Parathyroid disease and calcium metabolism

R. Mihai and J. R. Farndon

Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Historical notes

The parathyroid glands were first described in 1850 at the autopsy of an Indian rhinoceros by Sir Richard Owen, conservator of the Hunterian Museum of the Royal College of Surgeons of England.[69] Thirty years later, an illustrated anatomical and histological description in animals and humans was given by Ivar Sandstrom, a medical student from Uppsala.[82] Felix Mandl in Vienna was the first to undertake parathyroid surgery in 1925, successfully removing a parathyroid adenoma in a patient with osteitis fibrosa cystica.[58] In the same period, the first American patient diagnosed with hyperparathyroidism needed seven operations before an adenoma was found in the mediastinum.[6]

Parathyroid hormone (PTH) extracts were first prepared in the early 1920s.[17] [38] The understanding of parathyroid physiology was influenced by the landmark metabolic studies of Fuller Albright in the Renal Stone Clinic or 'Quarry' at the Massachusetts General Hospital.[1] In the 1980s, PTH was sequenced, its gene[42] [99] and its receptor were cloned[84] and improved chemiluminescent immunoassays for intact PTH were developed. The recent cloning of the calcium receptor in 1993[11] opened new perspectives for understanding the regulation of parathyroid function.

Parathyroid embryology and anatomy

In all vertebrate species, the parathyroid glands are derived from the endoderm of the pharyngeal pouches.[35] Before the appearance of the thymic rudiment from the third pharyngeal pouch, its epithelium differentiates as the primordium of the inferior parathyroid gland. Parathyroid III rudiments remain connected to the thymus and are carried with it in its caudal migration. They are usually found close to the inferior thyroid poles but may descend with the thymus into the thorax or may not descend at all, remaining above the carotid bifurcation.

The superior parathyroid glands develop from the fourth pharyngeal pouches and are therefore referred to as 'parathyroid IV'. They come into relation with the lateral lobes of the thyroid gland to which they become anchored and, therefore, usually remain cranial to parathyroid III. The superior parathyroid glands are more constant in location and are usually midway along the posterior thyroid borders (where the inferior thyroid artery enters the gland or at its intersection with the recurrent laryngeal nerve).

Gilmour, after dissection of 547 cadavers, found four parathyroid glands in the majority (87%); the others had three glands (6%), two glands (0.1%) or supernumerary glands.[32]

'Classical' embryology cannot explain the involvement of the parathyroid glands in multiple endocrine neoplasia type 2 (see review by Holdsworth in this issue), where patients present with tumours of endocrine cells of neuroectodermal origin, i.e. medullary thyroid carcinomas (thyroid parafollicular C cells) and phaeochromocytomas (adrenal medulla). It has been postulated that the parathyroid glands initially contain both endodermal and ectodermal elements and that, presumably, the endodermal component predominates when the functional stage of hormone production begins.[73] Although not agreed by all,[61] the mesenchymal components of the parathyroids are considered to have ectodermal origin, similar to that from the glands arising from the pharyngeal and buccal epithelium (e.g. pituitary, thyroid, salivary).[16] Furthermore, morphological characteristics of the parathyroid glands support an ectodermal origin: immunohistochemically, normal and neoplastic human parathyroid cells exhibit neuroendocrine markers, such as neurone-specific enolase, chromogranin and dopa decarboxylase and rat parathyroid cells contain the neuroendocrine marker, protein S100.[103] Taken together with prior findings of somatostatin, gastrin and pancreatic polypeptide in human parathyroid glands,[100] it is postulated that parathyroid glands and tumours contain neural crest elements.

Overview of calcium homeostasis

Calcium is an essential element throughout the phylogenetic tree; in mammals it has important extracellular and intracellular functions (Table 1). In humans, there are about 27 000 mmol of calcium in bone contained in hydroxyapatite and only 70 mmol of calcium within intracellular and extracellular fluids. The extracellular

Table 1 Site and function of calcium in humans (adapted from 12)

Form	Locations	Mass (% of total)	Functions
Intracellular soluble	Cytosol, nucleus, endoplasmic reticulum, mitochondria	0.2 mg	Intracellular second messenger, action potentials, nerve conduction, contraction, motility, metabolic regulation, cytoskeletal function, cell division, secretion
Intracellular insoluble (sequestered)	Cytosol, nucleus, endoplasmic reticulum, mitochondria	9 g (0.9)	Structural integrity, storage
Extracellular soluble	Extracellular fluids	1 g (0.1)	Blood clotting, exocytosis, contraction, intercellular adhesion
Extracellular insoluble	Bones, teeth	~1 kg (99)	Protection, locomotion, mineral storage

calcium occurs in three forms: as non-ionized, protein-bound (approximately 50%), as calcium–anion complexes (5%) and as ionized divalent cations (approximately 45%). For this reason the albumin concentration affects the amount of total calcium and the corrected concentration is always reported (reference range 2.20–2.70 mmol litre^{-1}). It is the free (ionized) extracellular calcium concentration ($[Ca^{2+}]_{ext}$) that influences all the physiological effects.

$[Ca^{2+}]_{ext}$ is maintained within a narrow range (1.0–1.3 mM) by regulating the fluxes of Ca^{2+} into and out of the skeleton and across the epithelial cells of the kidneys and intestine. This tight control of $[Ca^{2+}]_{ext}$ is achieved despite significant fluxes of Ca^{2+} across the Ca^{2+}-regulating tissues. For example, 10 g of Ca^{2+} is filtered daily (and potentially lost) by the kidney, but 9.8 g is reabsorbed.

Two major components of the control of calcium metabolism have been defined. First, Ca^{2+} sensors on cells recognize and respond to small, physiologically meaningful changes in the $[Ca^{2+}]_{ext}$, leading to appropriate changes in cellular function. For example, in response to hypercalcaemia, parathyroid cells secrete less PTH and C cells of the thyroid secrete more calcitonin. Second, effector tissues (intestine, kidney and bone) respond to calciotropic hormones with changes in the transport of ions, to restore $[Ca^{2+}]_{ext}$ to normal.

Calcium homeostasis is controlled by vitamin D and the hormones PTH and calcitonin.

Parathyroid hormone

PTH plays a central role in the rapid control of calcium homeostasis. Its co-ordinated actions on bone, kidney and intestine increase the flow of calcium into the extracellular fluid and increase the concentration of calcium in blood. PTH is an 84 amino acid peptide with a molecular weight of 9500 Da and a short half-life (2–3 min) in the circulation before being cleaved into an amino-terminal fragment (amino acids 1–34) and a carboxy-terminal fragment. Only the 1–34 fragment retains biological activity. PTH binds to specific receptors on the membrane of target cells: renal and bone cells, fibroblasts, chondrocytes, vascular smooth muscle, adipocytes and placental trophoblasts.[12]

Effects of PTH on the kidney

The distribution of PTH receptors and that of Ca^{2+} receptors overlap in the distal nephron,[76] allowing $[Ca^{2+}]_{ext}$ to have a direct effect (through action on Ca^{2+} receptors) and an indirect influence (through modulation of plasma PTH concentrations) on the renal component of calcium homeostasis. The intracellular mediator for PTH effects is intracellular cyclic adenosine monophosphate (cAMP), whose urinary secretion is a biochemical marker of PTH activity. The effects of PTH on the kidney include:

(i) Increased extraction of Ca^{2+} from the glomerular filtrate. The major physiological effect of PTH is enhancement of Ca^{2+} reabsorption. This is due to effects on: the thick ascending loop of Henle (it increases the transepithelial voltage gradient that drives passive Ca^{2+} transport); the granular portion of the distal convoluted tubule (it induces translocation of preformed Ca^{2+} channels on the cell surface to enhance luminal Ca^{2+} entry); and the collecting tubules (it enhances the activity of Na^+/ Ca^{2+} exchangers). Despite its direct effect of increasing Ca^{2+} reabsorption, excessive PTH secretion increases urinary Ca^{2+} excretion because of the high load of filtered Ca^{2+} resulting from hypercalcaemia. At any given Ca^{2+} load, Ca^{2+} clearance is decreased by PTH and increased in the absence of PTH.

