-line treatment includes administration of
- Bisphosphonates. These are pyrophosphate analogues that inhibit osteoclast activity in areas of high bone turnover. In the acute setting, these are given intravenously owing to poor absorption in the gastrointestinal tract.
- Calcitonin can be used to both decrease osteoclastic activity and increase renal excretion of calcium. It has a short duration of action and is usually used as a bridge to reduce calcium until the sustained action of the bisphosphonates is seen.
- Finally, glucocorticoids (prednisolone) can be used to enhance the action of calcitonin. They increase calciuresis and decrease intestinal absorption of calcium. As a result, they may also play a role in diseases associated with vitamin D excess.

# Pathology

- Is usually a solitary parathyroid adenoma; however, in a small number of patients (2–4%) there are double adenomas.
- It may occur in a sporadic fashion or it can be familial (approximately 10%) (MEN type 1, type 4, type 2A or hyperparathyroidism–jaw tumour syndrome [HPT-JT]) in nature.

- Risk factor is a history of prior neck irradiation.
- The underlying genetic pathogenesis remains unclear. However, genes regulating the cell cycle, such as MEN1 and CCND1, have been recognised as playing an important role owing to the clonal nature of adenomas. Somatic mutations in MEN1, which encodes menin, occur in 12–35% of sporadic cases and rearrangements or overexpression of CCND1, which encodes cyclin D1, have been demonstrated in 20–40% of patients. Upregulation of cyclin D may lead to a clonal proliferation within the parathyroid glands. This does not alter the set point of calcium but the hyperplastic nature of the parathyroid cells themselves causes excessive secretion of PTH.
- Multigland disease is less common, occurring in approximately 15% of patients. No clinical features differentiate single from multigland disease, although multigland disease is more commonly associated with familial syndromes such as MEN types 1 and 2A, as well as the chronic ingestion of lithium.

# Diagnosis

- PHPT is a biochemical diagnosis.
- When confirmed biochemically, should **localisation** studies be undertaken. Positive imaging does not confirm the diagnosis and negative findings cannot rule it out.
- PHPT is defined as an elevated total, or more specifically ionised, calcium in the presence of an inappropriately elevated or unsuppressed PTH. It is associated with a low serum phosphate in the setting of normal creatinine and vitamin D levels; 24-hour urinary excretion of calcium may be normal or elevated.
- It is important to perform a 24-hour urinary collection to rule out the presence of the rare familial hypocalciuric hypercalcaemia (FHH).
- Alkaline phosphatase may be elevated in patients in whom there is concomitant bone disease. This is important to recognise preoperatively as the surgeon should anticipate significant postoperative hypocalcaemia due to the development of hungry bone syndrome.



# Localisation studies

- Non-invasive radiology includes nuclear medicine-based studies, ultrasonography and fourdimensional (4D) computed tomography (CT) scanning.
- Invasive imaging is largely reserved for reoperative surgery and includes ultrasound or CT-guided fine-needle aspiration with concomitant PTH assays, parathyroid angiography or selective venous sampling for the PTH gradient.

# Ultrasonography

- Ultrasonography is a non-invasive, inexpensive method of imaging the parathyroid glands.
- Parathyroid adenomas are typically oval or elongated, bi- or multilobed hypoechoic structures. Rarely, adenomas may be cystic or heterogeneous in nature.
- Giant adenomas are over 3 cm in size.
- It helps to identify and facilitate biopsy of any concomitant thyroid pathology. However, ultrasonography is operator, lesion size and location dependent.

- Ultrasonography may miss adenomas located in retro-oesophageal, retrosternal or retrotracheal areas.
- It can also be difficult to differentiate between a small parathyroid gland and a normal-appearing lymph node.
- Ultrasonography and sestamibi-SPECT have comparable accuracy, with pooled sensitivities of 76.1% and 78.9%, respectively, and positive predictive values (PPVs) of 93.2% and 90.7%, respectively .

## Nuclear medicine-based studies (sestamibi scanning)

- The use of sestamibi (2-methoxy-2-methylpropylisonitrile [MIBI]) for parathyroid localisation is regarded as the most accurate and reliable method, safe and reproducible and, while it has a sensitivity and specificity similar to ultrasonography, it may image glands in ectopic positions better .
- Sestamibi accumulates in mitochondria and therefore washes out at differential rates depending on the number of mitochondria within individual tissues.
- Parathyroid adenomas often have a high concentration of oxyphilic cells with high mitochondrial content. These retain tracer, and adenomas are therefore associated with a slow washout when compared with the thyroid gland. There are three different protocols for sestamibi scanning: single-isotope dual-phase scan, dual-isotope subtraction imaging and single-photon emission computed tomography (SPECT). The sensitivity and specificity of sestamibi, regardless of the protocol used, are 79% and 90%, respectively.

- False positives are rare but may arise from some solid thyroid nodules, such as Hürthle cell nodules, that are associated with high oxyphilic content. These can be reduced by the addition of a thyroid-specific radioactive tracer, such as  $^{99}\text{Tc}$ -pertechnetate and subsequent subtraction images.

## Four-dimensional computed tomography scanning/positron emission tomography– computed tomography

- It gives both anatomical and functional information about the parathyroid glands, allows hyperfunctioning glands to be differentiated from lymph nodes that demonstrate a progressive enhancement pattern.
- The potential disadvantage of 4D-CT scanning is the higher radiation dose .
- Positron emission tomography (PET) scanning remains expensive and is not widely available. However, recent data suggest that there may be an incremental value to 18F-fluorocholine PET with the addition of CT scanning for localisation of ectopic adenomas.

# Magnetic Resonance Imaging

- Is not commonly used to image the parathyroid glands. However, on T2-weighted images, enlarged parathyroid glands demonstrate significantly increased intensity.
- In reoperative cases or where the adenoma is located in the mediastinum, MRI may be beneficial, with higher reported sensitivities (50–88%).
- It is expensive, patients can be poorly compliant owing to claustrophobia and the resolution for normal glands or adenomas <5 mm is poor.
- Similarly, it can be difficult to localise superior glands because of their posterior location, which allows them to be obscured by the thyroid gland.

# Parathyroid angiography and venous sampling for parathyroid hormone

- Parathyroid angiography is reserved for reoperative cases and is now rarely required owing to improvements in non-invasive imaging modalities.
- It involves examination of both thyrocervical trunks, both internal mammary arteries and both carotids, with occasional selective superior thyroid artery catheterisation. Vascular parathyroid adenomas appear as a persistent oval or round 'stain' on angiography.
- Serious complications such as contrast-induced renal failure, embolisation and neurological damage have limited its utility.



## Venous sampling for parathyroid hormone

- Selective venous sampling for PTH can allow accurate localisation of adenomas but an experienced interventional radiologist is vital for success.
- The venous drainage of the lesion is established when there is a twofold drop in the PTH between the sampled blood and the serum PTH. The sensitivity is reported to be 80% and is equally effective in localising cervical and mediastinal adenomas.

# Management strategies

- Surgical ( MIS, Bilateral neck exploration ).
- Medical

# Surgical management

- The mainstay of treatment for PHPT is surgery, addressing the underlying aetiology and allowing not only resolution of biochemical abnormalities but also sustained improvements in end-organ damage.
- Traditionally a bilateral cervical exploration was performed with reported cure rates of 95–98%. With improvements in preoperative radiological localisation, a more minimally invasive approach has been developed and widely adopted
- All symptomatic patients should be offered surgery. An expert panel published recommendations on which asymptomatic patients should be considered for surgical intervention

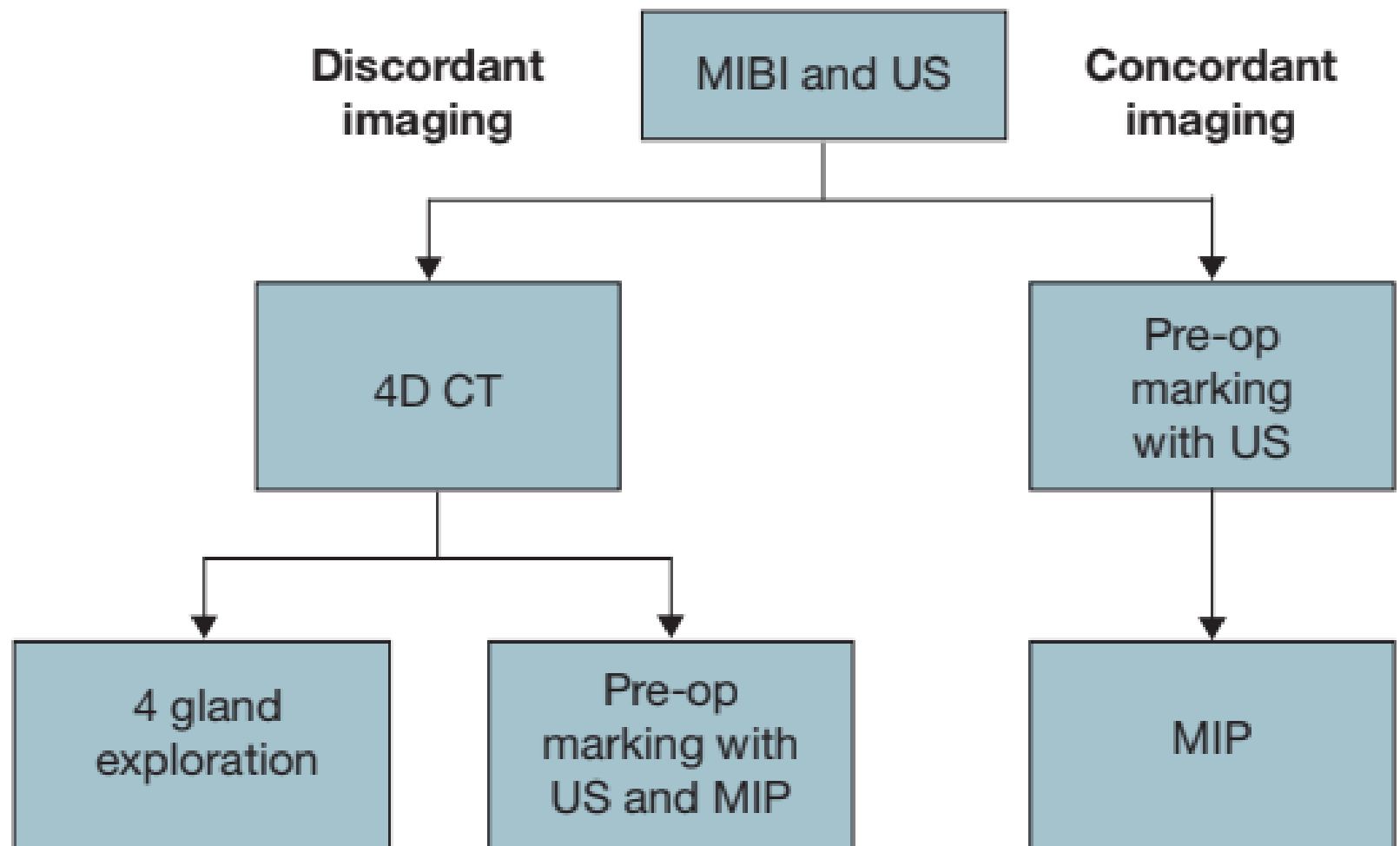
## **Guidelines from the American Association of Endocrine Surgeons**