(ii) Increased phosphate excretion. PTH acts on the proximal and distal convoluted tubules and inhibits Na^+-dependent phosphate transport.

(iii) Increased bicarbonate clearance and alkalinization of the urine result from inhibition of bicarbonate reabsorption in the proximal renal tubule. In patients with primary hyperparathyroidism, excessive secretion of PTH leads to a type of renal tubular acidosis.

(iv) Increased free water clearance and increased urinary flow. Inhibition of Na^+ reabsorption in the proximal tubule leads to an increase in Na^+ loading of the distal tubule. At this point, Na^+ is reabsorbed proportionally more than the associated water, leading to an increase in free water clearance.

(v) Increased activity of vitamin D1α hydroxylase.

(vi) In primary hyperparathyroidism, the renal effects of PTH are observed as hypercalciuria, hypophosphataemia, hyperchloraemic acidosis, polyuria, polydypsia and an increased excretion of nephrogenous fraction of cAMP.

Effects of PTH on the bone

PTH produces both anabolic and catabolic effects which can be distinguished as early phase (mobilization of Ca^{2+} from bone in rapid equilibrium with the extracellular fluids) and late phase (increased synthesis of bone enzymes, such as lysosomal enzymes which promote reabsorption and bone remodelling).

Osteoblasts are probably the primary bone cells that interact directly with PTH while osteoclasts seem to be devoid of PTH receptors. PTH inhibits osteoblasts and stimulates osteoclast-mediated bone resorption, leading to an increase in alkaline phosphatase and increased urinary hydroxyproline (markers of increased breakdown of bone matrix). In primary hyperparathyroidism, changes in alkaline phosphatase and hydroxyproline are markers of bone disease.

Effects of PTH on the intestine

PTH does not directly affect gastrointestinal absorption of Ca^{2+}. Its effects are mediated indirectly through regulation of synthesis of $1,25(OH)_2D_3$ in the kidney.

Other effects

Studies *in vitro* have identified effects whose physiological significance is not yet understood, including changes in blood flow in the coeliac axis, enhanced lipolysis in adipocytes and increased gluconeogenesis in liver and kidney.

Calcitonin

Calcitonin is a 32 amino acid protein secreted by the parafollicular C cells of the thyroid in response to high $[Ca^{2+}]_{ext}$. It induces a decrease in serum calcium by inhibiting osteoclast activity and by increasing urinary excretion of Ca^{2+}. Its exact physiological role in humans is uncertain since it has few long-term effects on serum calcium. Its complete absence following total thyroidectomy needs no replacement and severe excess of calcitonin (such as in patients with medullary thyroid carcinomas) has no major effect on calcium metabolism.

Control of parathyroid hormone secretion

Extracellular calcium

$[Ca^{2+}]_{ext}$ is the major determinant of the rate of PTH secretion: slight reductions in $[Ca^{2+}]_{ext}$ increase promptly the rate of PTH secretion. The magnitude and duration of hypocalcaemic stress has a significant effect on the manner in which the homeostatic system responds. The initial changes in rate of PTH secretion in response to low $[Ca^{2+}]_{ext}$ take place within seconds because of the release of preformed hormones from storage granules. Within 15–30 min, there is also an increase in the net rate of PTH synthesis. If the hypocalcaemic stimulus persists, modest increases in the amount of PTH mRNA take place (in 3–12 h in rats *in vivo* or within 1–2 days in bovine parathyroid cells *in vitro*). Prolonged hypocalcaemia promotes parathyroid cellular hypertrophy and proliferation within days to weeks (data reviewed in reference 74). The inverse sigmoidal relationship between PTH secretion and $[Ca^{2+}]_{ext}$ has been documented *in vivo* and *in vitro* and can be described using a four-parameter model.[9] In addition to its effect on PTH secretion, $[Ca^{2+}]_{ext}$ modulates the synthesis of PTH and the intracellular degradation of PTH into smaller fragments.

In 1991, Brown thought that a body of indirect evidence suggested that $[Ca^{2+}]_{ext}$ acted on parathyroid cells through a cell surface, receptor-like mechanism.[10] A plasma membrane Ca^{2+} receptor was subsequently cloned from bovine parathyroid cells[11] and its presence demonstrated on human cells from parathyroid adenomas.[30] This was the first example of a cell surface receptor recognizing an ion rather than a molecule as a principal ligand. The current knowledge about Ca^{2+} receptor intracellular signalling is summarized in Fig. 1.

The human Ca^{2+} receptor is encoded by a gene on chromosome 3q13-21 and consists of 1078 amino acids. The predicted Ca^{2+} receptor protein has a large extracellular amino-terminus (which binds polycationic Ca^{2+} receptor agonists), a central core with seven membrane-spanning helices (documenting that the Ca^{2+} receptor is a G-protein-coupled receptor) and an approximately 200 amino acid carboxy-terminal intracytoplasmic tail.[11 12] Over 30 different mis-sense mutations have been identified in kindreds with familial hypocalciuric hypercalcaemia.[72] Mutations that activate the Ca^{2+} receptor have also been identified and lead to familial hypoparathyroidism. A knock-out mouse model of inherited human Ca^{2+} receptor gene defects has been reported: heterozygous animals (i.e. Ca^{2+} receptor$^{+/-}$) reproduce most features of familial hypocalciuric hypercalcaemia and homozygous mutant mice (i.e. Ca^{2+} receptor$^{-/-}$) display markedly elevated $[Ca^{2+}]_{ext}$, increased PTH concentrations and parathyroid gland hyperplasia, as do patients with severe neonatal hyperparathyroidism.[45]

The Ca^{2+} receptor is widely expressed, both on cells involved with control of $[Ca^{2+}]_{ext}$ (e.g. parathyroid, calcitonin-secreting and bone cells) and also on cells not involved in Ca^{2+} homeostasis (e.g. pituitary, placenta, keratinocytes and gastrin-secreting cells).

A different membrane Ca^{2+}-sensor has been identified on parathyroid, proximal tubule and human placenta using immunocytochemistry.[49] This approximately 500 kDa protein is a member of the low density lipoprotein receptor
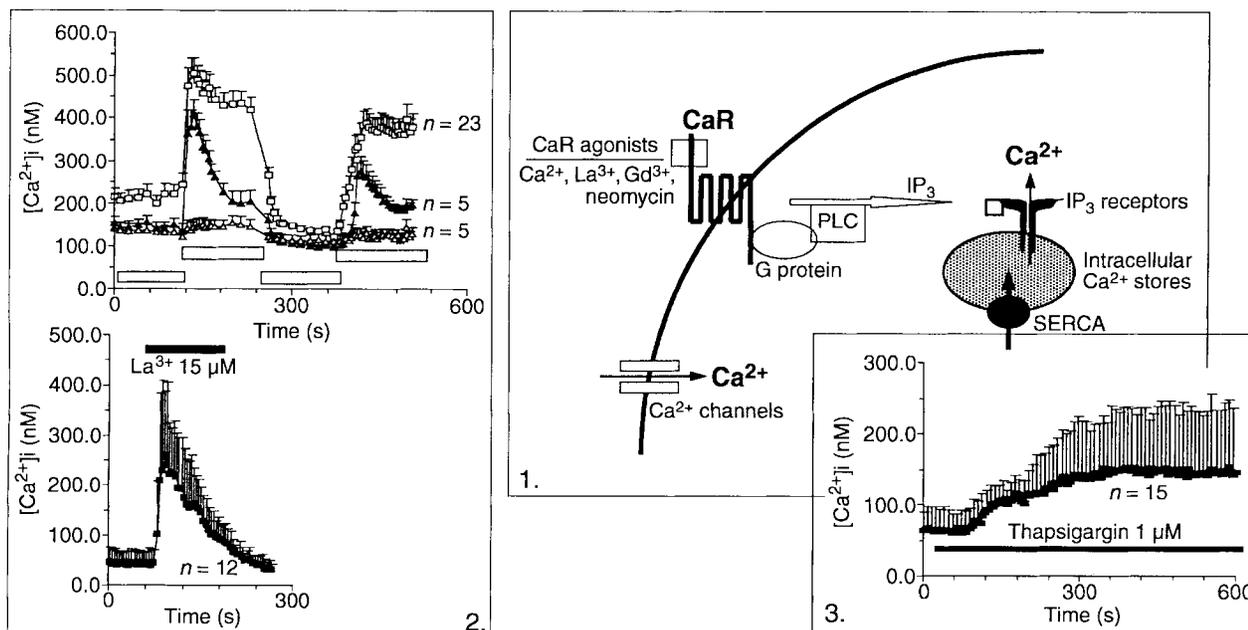
Fig 1 (1) Schematic representation of the Ca^{2+} receptor's signalling mechanisms. Ca^{2+} receptor agonists bind to the extracellular domain of the Ca^{2+} receptor and trigger activation of the G protein–phospholipase C (PLC) pathway. PLC generates inositol-trisphosphate (IP_3), which binds to specific receptors situated on intracellular Ca^{2+} stores. Upon binding of IP_3 the three-dimensional structure of IP_3 receptors changes and allows the release of Ca^{2+}. The responsiveness of IP_3 receptors modulates the amplitude of $[Ca^{2+}]_i$ responses following activation of the Ca^{2+} receptor.[63] The filling state of the intracellular Ca^{2+} stores is maintained by the action of specific Ca^{2+} pumps, i.e. the smooth endoplasmic reticulum Ca^{2+}-ATPases (SERCA). (2) The graphs illustrate changes in cytoplasmic concentration of calcium ($[Ca^{2+}]_i$) in parathyroid cells. $[Ca^{2+}]_i$ was measured using quantitative fluorescent microscopy in Fura-2-loaded cells. The upper panel illustrates responses to changes in $[Ca^{2+}]_{ext}$ from 0.5 to 3 mM. The lower panel illustrates $[Ca^{2+}]_i$ responses to the Ca^{2+} receptor agonist lanthanum (La^{3+}; 15 μM). (3) $[Ca^{2+}]_i$ increases rapidly following incubation with thapsigargin, an inhibitor of SERCA.

superfamily[59] and has recently been cloned.[44] Its role in controlling $[Ca^{2+}]_i$ and PTH secretion requires further study.

Magnesium

In acute studies *in vivo* and *in vitro*, changes in the extracellular concentration of magnesium ($[Mg^{2+}]_{ext}$) have similar effects to changes in $[Ca^{2+}]_{ext}$. As Mg^{2+} is a much less potent Ca^{2+} receptor agonist[11] and because the blood concentration is lower than that of Ca^{2+}, changes of $[Mg^{2+}]_{ext}$ in the physiological range have little influence on PTH secretion.

High $[Mg^{2+}]_{ext}$ (as in renal failure) can inhibit PTH secretion. Chronic severe hypomagnesaemia causes a paradoxical decrease in PTH secretion rather than the expected increase, suggesting that intracellular Mg^{2+} deficiency interferes with secretory mechanisms and blocks PTH secretion.[2]

Vitamin D

The main effect of vitamin D is a specific, dose-dependent and reversible suppression of PTH gene transcription.[80] Furthermore, 1,25-$(OH)_2D_3$ suppresses the secretory process at low $[Ca^{2+}]_{ext}$ and increases the intracellular degradation of PTH.

Catecholamines

The responsiveness of normal parathyroid tissue to β-adrenergic agonists is well established, but the role of catecholamines in the pathophysiology of the glands is undefined.

Specific α-adrenergic agonists inhibit PTH secretion *in vitro* but have little effect *in vivo*. Epinephrine increases PTH secretion by acting on β-adrenergic receptors. The response is transient and is influenced by $[Ca^{2+}]_{ext}$: minimal effects occur during hypercalcaemia whereas the response becomes more dramatic as the $[Ca^{2+}]_{ext}$ is lowered. β-Adrenergic antagonists (propranolol) reduce PTH concentrations acutely in normal subjects. Propranolol neither modulates basal output nor inhibits isoproterenol-induced secretion from forearm autografts of hyperplastic parathyroid tissue, suggesting an altered responsiveness to β-adrenergic agents in patients with secondary hyperparathyroidism.[25] Dopamine stimulates secretion from bovine parathyroid glands *in vitro* and *in vivo* by releasing a storage pool of intact PTH, but no effect has been documented in humans.

Steroids

Glucocorticoids stimulate PTH release *in vitro* in a dose-dependent manner.[89] Oestrogen and progesterone stimulate

PTH secretion from bovine parathyroid cells. Furthermore, oestrogen may modulate the sensitivity of PTH secretion to regulation by $[Ca^{2+}]_{ext}$,[8] directly stimulate PTH gene transcription and secretion and reduce peripheral actions of PTH.[48]

Ultradian rhythms of PTH secretion

Narrow pulses (half-life <60 s) and bursts of narrow pulses of PTH secretion can be detected, but the time-keeping mechanism has not been identified. The pulsatile component of PTH secretion accounts for 25% of total release.[81] During induced hypocalcaemia, a brisk increase in plasma PTH appears in the first 30 min, with a preferential increase in the pulsatile component of secretion (>10-fold) through increased frequency and amplitude of secretory bursts. The tonic secretion increases only during steady-state hypocalcaemia. Secretory bursts disappear during the initial 30 min of induced hypercalcaemia and reappear in the subsequent 75 min with a decreased frequency and amplitude.[83]

Primary hyperparathyroidism

Epidemiology

Primary hyperparathyroidism is a common endocrine disorder, with an incidence influenced by the means of diagnosis and the population studied. The increased use of multichannel biochemical analysers has influenced the pattern of presentation. In the UK the incidence was estimated to be about 25 per 100 000 general population, the majority of subjects being asymptomatic.