- These included patients with cognitive or psychiatric symptoms attributable to PHPT, cardiovascular disease (excluding hypertension) and more non-specific symptoms, such as muscle weakness, impaired functional capacity and abnormal sleep patterns.
- When criteria have been met and where a single adenoma has been confidently identified by radiological means, a minimally invasive parathyroidectomy may be offered.

**TABLE 56.2** Consensus guidelines for surgical intervention in asymptomatic primary hyperparathyroidism.

Measurement of serum calcium	0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
Skeletal	<ul style="list-style-type: none"><li>• BMD by DEXA; T score <math>-2.5</math> at lumbar spine, total hip, femoral neck or distal one-third of radius</li><li>• Vertebral fracture</li></ul>
Renal	<ul style="list-style-type: none"><li>• Creatinine clearance <math>&lt;60</math> mL/min</li><li>• 24-hour urinary calcium <math>&gt;10</math> mmol/dL (<math>&gt;400</math> mL/day) or increased risk of stone formation by risk analysis</li></ul>
Age	$<50$ years

BMD, bone mineral density; DEXA, bone densitometry.  
Adapted from Bilezikian *et al.* (2014).



Localisation paradigm and management strategies. 4D CT, four-dimensional computed tomography; MIBI, 2-methoxy-2-methylpropylisonitrile; MIP, minimally invasive parathyroidectomy; US, ultrasonography.

- Conversely, where there is discordant imaging or where imaging fails to identify any parathyroid abnormalities, then a bilateral neck exploration and a three-and-a-half-gland parathyroidectomy or a four-gland parathyroidectomy and autotransplantation should be performed.
- Consent for a parathyroidectomy must include the possibility of recurrent laryngeal nerve damage (risk <1%), permanent hypoparathyroidism (requiring lifelong calcium and vitamin D supplementation; risk 0.5%) and persistent (5%) or recurrent hyperparathyroidism.
- Persistent disease is defined as an elevated serum calcium within 6 weeks of surgical intervention and recurrent disease is defined as an increase in calcium levels after 6 months but with an intervening period of normocalcaemia.

- **Minimally invasive (focused) parathyroidectomy**
- Minimally invasive approaches are based on the principle that over 80% of individuals with PHPT have a single adenoma.
- Although there is no strict definition of the procedure, it commonly refers to the removal of a localised abnormal parathyroid gland through an incision less than 3 cm in length .
- The term encompasses open approaches (central and lateral incisions) and video-assisted and radioguided parathyroidectomies.
- A number of randomised studies have shown that the focused approach has similar cure rates to a cervical exploration but with reduced rates of postoperative hypocalcaemia, shorter operating times, potentially less pain and better cosmesis.