Aetiology

Most patients have a single parathyroid adenoma (80%); multiple gland hyperplasia is found in 10–20% of patients and parathyroid carcinoma is rare (1%). Monoclonality occurs in parathyroid adenomas[3 29] and can be found in sporadic multigland hyperplasia[23] and familial multiple endocrine neoplasia (MEN) type 1.[28 91] At least three tumour-specific molecular genetic defects are implicated in the development of parathyroid tumours:

Cyclin D1
Some parathyroid adenomas present a clonal chromosomal inversion by which the 5′-regulatory region of the PTH gene (normally located at chromosomal position 11p15) is juxtaposed to the PRAD1/cyclin D_1 oncogene located at 11q13.[65 78] This rearrangement leads to overexpression of the cyclin D_1 oncogene, a cell cycle regulator overexpressed in many types of cancer.[5]

Loss of a tumour suppressor gene
This has been suggested by the loss of heterozygosity in >25% of parathyroid adenomas on chromosome arms 1p, 6q, 11p, 11q and 15q.[90] None of these tumour suppressor genes has yet been identified and cloned. The tumour suppressor gene p53 shows no mutations in parathyroid adenomas or carcinomas[36] and allelic loss of the p53 gene has been identified in only a minority of carcinomas.[18]

Retinoblastoma gene deletion
This occurs commonly in parathyroid carcinomas and has potential diagnostic, prognostic and therapeutic implications.[19]

As many as 15–20% of patients with primary hyperparathyroidism gave a history of previous irradiation but an aetiological relationship cannot be established in individual cases. Analysis of a cohort (2555 patients, follow up 36 years) identified a dose–response relationship, with an excess relative risk increased significantly by 0.11/centigray and not influenced by gender or age at first presentation.[85]

Mechanisms for functional abnormalities in primary hyperparathyroidism

Different mutations identified in parathyroid adenomas may explain the abnormal growth or proliferation of parathyroid cells but do not account for the disordered function in primary hyperparathyroidism. PTH secretion in primary hyperparathyroidism is not influenced by changes in calcium within the physiological range because of a decreased sensitivity to $[Ca^{2+}]_{ext}$, which results in a shift to the left of the sigmoidal relationship and therefore a higher set-point. A specific abnormality of the mechanism(s) controlling secretion in individual adenomatous cells is suggested by the general lack of correlation between the size of the tumour and the severity of biochemical abnormalities (i.e. PTH concentration and hypercalcaemia) (Fig. 2). Overall, the excessive PTH secretion is the result of increased basal secretion and increased frequency and amplitude of PTH pulses.[39]

A tempting hypothesis is that, in sporadic parathyroid tumours, there are defects in the gene encoding the recently cloned Ca^{2+} receptor.[11] However, no such mutations have been identified in such patients[46] and allelic loss appeared in <10% of tumours.[93] The role of mutations in the Ca^{2+} receptor gene in the pathogenesis of primary hyperparathyroidism, therefore, remains controversial.

The role of vitamin D in the pathogenesis of primary hyperparathyroidism has been investigated extensively. Preoperative serum calcitriol concentrations correlate inversely with calcitriol receptor number in normal parathyroid tissue but not in parathyroid adenomas.[97] Vitamin D receptor (VDR) gene polymorphism could also be important: 60% of postmenopausal women with primary hyperparathyroidism express the VDR genotype *bb*, compared with 33.3% in controls. As the *b* allele has been linked to decreased transcriptional activity or messenger RNA stability, the *bb* genotype will reduce VDR expression, which may impede regulatory actions of vitamin D and contribute to parathyroid tumorigenesis.[13]
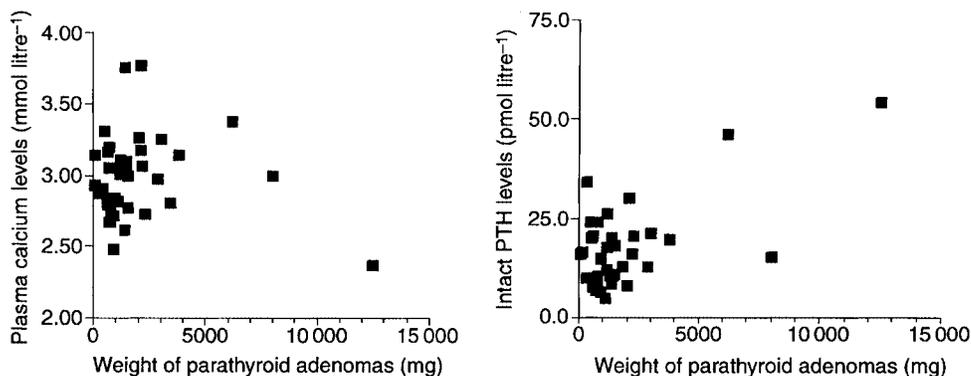
Fig 2 Lack of correlation between the weight of parathyroid adenomas and the biochemical abnormalities. In 37 patients with primary hyperparathyroidism, the weight of parathyroid adenomas was determined immediately after surgical removal. Preoperative values for calcium (corrected for albumin concentration) and PTH were recorded. Intact PTH (1–84) was measured using a chemiluminescent assay (Immulite, DPC, Gwynedd, UK; coefficient of variance 4.7% and 5.5% for intrassay and interassay precision, respectively).

Clinical picture of primary hyperparathyroidism

The classical picture of 'moans, groans and stones' is rarely seen today. Instead, many non-specific symptoms may be elicited on direct questioning. The assessment and assignment of these symptoms provide a major problem, especially in the elderly.

Asymptomatic HPT

Currently most patients present with no or minimal symptoms. When no treatment is offered to these patients, follow-up for 10 yr reveals that most deteriorate (in one study, 26% developed a need for surgery and 24% died[86]). The arguments for offering surgical treatment to asymptomatic patients are presented later.

Renal manifestations

Renal involvement used to occur in 60–70% of patients but early diagnosis has reduced the incidence to 10–20% and many patients now lack renal manifestations despite having had the disease for many years.

Anatomical (nephrolithiasis and nephrocalcinosis) and functional (a spectrum of tubular and glomerular disorders) abnormalities occur. In severe primary hyperparathyroidism, impairment of proximal tubular function causes proximal tubular acidosis type II, aminoaciduria, glycosuria and nephrogenous diabetes insipidus. Functional changes can occur in the absence of any radiographic demonstrable renal calcification.

The pathogenesis of nephrolithiasis remains unclear since hypercalciuria does not correlate directly with stone formation. The propensity for crystallization and crystal growth of stone-forming constituents of urine is increased by urinary acidosis (i.e. PTH effects on bicarbonate transport in the proximal tubule).

Skeletal involvement

The incidence of osteitis fibrosa cystica has decreased sharply from >50% in the 1930s to the 1950s to 9% in the 1970s and to nearly zero in patients diagnosed by screening.

Furthermore, patients with mild disease have already experienced major bone loss at diagnosis and, although parathyroidectomy has an initial positive effect on bone mineralization, there is no long-term advantage.[21] Increased bone resorption is associated with enhanced bone formation. There are region-specific differences in bone mass: it is low in areas with cortical bone (such as the radius) and normal or high in vertebrae and iliac crest (trabecular bone). Pathological fractures and brown tumours are now rare.

Articular manifestations

Chondrocalcinosis, pseudogout, juxta-articular erosions, traumatic synovitis, periarthritis and pericapsular calcification can occur.

Neuromuscular and neuropsychiatric manifestations

The real incidence of these symptoms is difficult to evaluate because some are so non-specific. Extreme weakness and fatigue, particularly involving proximal musculature of the lower extremities, can be present and improves postoperatively. Depression, personality changes, memory impairment and, occasionally, overt psychosis can occur. Obtunded consciousness occurs only when the serum calcium is extremely elevated.

Gastrointestinal involvement

Peptic ulcer can be a true manifestation of primary hyperparathyroidism and in a minority of patients, ulcers are part of Zollinger–Ellison syndrome or MEN1 with gastrin-producing tumours. However, it is not worth screening for MEN1 syndromes in patients with apparently sporadic primary hyperparathyroidism.[24]

Pancreatitis may also occur but a cause–effect relationship is uncertain. In acute primary hyperparathyroidism, 25% of patients may have pancreatitis. Normocalcaemia in a patient with severe acute pancreatitis should raise the question of primary hyperparathyroidism as an aetiological factor since pancreatic saponification and calcium binding can produce a spuriously low serum calcium concentration.