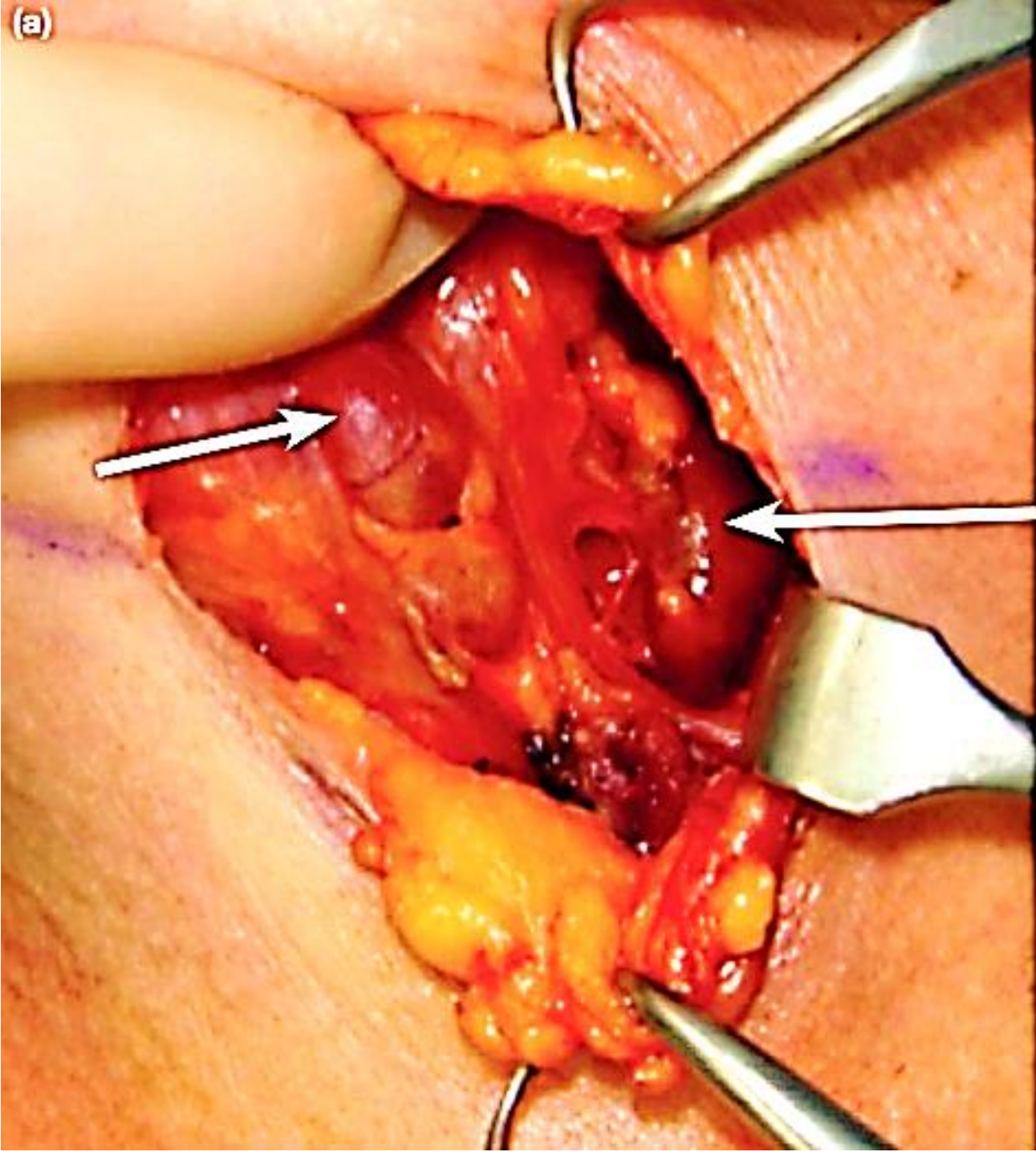


- The need to **convert** to a cervical exploration may be guided by the use of intraoperative PTH measurements.
- Routine use is, however, controversial owing to high false-positive and false-negative rates.
- The basic concept is that the half-life of circulating PTH is 3–5 minutes and there should therefore be a significant drop detected in the plasma PTH following resection of a single adenoma. If no such drop is detected, then multigland disease may be suspected and conversion to a bilateral neck exploration should be considered.
- The Miami criteria were developed to determine the extent of resection. A drop in the PTH into the normal range and to less than half the maximum preoperative PTH at 10 minutes appears to accurately predict single-gland disease .

# **Bilateral neck exploration**

- A traditional cervical neck exploration is required where imaging is negative or discordant, in MEN (type 1 or type 2A) or in lithium-induced PHPT.
- A transverse collar (Kocher's) incision is made and the subplatysmal plane developed. The deep cervical fascia is divided between the strap muscles and these are retracted. The thyroid lobes are mobilised and the middle thyroid vein may be divided when present.
- Identification of the recurrent laryngeal nerve and the middle thyroid artery allows a starting point for a systematic exploration .

- All four glands are identified. Three and a half glands are resected, with half of a vascularised parathyroid left in situ. The other half of the gland should be sent for frozen section to confirm the presence of parathyroid tissue. Ideally the most normal-appearing parathyroid is left in situ. With this caveat in mind, where possible an inferior gland should be left. It is marked with a non-absorbable suture to aid identification in the presence of recurrent disease, where resection can be achieved without increasing the risk of damage to the recurrent laryngeal nerve. Alternatively, all four glands can be resected and a forearm autotransplant created. Small pieces of parathyroid are sutured into pockets created in the brachioradialis muscle. Cure rates and rates of persistent and recurrent disease appear to be similar, regardless of the type of procedure used. However, in recurrent disease it can be difficult to identify the location of the recurrent tissue when an autotransplant is performed.



# Thymectomy and resection of mediastinal adenomas

- The incidence of clinically significant supernumerary glands is increased in patients with multigland disease or those with hereditary syndromes.
- A thymectomy should be routinely undertaken for patients with MEN1-associated PHPT or in secondary hyperparathyroidism.
- A cervical thymectomy is performed by dissecting close to the thymic capsule, exploring the cervical part of the gland. The mediastinal part of the gland can be removed by gentle upwards traction, with ligation of the veins draining into the innominate vein

- The end of the gland is tapered and rarely requires formal ligation.
- A median sternotomy is not required where a prophylactic thymectomy is being performed.
- Mediastinal adenomas are rare, accounting for less than 1% of all parathyroid adenomas. They will be typically identified on preoperative imaging.
- Resection can be achieved either by an open sternotomy or increasingly by a thoracoscopic approach. A minimally invasive approach can be particularly effective where the abnormal gland lies immediately deep to the mediastinal pleura. It can confer significant advantages in length of hospital stay and complication rates.

# **Permanent hypoparathyroidism**

**The continuing need for calcium and/or vitamin D replacement at 1 year postoperatively.**



- It is a rare complication when surgery is undertaken for PHPT (0.5%), but in secondary hyperparathyroidism it can range from 4% to 12%.
- Symptoms include mild circumoral or digital numbness and paraesthesia, carpopedal or laryngeal spasms and cardiac arrhythmias.
- Chvostek's and Trousseau's signs may be elicited.
- **Chvostek's sign** refers to contraction of the ipsilateral facial muscles on percussion of the facial nerve below the zygoma.
- **Trousseau's sign** refers to the development of carpopedal spasm secondary to occlusion of the arm (usually with a blood pressure cuff).

- Biochemical investigations include total and ionised calcium levels as well as serum magnesium levels. An ECG may demonstrate a prolonged QT interval or QRS complex changes.
- Mild hypocalcaemia can be treated with oral calcium and vitamin D supplementation. Acute symptomatic hypocalcaemia is an emergency and should be corrected with intravenous as well as oral calcium and vitamin D replacement. Traditionally, 10 mL of 10% calcium gluconate is administered slowly intravenously. Supplemental magnesium may also be required, owing to the synergistic action of transporters for calcium and magnesium.

## **Medical management** **(Bisphosphonates/Denosumab )**

- **For unfit** or who have contraindications to surgical intervention, in patients with failed surgical intervention or in the long-term management of parathyroid carcinoma.
- The aims are **to prevent skeletal complications** (improve bone mineral density and reduce fracture risk) and to stabilise biochemical parameters.
- **Bisphosphonates** are pyrophosphate analogues that are concentrated in areas of high bone turnover. They inhibit osteoclast activity and apoptosis, thereby increasing bone mineralisation and reducing bone turnover.
- **Denosumab** is a monoclonal antibody that works as a receptor activator of nuclear factor- $\kappa$ B (RANK) ligand inhibitor. Data from the DENOCINA trial suggest that it may be a valid treatment option for patients in whom surgery is undesirable.

## Hormone replacement therapy (HRT) and selective oestrogen receptor antagonists

- (HRT) has been shown to improve bone mineral density and reduce the associated fracture risk in postmenopausal women by reducing bone turnover.
- Two non-randomised controlled trials have shown a durable and similar response to surgery for PHTP at 4 years, with improvements in bone mineral density but without any improvement in the underlying serum biochemistry.
- **Selective oestrogen receptor antagonists** (SERMs) is that they should confer the benefits of HRT but without the potential adverse vascular and breast effects. The effect on the bone mineral, however, appears to be less significant than that of HRT.

# Calcimimetics

- The extracellular calcium-sensing receptor on the parathyroid cell surface negatively regulates secretion of PTH. Activation of the receptor decreases secretion of PTH, thereby decreasing bone turnover. Calcimimetics, such as cinacalcet, amplify the sensitivity of the calcium-sensing receptor to extracellular calcium, altering the set point and thereby decreasing PTH production.
- Cinacalcet was for the treatment of severe hypercalcaemia in patients with PHPT who were unfit for parathyroidectomy.
- Normalisation of serum calcium levels can be achieved with a similar reduction in the level of PTH, although not to within the normal range. Despite this, neither the urinary calcium nor the bone mineral density appear to change even after 3 years of treatment.
- Drug tolerance, especially gastrointestinal side effects, can be problematic and may limit the duration of usage.

# SPECIAL CASES

- Lithium-induced hyperparathyroidism
- Familial syndromes

# Lithium-induced hyperparathyroidism

- Lithium-induced hyperparathyroidism occurs in 10–15% of patients treated with long-term lithium.
- It is generally associated with a mild elevation in calcium with failure to suppress PTH. The underlying aetiology can be either gland **hyperplasia**, with lithium originally thought to stimulate all parathyroid tissue, or a **single adenoma**, which has been shown to occur in 33–49% of cases.
- It may be caused by interference with the parathyroid kinase C signal transduction system and the Wnt pathway.

- Biochemical abnormalities may resolve with discontinuation of lithium.
- Surgery is indicated where ongoing treatment with lithium is required or where abnormalities persist following withdrawal of lithium.
- Minimally invasive surgery is relatively contraindicated in these patients because of the high incidence of multigland disease. Excision, however, should be limited to those glands that are obviously enlarged at exploration rather than a formal three-and-a-half-gland excision.



# Familial syndromes

- Familial hyperparathyroidism can be part of a well-recognised endocrine disorder, but it may also occur in isolation in a non-syndromic form.
- PHPT occurs as a central facet in multiple MEN type 1, type 4, type 2A, HPT-JT, autosomal dominant mild hyperparathyroidism and FHH.

## Familial isolated hyperparathyroidism

- Familial isolated hyperparathyroidism occurs when patients have PHPT without any other associated endocrinopathies.
- The underlying genetic abnormality has yet to be fully elucidated, but the syndrome has been linked to known mutations in the MEN1 gene, the HRPT2 gene as well as the calcium-sensing receptor gene. A significant proportion of patients will belong to the MEN 1 family, with documented recognised mutations but without expression of other endocrinopathies.
- Hyperparathyroidism should be treated with a formal bilateral neck exploration and management as per patients with MEN.

- **MEN type 1-associated hyperparathyroidism**
- MEN type 1 is a rare autosomal dominant syndrome consisting of tumours of the parathyroids, endocrine pancreas–duodenum and the pituitary (the three Ps).
- It occurs in approximately 1 per 30 000 individuals. It can also be associated with adrenal adenomas or carcinoma, foregut carcinoids and lipomas. Mutations, of which there are over 1000 identified in different families, occur in the MEN1 gene, which encodes the protein menin. Menin acts as a tumour suppressor. Patients typically present with young onset (20–30 years of age) of symptomatic hyperparathyroidism and over 95% of patients will have PHPT before the age of 40 years.

- Surgical intervention in MEN type 1 aims to obtain and maintain normocalcaemia for the longest time possible.
- In general, it is associated with the presence of multigland parathyroid disease and as such has mandated a bilateral cervical exploration with at least a subtotal parathyroidectomy and cervical thymectomy. A subtotal parathyroidectomy removes three and a half glands with half of the most normal-appearing parathyroid left in situ with a marking stitch to facilitate reoperative intervention.
- A total parathyroidectomy and forearm autotransplantation is an acceptable alternative.