Table 2 General symptoms found in patients with primary hyperparathyroidism

System affected	Symptoms
Renal	Polyuria, back pain, colic, haematuria
Musculoskeletal	Aches and pains, bone pain, arthritis, 'pathological' fractures
Gastrointestinal	Anorexia, nausea, dyspepsia, constipation, abdominal pain
Neurological	Depression, weakness, apathy, lethargy, confusion, psychosis
Cardiovascular	Hypertension

Table 3 Differential diagnoses of hypercalcaemia

Primary hyperparathyroidism	
Malignancy	
haematogenous malignancy	Multiple myeloma, Burkitt lymphoma, Hodgkin lymphoma
solid malignancy with bone metastasis	Breast, lung
solid malignancy without bone metastasis	Hypernephroma, squamous carcinoma
Granulomatous diseases	Sarcoidosis, tuberculosis
Iatrogenic	Thiazide diuretics, lithium, vitamin D intoxication, hypervitaminosis A
Familial hypocalciuric hypercalcaemia	

Hypertension

This is more frequent in patients with primary hyperparathyroidism than in the general population.[54] Efforts to identify a parathyroid-derived hypertensive factor continue. Parathyroidectomy has little or no effect on the severity of the hypertension.

Increased risk of premature death

Although an overall biochemical cure rate of 97% can be achieved in patients undergoing surgery, a study of 896 patients revealed a decreased risk of premature death and better survival for those operated upon at an early stage of disease. It is possible to derive a mathematical function to correlate the estimated hazard for death in relation to gender, age and tumour weight.[41]

Normocalcaemic hyperparathyroidism

Patients with symptoms or complications of primary hyperparathyroidism but presenting with normocalcaemia represent a diagnostic challenge.[64] Most such patients present with a renal calculus and many will have hypercalciuria. They need to be differentiated from those with idiopathic hypercalciuria (increased intestinal Ca^{2+} absorption, diminished tubular resorption of Ca^{2+} resulting in a renal leak or a primary urinary phosphate leak). Identifying patients with normocalcaemic primary hyperparathyroidism is important because surgery should reduce the chance of further stone formation. Failure to consider these other causes and assuming that the patients has normocalcaemic primary hyperparathyroidism will lead to inappropriate neck exploration.

Hypercalcaemic crisis

The severity of clinical manifestations frequently correlates with the degree of hypercalcaemia. Neuromuscular, renal and gastrointestinal manifestations are influenced by the time course of developing hypercalcaemia and intercurrent medical conditions.

Marked dehydration results in anorexia, nausea and vomiting and leads to even more severe hypercalcaemia. Weakness and lethargy lead to immobility, which may accentuate increased bone resorption. Profound mental changes, confusion, cognitive impairment and coma are possible. If untreated, the process evolves to oliguric renal failure, cardiac arrhythmia and death.

Assays for PTH1–84 completely separate individuals with primary hyperparathyroidism (having high or non-inhibited PTH concentrations) from other causes of hypercalcaemia (with low or undetectable PTH levels). As a general rule, the higher the concentrations of plasma calcium, the more likely that malignancy is the underlying cause.

Differential diagnosis of hypercalcaemia

The main differential diagnoses of hypercalcaemia are summarized in Table 3. Other causes that used to be considered but are rare now include: milk-alkali syndrome, immobilization associated with fractures, acute renal failure and other endocrine diseases (thyrotoxicosis, phaeochromocytoma and adrenal crisis).

The majority of patients with acute primary hyperparathyroidism have long-standing hypercalcaemia, large parathyroid adenomas, radiographic evidence of osteitis fibrosa cystica (50%) and a history of nephrolithiasis (60%).[27] Ectopic secretion of PTH has been demonstrated only very rarely (e.g. in ovarian carcinoma).

Investigations used to confirm primary hyperparathyroidism

Biochemical features of primary hyperparathyroidism

These include (i) high total serum calcium (corrected for albumin) or elevated serum ionized calcium; (ii) hypophosphataemia, phosphaturia; (iii) hyperchloraemia and increased chloride:phosphate ratio (see above); (iv) hypercalciuria (>10 mmol/day) is present in >75% of hypercalcaemic patients (excess calcium spillage supports a diagnosis of primary hyperparathyroidism but, more importantly, loss of <2 mmol of calcium per day suggests a diagnosis of familial hypercalcaemic hypocalciuria; this autosomal dominant disease may mimic primary hyperparathyroidism very closely, with normal levels of parathyroid hormone which are judged to be inappropriate in the face of

Table 4 Therapeutic options adapted to the severity of disease[7]

Degree of hypercalcaemia Mild (2.6–2.85 mM)	Moderate (2.85–3.30 mM)	Severe(>3.30 mM)
Symptomatic patients (50%): surgery Asymptomatic patients (50%): mobilize; keep well hydrated; include moderate amount of calcium in diet; give oestrogens to menopausal women; give oral clodronate	Surgery	Emergency medical treatment followed by surgery

hypercalcaemia. A repeat urinary calcium determination, enquiry into family history and measurement of the serum calcium in first-degree siblings will confirm the correct diagnosis and save the patient an unnecessary neck exploration); (v) increased concentration of intact PTH: high or non-inhibited PTH concentration in the face of hypercalcaemia is diagnostic of primary hyperparathyroidism. Care is required in its interpretation, especially if there is any evidence of renal failure. In this situation the carboxy-terminal, biologically inactive, PTH fragments may accumulate and give a falsely reassuring weight to the diagnosis; (vi) increased serum alkaline phosphatase and increased urinary excretion of cyclic adenosine monophosphate and hydroxyproline can be demonstrated as markers of bone involvement.

Radiological investigations
(i) Parathyroid imaging: the advantage and cost-effectiveness of preoperative localization and unilateral neck exploration in primary hyperparathyroidism are controversial issues. Some surgeons favour such an approach because unilateral exploration may save approximately 30 min of operating time and decrease the risk of damaging the contralateral recurrent laryngeal nerve and normal parathyroid glands.[101] Others report unacceptably high failure rates for unilateral neck exploration compared with a bilateral neck exploration by an experienced surgeon and question the cost-effectiveness of preoperative localizing studies.[43 105]

(ii) Imaging of bone lesions: hand x-ray may demonstrate early subperiosteal erosion on the radial aspect of the middle phalanges and, in advanced disease, generalized demineralization is seen, with local cystic destructive lesions, such as 'salt and pepper' skull. Changes in bone density can be studied by ^{125}I bone densitometry, x-ray spectrophotometry or single-photon absorptiometry. Bone mass can be evaluated by single- and dual-photon absorptiometry, quantitative CT and dual-energy x-ray absorptiometry (DEXA scan). In many patients there is an initial rapid loss in bone mass followed by a period of stable disease with little progression at the time of diagnosis of primary hyperparathyroidism.

Treatment of primary hyperparathyroidism
For many years, the management options have been adapted to the severity of primary hyperparathyroidism (Table 4)

and surgery was considered clearly recommended for patients with symptomatic primary hyperparathyroidism, for younger patients and for those in whom consistent long-term follow-up could not be assured. The current trend is to recommend parathyroidectomy for all patients with a definite diagnosis of primary hyperparathyroidism (see below).