## MEN type 4-associated hyperparathyroidism

- An autosomal dominant syndrome that comprises the same combination of tumours as MEN type 1 but is a rarer cause of hereditary PHPT.
- It arises as a result of an inactivating pathogenic variant in the cyclin-dependent kinase inhibitor CDKN1B gene.
- It should be managed in the same fashion as MEN type 1.

## MEN type 2A-associated hyperparathyroidism

- MEN type 2A consists of medullary thyroid carcinoma (MTC), unilateral or bilateral pheochromocytomas and PHPT.
- PHPT occurs in approximately 20% of patients and is associated with mutations in codon 634 in the RET proto-oncogene.
- The majority of patients will be asymptomatic, with a mild elevation in calcium and asymmetrically enlarged parathyroid glands. It is extremely important that the presence of a pheochromocytoma is excluded prior to surgical intervention.
- Surgery is usually performed for MTC, with the parathyroid enlargement often being a coincidental intraoperative .
- The primary aim of treatment is to avoid hypoparathyroidism. A conservative stance is adopted with resection of grossly enlarged glands, but with preservation of parathyroid tissue where possible and identification with a marking stitch in the neck.

# Hyperparathyroidism–jaw tumour syndrome

- HPT-JT is a rare cause of PHPT. It arises as a result of inactivating mutations in the HRPT2/CDC73 gene on chromosome 1q21–q31, encoding parafibromin.
- It classically presents with early-onset PHPT (mean age of 32 years), the aetiology of which can be either single- or multigland disease but is predominantly cystic in nature. It presents with severe hypercalcaemia and is associated with an increased risk of an underlying parathyroid carcinoma.
- 40% of patients will have the pathognomonic ossifying jaw fibromas of the maxilla or mandible.

- Other associated abnormalities include renal pathology (hamartomas, polycystic kidney disease and adult Wilms' tumours) and female patients may have uterine malignancies. Surgical intervention involves removal of all enlarged parathyroid glands.
- Where there is concern for a parathyroid carcinoma, great care must be taken to avoid tumour spillage. Whether or not an en bloc resection of the enlarged suspicious parathyroid and the adjacent thyroid lobectomy is required remains controversial.



# Autosomal dominant mild hyperparathyroidism

- This is a rare autosomal dominant syndrome presenting with hypercalcaemia and hypercalciuria.
- It is associated with a mutation in the calcium-sensing receptor gene.
- It typically presents in patients who are over 40 years of age and all patients have PHPT.
- Surgical intervention requires a bilateral neck exploration as it is associated with multigland disease.

# Familial hypocalciuric hypercalcaemia

- FHH is not a surgical disease and therefore preoperative diagnosis is imperative for the surgeon.
- It arises as a result of heterozygous mutations in the calcium-sensing receptor gene on chromosome 3.
- Benign FHH typically presents with mild hypercalcaemia in young (<10 years of age) asymptomatic patients.
- Patients with FHH have a normal or slightly elevated PTH level, increased serum magnesium levels and hypocalciuria. A low urinary calcium–creatinine clearance ratio is used to discriminate between FHH and mild PHPT.
- Patients rarely require intervention and surgical intervention is not indicated.

# Criteria for genetic testing

- In clinical practice, specific criteria can be employed to determine which patients are at the highest risk of hereditary PHPT.
- The current NHS England National Genomic Test Directory testing criteria from March 2019 for familial hyperparathyroidism state that testing should be considered for patients with PHPT and a creatinine clearance ratio  $>0.02$  who meet one of the following criteria:
  - 1 presenting before the age of 35 years or
  - 2 presenting before the age of 45 years with one of :
    - a proven multigland involvement or
    - b hyperplasia on histology or
    - c ossifying fibroma(s) of the maxilla or mandible or
    - d at least one first-degree relative with unexplained hyperparathyroidism.
- The testing criterion for FHH is a creatinine clearance ratio  $<0.02$ .

# SECONDARY HYPERPARATHYROIDISM

- Definition and presentation.
- Calciphylaxis.
- Diagnosis.
- Management.

# SECONDARY HYPERPARATHYROIDISM

- A derangement in calcium homeostasis, which leads to a compensatory increase in PTH secretion
- It occurs primarily as a result of chronic kidney disease and is therefore sometimes referred to as renal hyperparathyroidism.
- Other underlying causes include gastrointestinal malabsorption, vitamin D deficiency, liver disease or chronic lithium usage.

- Primarily due to underlying chronic kidney disease
- Associated with parathyroid hyperplasia
- Diagnosis is made biochemically with a hypocalcaemia or normocalcaemia and an elevated PTH. High phosphate levels and low vitamin D levels are seen
- No localisation studies are required
- Mainstay of treatment is renal transplantation. Medical management with calcium and vitamin D replacements and phosphate binders is a bridge to transplantation
- Use of calcimimetics has reduced the requirement for surgical intervention
- Subtotal parathyroidectomy remains the surgical intervention of choice when indicated

- Abnormalities in the renal tubular absorption of phosphate lead to hyperphosphataemia, acting directly on the parathyroid cells and stimulates PTH secretion.
- (FGF23) phosphaturia hormone fibroblast growth factor 23 .This is progressively secreted from osteocytes to compensate for chronic phosphate retention that in turn leads to a reduction in 1,25-dihydroxyvitamin D, which by reducing the intestinal absorption of calcium also acts to increase secretion of PTH.
- There is a reduction in the expression of the vitamin D receptor and the calcium-sensing receptor, with associated skeletal resistance to PTH. These factors interact to form the complex pattern leading to progressive secondary hyperparathyroidism in the setting of chronic renal disease.
- The pathological characteristics associated with secondary hyperparathyroidism include: ( hyperplasia, asymmetrical glandular enlargement or nodularity ). When the parathyroid gland becomes nodular, it loses expression of the vitamin D receptor and the calcium sensing receptor gene. It has been proposed that nodular parathyroid glands may be resistant to calcimimetics and therefore refractory to medical management.

- **Calciophylaxis** (calcific uraemic arteriopathy) is a syndrome of disseminated calcification resulting in both vascular calcification and skin necrosis. It accounts for approximately 4% of patients undergoing surgical intervention for secondary hyperparathyroidism.
- It presents with expanding painful cutaneous purpuric lesions, predominantly on the extremities, although they can also be seen on the lower abdomen.
- leads to ischaemic necrosis and the development of gangrene, which in turn leads to overwhelming sepsis and death.
- The majority of these patients will have an elevated calcium  $\times$  phosphate product but it is not usually associated with an extremely high PTH level.
- The underlying aetiology remains unclear but a number of potential factors have been postulated. A reduction in the serum levels of a calcification inhibitory protein,  $\alpha$ 2-Heremans–Schmid glycoprotein, and abnormalities in smooth muscle cell biology in uraemic patients may play a role in the development of the syndrome.
- Prognosis for these patients is extremely poor, with a mortality of up to 87%.
- An urgent parathyroidectomy has been shown to decrease pain, improve wound healing and reduce the risk of amputation in these patients. It has also been associated with an increase in median survival.



## Presentation

- Progressive bone disease, especially bone pain, can occur with associated soft-tissue calcium deposits .

## Diagnosis

- The diagnosis is a biochemical one ( characterised by hypocalcaemia or normocalcaemia with an elevated PTH , high serum phosphate and a low vitamin D.
- Traditional plain rarely demonstrate the pathognomonic osteitis fibrosa cystica.
- Bone densitometry (DEXA scan) demonstrates osteopenia or osteoporosis.

- Neck ultrasonography is performed to identify patients with nodular hyperplasia who may be refractory to medical management.
- Localisation studies are not undertaken as minimally invasive surgery is not indicated. They are helpful in patients with recurrent disease in order to identify ectopic parathyroid tissue, especially in the mediastinum.
- In cases of recurrent disease, when there is no evidence of active disease in the neck and a previous allograft has been used to the forearm, selective venous sampling for PTH in the neck and the brachial vein on the side of the graft can be useful. This is known as the Casanova test and to prove that the recurrent disease is located in the grafted arm (graft hyperplasia) the ratio must be greater than 20:1.

# Management OF Secondary HPT

- Renal transplantation remains the only definite treatment for secondary hyperparathyroidism.
- Other therapies to provide symptom relief.
- Standard management includes replacement of calcium and vitamin D and the reduction of phosphate levels by the use of phosphate binders.
- Treatment of this disease changed radically with the introduction of calcimimetic drugs, such as cinacalcet.
- Calcimimetics alter the set point of the calcium-sensing receptor, thereby reducing the constant stimulation of the parathyroid glands and lowering the PTH level. This obviously does not address the underlying renal disease. It remains controversial as to which patients may benefit from the use of calcimimetics and which patients may benefit from earlier surgical intervention.

- Indications for pursuing medical management include those patients who are deemed non-surgical candidates by reason of medical comorbidities. Similarly, where there is persistent or recurrent disease, the origin of which cannot be clearly elucidated, surgical management should be avoided.
- However, there are definite indications for surgical intervention in secondary hyperparathyroidism , although these have been modified to reflect the current use, where available, of calcimimetics .

- There are a wide variety of operations that can be utilised for the management of secondary hyperparathyroidism, none of which appears significantly superior in terms of clinical outcomes (persistent or recurrent disease).
- These include a subtotal parathyroidectomy, a total parathyroidectomy with autograft or a total parathyroidectomy without autograft.
- Cryopreservation of resected tissue, where available, should be performed in cases of significant postoperative hypocalcaemia. The first two procedures are most widely accepted and the type of operation performed depends upon the surgeon.

- A subtotal parathyroidectomy is where three and a half parathyroid glands are excised, with the remnant being marked with a non-absorbable stitch to facilitate identification in the event of recurrent disease.
- A biopsy of the final gland that is to be left in situ is mandatory to confirm the presence of residual parathyroid tissue.
- Ideally an inferior gland is left in situ to facilitate reoperative surgery and minimise potential damage to the recurrent laryngeal nerve in that setting .
- A total parathyroidectomy with a forearm autograft involves removal of all parathyroid tissue in the neck, with reimplantation of a small amount of morcellated tissue within a pocket formed in the brachioradialis muscle.
- Overall, regardless of the operative approach utilised the cure rate ranges between 90% and 96%, with similar complication rates. A randomised study looking at 40 patients who underwent either a subtotal or total parathyroidectomy with autotransplant demonstrated no significant difference between the two operations in terms of efficacy and recurrence rate .

- The response to surgical intervention is often dramatic.
- The biochemical parameters may resolve almost immediately and appear to be sustained for up to 3 years postoperatively.
- Symptoms of improvements: (bone pain, pruritus, fatigue and depression).
- Finally, bone metabolism is improved with an approximate 10% increase in trabecular bone, with almost immediate suppression of bone resorption and acceleration of new bone formation.