Medical treatment
Hypercalcaemic crisis treatment involves (i) rehydration: 4–6 litres of fluid are often required to restore normal fluid volumes in the first 24 h. This increases calcium excretion by 25–75 mEq day^{-1} but rarely normalizes serum calcium if used alone; (ii) forced saline diuresis: loop diuretics depress the proximal tubular reabsorption of calcium and can increase urinary calcium excretion by 200–250 mEq day^{-1}. Furosemide (40 mg i.v. every 4 h) should not be initiated until volume repletion has been achieved. The risks of forced diuresis include cardiac decompensation (central venous pressure monitoring is needed for some patients), hypophosphataemia, hypokalaemia and hypomagnesaemia; (iii) antiresorptive agents: bisphophonates (pamidronate, etidronate, clodronate) are now first-line treatment because of their rapid and longer-lasting effect; (iv) calcitonin: salmon, porcine and human calcitonin rapidly decrease the skeletal release of calcium and phosphorus but the effects are temporary and not usually significant.

Dialysis is reserved for patients with renal failure. Peritoneal dialysis can remove 100–500 mEq of calcium in 24 h, and haemodialysis approximately 70 mEq h^{-1}.

Glucocorticoids are not effective in primary hyperparathyroidism but may be useful in treating patients with myeloma, lymphoma or granulomatous diseases (increased vitamin D production by activated macrophages in granulomas) or with vitamin D intoxication. Intravenous phosphate therapy is dramatically effective but is seldom indicated because of serious potential hazards associated with precipitation of calcium phosphate.

Somatostatin may reduce hypercalciuria[58] but in a controlled, prospective, blinded, randomized clinical trial, a single i.v. application of 200 μg of the somatostatin analogue octreotide (SMS 201-995, Sandostatin) failed to induce any significant changes in serum calcium, phosphate, parathyroid hormone, calcitonin or osteocalcin.[40]

The recent cloning of the Ca^{2+} receptor has triggered efforts to develop drugs which could increase the affinity of Ca^{2+} receptor for $[Ca^{2+}]_{ext}$ and thereby potentially correct

the biochemical abnormalities in primary hyperparathyroidism. One such compound is NPS R-568, an allosteric modulator of the Ca^{2+} receptor that potentiates the effects of cation agonists on Ca^{2+} receptors.[37] Pharmacological activation of Ca^{2+} receptors *in vivo* with NPS R-568 inhibits PTH secretion. In clinical studies, NPS R-568 inhibited PTH secretion in healthy postmenopausal women. A randomized, placebo-controlled, double-blinded trial concluded that single and increasing doses of NPS R-568 (20–160 mg) inhibit PTH secretion by <70% for <4–8 h in postmenopausal women with mild primary hyperparathyroidism.[87] Clinical trials to establish the therapeutic potential of this Ca^{2+} receptor agonist are in progress. Two years of treatment of a woman with hypercalcaemia secondary to parathyroid carcinoma with NPS R-568 produced no adverse clinical effects and the drug appeared effective in long-term control of hypercalcaemia.[16]

Surgical treatment for primary hyperparathyroidism

Once the biochemical diagnosis is confirmed, neck exploration can be undertaken since the use of imaging techniques provides no benefit in patients with primary hyperparathyroidism attending for first exploration. Patients must be informed about the risk of damage to the recurrent laryngeal nerve (should be <0.5%) and normal parathyroid glands (should be almost zero) and the possibility of failure to identify the parathyroid adenoma (perhaps 1%, due to intrathoracic or ectopic tumour, or wrong diagnosis).

For parathyroid adenomas, because of the possibility of double adenomas, several methods have been proposed to ensure complete excision of the excess PTH source, including measurement of urinary cAMP or rapid intraoperative serum PTH concentrations.[96]

Sporadic multiple gland hyperplasia requires excision of the enlarged glands, leaving the normal sized glands intact,[92] excision of three or three and a half glands has also been recommended.[34]

If parathyroid carcinoma is suspected preoperatively (suggestive features on CT scan or palpable lymphadenopathy), *en bloc* resection offers the best results with central compartment dissection when there is evidence of regional node metastases.

A recent report of 286 patients with parathyroid carcinomas followed for 10 yr concluded that neither tumour size nor lymph node status was a significant prognostic factor.[47] Serum calcium and PTH measurements are postoperative markers of tumour recurrence. Recurrence in the neck or lungs can often be treated by further surgery and, although rarely curative, appears to prolong survival and palliate the symptoms of hypercalcaemia.[98] Radiotherapy is of little use. Mithramycin is a potent hypocalcaemic agent which is often effective for many months; more recently, symptomatic relief has been obtained by using disodium clodronate. The outlook is variable and, as with many endocrine tumours, some patients survive for many years with indolent metastatic disease.

It is now accepted that, for many asymptomatic patients, the time and expense involved in rigorous follow-up outweigh the burden of surgery. Further arguments in favour of parathyroidectomy for patients with absent, minimal or unrecognized symptoms of primary hyperparathyroidism are:[88] (i) subtle physical and psychological changes are only appreciated on restoration of biochemical normality; (ii) there is a risk of developing renal impairment in the long term; (iii) there is a risk of bone loss, which is especially important in elderly females; (iv) hypercalcaemia may contribute to confusion in the elderly; (v) there is a risk of hypercalcaemic crisis in the elderly, especially if there is intercurrent illness, producing dehydration; (vi) the incidence and mortality from cardiovascular disease are greater in untreated patients.

When surgery is contemplated in such patients, the preoperative risk factor profile is altered. These patients are more likely to be receiving antihypertensive medication and frequently have a history of congestive heart disease, ST-segment depression and T-wave abnormalities on ECG, thromboembolic disease, stroke or diabetes mellitus.[55]

Serum calcium need not be checked until 24 h after surgical treatment for primary hyperparathyroidism.[102] Serum PTH concentrations return to within the normal range after 24–48 h; the increased set-point is normalized on the first postoperative day; and the suppression of PTH concentrations during an oral calcium load is normalized on the second postoperative day.

The British Association of Endocrine Surgeons is producing guidelines which will recommend uniform collection of endpoint data for comparative audit, which will include: percentage of patients achieving normocalcaemia at 12 months, recurrent laryngeal nerve injuries (%) and incidence of drug-dependent hypocalcaemia at 12 months. The number of negative operations and reoperative rates will also be measured.

Persistent hyperparathyroidism is the commonest cause of postoperative hypercalcaemia and is defined as hypercalcaemia in the immediate postoperative period or occurring within 1 yr of surgery. Recurrent hyperparathyroidism is defined as hypercalcaemia occurring after a normocalcaemic phase of ≥1 yr after an operation that identified all four parathyroid glands and removed all abnormal parathyroid tissue.

Secondary hyperparathyroidism

Secondary hyperparathyroidism is the condition in which PTH secretion is increased to compensate for a chronically low concentration of calcium (Table 5) with no intrinsic parathyroid abnormality. Most patients with chronic renal failure develop some degree of parathyroid hyperplasia: the prevalence has been evaluated at 67% using a bone biopsy technique.[57] Largely as a result of improved and early

Table 5 Possible causes of secondary hyperparathyroidism

Chronic renal failure
Rickets
    vitamin D deficiency
    vitamin D resistance syndromes
    renal tubular phosphate-wasting disorders
Osteomalacia
Malabsorption
Pseudohypoparathyroidism
Complication of high-dose phosphate therapy in patients with X-linked
hypophosphataemia

medical treatment (calcium and vitamin D replacement therapy), <5% of these patients eventually require parathyroidectomy.[20]

Mechanisms of secondary hyperparathyroidism

In early renal failure, deficient calcitriol synthesis is an important factor but a reduced number of vitamin D receptors[51] or of the newly cloned Ca^{2+}-sensor receptor, may also be present in the parathyroid cells. With advanced chronic renal failure, hyperphosphataemia worsens the condition. Parathyroid cells are resistant to calcitriol because of a reduced density of calcitriol receptors. Finally, uraemia *per se* may not only cause a receptor abnormality in parathyroid cells but may also aggravate the impaired calcaemic response to PTH in the skeleton.[56]

In vivo dynamic tests of parathyroid gland function suggest that calcium-regulated PTH release does not differ with the degree of disease and that set-point abnormalities do not account for excess PTH secretion. Variations in the size of the parathyroid gland may therefore be the major contributor to excessive PTH secretion.[33]

Clinical presentation of secondary hyperparathyroidism

The vast majority of patients are on dialysis and present with a highly variable frequency and severity of symptoms. Patients develop osteitis fibrosa cystica or osteomalacia, which may eventually lead to skeletal deformities or fractures. Physical findings may include a funnel chest deformity and sternal bowing due to rib deformities, and height reduction from kyphosis and vertebral crush fractures. Bone pain occurs primarily in the thoracolumbar spine and lower extremity and is exacerbated by weight bearing, sudden movements and pressure. Subperiosteal bone resorption is seen in <86% of patients, especially in the phalanges, pelvis, distal clavicles, ribs, femur, mandible or skull. The earliest radiographic lesion seen is an irregularity of the radial aspect of the second digit middle phalanx. In a patient maintained on dialysis with appropriate medical treatment, radiographic findings of bone disease should serve as an indication for operation. Osteomalacia is now seen only rarely, thanks to better attention to prevention of aluminium toxicity. Aluminium bone disease must be correctly identified and serum aluminium measurement and scintigraphy may be necessary. The prevalence of aluminium bone disease is decreasing as the use of aluminium-based phosphate binders and antacids is decreasing in favour of calcium salts.

Soft tissue calcification is a frequent manifestation of secondary hyperparathyroidism, affecting 27% of patients at the outset of dialysis and 58% of those who have been dialysis dependent for >5 yr.[68] Calcification may involve vascular and soft tissues, including kidneys (nephrocalcinosis), lungs, heart and skin. A simplistic mechanism for metastatic calcification is crystallization occurring if the serum calcium phosphate product increases above a certain level. Some suggest that high concentrations of the serum calcium phosphate product are an indication for parathyroidectomy.[15]

Calciphylaxis is a rare condition associated with haemodialysis or transplantation, high PTH concentrations and increased serum calcium phosphate product. Patients present with severe calf pain and tenderness with extensive, non-ulcerating, large, hard and tender subcutaneous plaques. These painful, violaceous, mottled cutaneous lesions progress to skin and subcutaneous necrosis, deep non-healing ulcers and gangrene. The lesions are reticular in pattern, appear characteristically on fingers and toes (although the forearms, arms, trunk, buttocks, thighs and legs may also be involved) and may be very large (up to 20 cm). This severe complication can threaten digits, limbs or the patient's life. Calcium deposition can be confirmed radiologically and by bone scanning. The condition is not uncommon and can occur in predialysis patients.[26]

Pruritus can be severe, intractable and disabling and has been attributed to increased calcium concentrations in the skin. This usually improves after parathyroidectomy.

Patients may also tire easily and have muscle weakness, proximal myopathy and peptic ulcer.

'Cardiotoxicity' of PTH

A 5 yr longitudinal echocardiographic study of 52 patients dependent on haemodialysis demonstrated that one of the best clinical predictors for the presence of left ventricular hypertrophy was an increased PTH concentration. A possible direct effect is mediated by specific receptors for PTH in the cardiomyocytes and by a permissive role on activation of interstitial cells in the heart. A raised calcium phosphate product leads to myocardial and valve calcification and to cardiac dysfunction. An increased cytosolic calcium concentration in the cardiomyocytes in uraemic patients lessens myocardial performance.[94]

Laboratory diagnoses of secondary hyperparathyroidism

Hyperphosphataemia is accompanied by normocalcaemia or hypocalcaemia; increased concentrations of intact PTH are decisive for diagnosis and exclude the diagnostic

confusion created by measuring the carboxy-terminal fragment of PTH (as in previous assays), which accumulates as a result of decreased renal clearance; increased alkaline phosphatase demonstrates the severity of bone disease; serum levels of vitamin D are monitored to confirm adequate substitution; serum aluminium concentration is checked to exclude aluminium toxicity as a cause of bone disease.

Medical treatment of secondary hyperparathyroidism

The goals of such treatment are to maintain calcium and phosphate concentrations close to normal levels, to suppress PTH secretion and ameliorate pre-existing bone disease. The methods available include the following.

(i) Dietary phosphate restriction (<1000 mg 24 h^{-1}) can be coupled with phosphate-binding agents to reduce phosphate absorption from the intestinal tract. Calcium carbonate is preferred to aluminium hydroxide and the dose is adapted to the phosphate content of foods.

(ii) Daily calcium intake of ≥1500 mg is necessary and can be achieved using oral supplementation. If the patient is still hypocalcaemic, calcium may be added to the dialysis fluid to achieve normocalcaemia.

(iii) Long-term treatment with calcium α-ketoglutarate (approximately 4.5 g day^{-1}) normalizes secondary hyperparathyroidism by simultaneously binding phosphate and correcting the calcium:phosphate ratio in serum without vitamin D treatment.[104]

(iv) Routine vitamin D supplementation is started before a patient becomes dependent on dialysis. The risks of vitamin D treatment include the development of hypercalcaemia and persistent hyperphosphataemia. Calcitriol concentrations should be measured during treatment with vitamin D. Weekly intravenous bolus administration is safe and cost-effective.

(v) Aluminium toxicity can be treated successfully with desferroxamine.

(vi) Pruritus is ameliorated by charcoal haemoperfusion in conjunction with standard haemodialysis.

(vii) The use of disphosphonates in the treatment of secondary hyperparathyroidism is being evaluated. These drugs have a high affinity for hydroxyapatite, inhibit osteoclast mediated bone-resorption, reduce bone resorption and decrease calcium and phosphate concentrations, but PTH concentrations increase.

(viii) PTH removal during continous ambulatory peritoneal dialysis (CAPD) is greater than with haemodialysis, but CAPD has the disadvantage of greater protein losses. Vitamin D and its binding protein are lost in peritoneal dialysate.

(ix) In an experimental model of secondary hyperparathyroidism, chronic administration of the Ca^{2+} receptor agonist NPS R-568 inhibited PTH synthesis and secretion and decreased parathyroid cell volume.[31]

Medical therapy fails in 5–10% of patients on long-term dialysis, and surgery becomes necessary.

Surgical treatment for secondary hyperparathyroidism

Indications for operation are based in part on the knowledge that bone and joint pain, pruritus and malaise are likely to improve in about 80% of patients after parathyroidectomy. When this treatment is offered, patients must be informed about the potential risks (bleeding, recurrent hyperparathyroidism, hypoparathyroidism and injury to the recurrent laryngeal nerves).

Patients should undergo dialysis within 1 day of surgery and then 48 h postoperatively or as needed. The risk of bleeding should be kept in mind since heparin is used during haemodialysis and platelets are dysfunctional in severely uraemic patients. Preoperative vitamin D treatment should continue since it decreases the chance of postoperative hypocalcaemia.