## Indications for surgical intervention in secondary hyperparathyroidism.

### • Essential components

1. Persistently high serum level of intact PTH  $>500$  pg/mL
2. Hyperphosphataemia (serum  $\text{PO}_4 >6$  mg/dL) or hypercalcaemia (serum Ca  $>2.5$  mmol/L or 10 mg/dL) which is refractory to medical management
3. Estimated volume of the largest gland  $>300\text{--}500$  mm<sup>3</sup> or long axis  $>1$  cm

### • Clinical findings

If patients have one of these symptoms, parathyroidectomy should be recommended:

- Severe osteitis fibrosa with associated high bone turnover
- Subjective symptoms (bone and joint pain, arthralgia, muscle weakness, irritability, pruritus, depression) .
- Progressive ectopic calcification
  - Calciphylaxis
  - Progressive reduction in bone mineral content
- Anaemia resistant to ESA
- Dilated cardiomyopathy/cardiac failure

ESA, erythropoietin-stimulating agent; PTH, parathyroid hormone.



## Proposed indications for surgical management of secondary hyperparathyroidism (SHPT) in the era of calcimimetics.

- When SHPT is refractory to vitamin D replacement or vitamin D analogues and prolonged survival is anticipated
- Severely impaired quality of life owing to either SHPT or intolerance to calcimimetics
- When sufficient reduction in parathyroid hormone cannot be achieved with use of calcimimetics
- Thyroid surgery is also required (thyroid carcinoma)

# TERTIARY HYPERPARATHYROIDISM

Is a persistent autonomous hypercalcaemic hyperparathyroidism occurring after kidney transplantation.

A number of proposed factors may prevent involution of the hyperplastic parathyroid glands following resolution of the underlying renal impairment :

- Impaired graft function,
- Non-suppressible PTH secretion.
- Slow involution of enlarged glands .
- Insufficient calcitriol conversion by the transplanted kidney.

- The biochemical diagnosis is confirmed by an elevated total or ionised calcium, with an associated elevated or unsuppressed PTH and a reduced phosphate occurring at least 1 year post renal transplantation.
- Differentiation from PHPT can be difficult.
- Control of hypercalcaemia with minimal side effects in individual patients. Surgical intervention remains the definitive management strategy. Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation are acceptable surgical options.

# Indications for surgical intervention in tertiary hyperparathyroidism

- Subacute severe hypercalcaemia ( $>3$  mmol/L)
- Impaired graft function
- Nodular hyperplasia of the parathyroid gland(s)
- Progressive symptoms ( $>2$  years following transplantation)
  - Worsening bone disease (pain, fracture, bone loss)
  - Renal stones/nephrocalcinosis
  - Soft-tissue or vascular calcifications

# PARATHYROID CARCINOMA

- It is an indolent but progressive disease.
- It remains difficult to diagnose preoperatively as it biochemically resembles PHPT.
- Histological confirmation of a parathyroid carcinoma remains difficult. The World Health Organization criteria (2017) for the diagnosis of a parathyroid carcinoma emphasises the need for definite invasion of the surrounding soft tissue and/or metastatic disease.
- Parafibromin immunohistochemistry and immunohistochemistry for PGP 9.5. All parafibromin-negative and PGP 9.5-positive tumours should be considered for genetic screening.
- Treatment is focused on controlling hypercalcaemia and removal of the carcinoma where possible.

- Surgery remains the mainstay of treatment for primary presentations and locally recurrent disease.
- Complete resection of the tumour , avoiding spillage is vital in preventing seeding and thus recurrent disease and cervical lymph node mapping for excision.
- Complete R0 resection was thought to provide the only means of a cure (local recurrence rates ).
- Adjuvant chemotherapy has not been shown to confer a disease-free or overall survival benefit. Use of external beam radiotherapy should be considered on an individual basis.
- Metastatic spread can occur to the lungs, liver and bones. Recurrence rates range from 33% to 80% and it typically occurs in the first 3 years.
- Overall survival is reported to be 85–90% at 5 years and 49–77% at 10 years.

# PERSISTENT HYPERPARATHYROIDISM

- An elevated calcium within 6 weeks of surgical intervention, as a result of a technical error during the first operation because of either a missed adenoma or asymmetrical disease.
- For all parathyroid operations (minimally invasive parathyroidectomy [MIP] and bilateral exploration) the rate of persistent hypercalcaemia is approximately 6% in sporadic disease and between 16% and 20% in hereditary disease.

- All preoperative biochemistry, radiological imaging, intraoperative findings and pathology must be carefully reviewed.
- Investigations: repeat imaging of the neck and mediastinum is required (sestamibi, ultrasonography and 4D-CT scanning).
- Surgical intervention can be straightforward where there are intact tissue planes, such as following a minimally invasive parathyroidectomy.
- Complications (Recurrent laryngeal nerve damage and permanent hypocalcaemia), are increased when extensive previous dissection has occurred and the patient must be consented appropriately.



# **RECURRENT HYPERPARATHYROIDISM**

Hypercalcaemia occurring 6 months after surgery but with an intervening period of normocalcaemia.

## Common causes include

- Missed pathology at the first operation.
- Hyperplasia in remaining or autotransplanted tissue.
- Parathyromatosis (disseminated parathyroid tissue within the soft tissues of the neck and superior mediastinum owing to rupture of the parathyroid gland during the primary surgery. ) .
- Very rarely, the development of a second parathyroid adenoma.

- A definitive indication for surgical intervention must be present prior to embarking on localisation studies.
- Surgical intervention will be guided by the radiological imaging.
- Complication rates of recurrent laryngeal nerve damage and permanent hypocalcaemia are higher in re-operative surgery.

حَمْدُ اللَّهِ

**PRAISE BE TO ALLAH**