The typical histopathological findings are asymmetric enlargement, nodularity and increased numbers of oxyphil cells. Nodular hyperplasia indicates a more aggressive proliferation than diffuse hyperplasia.[95]

Severe postoperative hypocalcaemia may occur as a result of 'hungry bone syndrome', hypomagnesaemia and failure of parathyroid grafts. Oral supplementation (<6 g of elemental calcium can be given daily) suffices for mild symptoms but severe hypocalcaemia requires intravenous calcium and magnesium.

Technical options

A small viable portion of one parathyroid gland (the one showing diffuse hyperplasia on frozen section) is left *in situ* (subtotal parathyroidectomy) or is used as an autograft in the forearm (total parathyroidectomy). If all four glands are not found in the 'classical' locations, the retro-oesophageal space, superior thyroid pedicles and the area along the carotid sheath and thymus should be explored. Median sternotomy should not be performed as part of the initial operation. Pathology reports, postoperative PTH and calcium concentrations and the clinical response should influence further decisions about localization studies in anticipation of re-exploration. Recently, total parathyroidectomy has become a preferred option.

The relative merits of subtotal and total parathyroidectomy plus autograft are still controversial. Subtotal parathyroidectomy involves resection of three and a half glands and approximately 50 mg viable tissue is left *in situ* with preserved vascularity. The disadvantage of this method is that a second operation in the neck is needed in the event of persistent or recurrent hyperparathyroidism. In total parathyroidectomy plus autotransplantation, a small gland that shows predominantly diffuse hyperplasia on frozen section

is selected for autografting in the forearm flexor muscle mass and some fragments can be cryopreserved. Primary graft failure is extremely rare. Parathyroid graft function can be further evaluated by measuring PTH gradients between grafted and non-grafted antecubital venous samples.

Some recommend subtotal parathyroidectomy without remnant implantation as a safe and durable intervention for secondary hyperparathyroidism and following renal transplantation.[75] In one series of 91 patients, this intervention was associated with an acceptably low recurrence rate (4.1% at 1 yr and 11.7% at 20 yr). Overall hospital mortality was 3% (3/91) and none of the deaths was directly attributable to parathyroidectomy.[79]

Tertiary hyperparathyroidism

Tertiary HPT is the condition in which parathyroid hyperplasia progresses to autonomous hypersecretion so that excessive PTH secretion continues despite correction of the underlying renal disease. It is estimated to occur in 25–50% of patients based on calcium concentrations, but PTH concentrations and bone biopsies suggest a prevalence of <70% soon after renal transplant. Only few require operation and about 60% of these patients become normocalcaemic within 12 months.

After transplantation, patients usually present with less severe disease, have better normalization of biochemical variables after parathyroidectomy and rarely develop recurrent hyperparathyroidism. Both total parathyroidectomy with autotransplantation and subtotal parathyroidectomy result in good control of renal hyperparathyroidism with excellent improvement of symptoms.[67]

Familial syndromes including hyperparathyroidism

Multiple endocrine neoplasia type 1

MEN1 is a rare autosomal dominant familial cancer syndrome with a prevalence estimated to be between one in 10 000 and one in 100 000. Affected individuals develop various combinations of tumours in parathyroid glands, enteropancreatic endocrine tissues and the anterior pituitary, with 94% penetrance by the age of 50 yr. Less commonly associated tumours include foregut carcinoids, lipomas, thyroid adenomas, adrenocortical adenomas, angiomyolipomas and spinal cord ependymomas (reviewed in 62).

Hyperparathyroidism is the most common lesion in MEN1, with an estimated 90% prevalence in autopsy and screening studies. It is usually the first abnormality detected on screening and the parathyroid glands are almost always hyperfunctional by the time islet cells or pituitary involvement becomes clinically evident. Patients are first detected in their teens; by the age of 40 yr, >95% of patients have hypercalcaemia. The clinical picture is similar to sporadic hyperparathyroidism, apart from the symptoms, which may relate to other tumours (e.g. peptic ulcer caused by the presence of a gastrinoma). Characteristically, multigland parathyroid hyperplasia is found, but one or more glands can be macro- and microscopically normal.

In 1988, *MEN1* was mapped to chromosome position 11q13 by linkage analysis.[52] In 1997, two independent groups cloned the *MEN1* gene and showed that it encodes a ubiquitously expressed 610 amino acid protein, referred to as MENIN.[14 22] Over 40 mutations of the *MEN1* gene have been identified so far[4] and are likely to inactivate the MENIN function, which is consistent with the proposal that MEN1 results from inactivating mutations of a tumour suppressor gene.

MEN2

MEN2 is an autosomal dominant syndrome with incomplete penetrance and varying expression. MEN2A associates medullary thyroid carcinoma with a phaeochromocytoma (in 50% of patients) and hyperparathyroidism (in 15–30% of patients). In MEN2B there is a general (not absolute) lack of parathyroid involvement. General clinical features of MEN2 syndromes have been reviewed recently.[62] Hyperparathyroidism develops in 10–25% of patients, is characterized by mild hypercalcaemia (usually asymptomatic); the median age at diagnosis is 38 yr. Biochemical screening involves annual measurement of serum calcium concentrations followed by measurement of intact PTH only in hypercalcaemic patients. Generalized but asymmetric parathyroid hyperplasia is the most common histological abnormality.

MEN2 is a familial cancer syndrome arising from germline point mutations in the *RET* proto-oncogene located on chromosome 10 (at position 10q11.2). Multiple *RET* mutations have been described and are currently being collected by a *RET* Mutation Consortium for confirmation of a predicted genotype–phenotype correlation.[66] The *RET* proto-oncogene encodes a cell-surface glycoprotein related to the family of receptor tyrosine kinases[70] and is normally expressed in derivatives of the neural crest, including C cells, chromaffin and parathyroid cells.[71]

Familial isolated hyperparathyroidism

Familial isolated hyperparathyroidism is a rare autosomal dominant disorder which occurs as a genetically and clinical distinct entity. More than 30 kindred have been reported to display primary hyperparathyroidism with no evidence of other associated endocrinopathies. A study of 37 members of such a family has shown no linkage between familial isolated hyperparathyroidism and MEN1 or MEN2A.[50]

Other familial syndromes involving parathyroid disease are very rare and have been reviewed elsewhere.[62]

Relevance of parathyroid disease for anaesthesia

ECG changes

Increases in $[Ca^{2+}]_{ext}$ enhance myocardial contractility. When large amounts of calcium are infused into experimental animals, the heart relaxes less during diastole and eventually stops in systole (calcium rigor). In clinical conditions, however, the plasma calcium concentration is rarely high enough to affect the heart. On ECG, hypocalcaemia causes prolongation of the ST segment and QT interval but hypercalcaemia has less specific effects.

Drug interactions

Hypercalcaemia enhances digitalis toxicity so care should be taken in the preoperative assessment of older patients who may be taking or require this drug.

Recurrent laryngeal nerve injuries

During extubation, the anaesthetist should check the position of the vocal cords. If they are in the normal position, this confirms that the recurrent laryngeal nerves have not been damaged during dissection of the parathyroid glands. The recurrent laryngeal nerves supply all the muscles of the larynx except the cricothyroid (which is innervated by the external laryngeal nerve) and the mucous membrane below the vocal cords. With complete recurrent laryngeal nerve paralysis, the vocal fold takes a half-abducted position, there is vibration of the fold and stridor and the voice becomes hoarse. With partial lesions of the recurrent laryngeal nerve, the vocal fold takes an adducted position. From the point of view of airway obstruction, a partial lesion is more serious than a complete lesion; a bilateral partial lesion is life-threatening.

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