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13.4 Parathyroid disorders and diseases altering calcium metabolism 2313

ESSENTIALS The control of body calcium involves a balance—chiefly under the control of parathyroid hormone (PTH)—between the amounts that are absorbed from the gut, deposited into bone and into cells, and excreted from the kidney. Under normal physiological circumstances PTH secretion from the parathyroid glands is increased by hypocal- caemia and diminished by hypercalcaemia. Hypercalcaemia Clinical presentation—this is very variable, ranging from a mild asymptomatic biochemical abnormality to (in extreme cases) a life- threatening medical emergency. Clinical manifestations can be renal (nephrocalcinosis, kidney stones), musculoskeletal (bone pain, mus- cular weakness), gastrointestinal (anorexia, nausea, vomiting, con- stipation, peptic ulceration, pancreatitis), neurological (depression, confusion, coma), and cardiac (arrhythmia). Aetiology—primary hyperparathyroidism and malignancy account for more than 90% of patients with hypercalcaemia. Other causes include (1) excess vitamin D—exogenous or endogenous (e.g. granulomatous disorders); (2) drugs (e.g. thiazide diuretics, lithium, milk-alkali syndrome); (3) nonparathyroid endocrine disorders (e.g. thyrotoxicosis, immobilization); (4) inappropriate PTH levels due to altered set point (e.g. familial benign hypocalciuric hypercalcaemia). Management—aside from appropriate treatment of the underlying condition, management of hypercalcaemia depends on its severity and the presence of symptoms. Asymptomatic patients with serum calcium less than 3.00 mmol/litre do not usually need urgent treat- ment. Patients with serum calcium below 3.50 mmol/litre, or above 3.00 mmol/litre with symptoms, require (1) vigorous hydration with 0.9% saline (assuming adequate renal function), with diuresis en- couraged with a loop diuretic (e.g. furosemide) if necessary; (2) par- enteral bisphosphonate (e.g. pamidronate, zoledronic acid); with (3) glucocorticoids—if the hypercalcaemia is mediated by the actions of 1,25-dihydroxy vitamin D (e.g. granulomatosis disease, lymphoma, myeloma) and in exceptional circumstances; (4) haemodialysis. Specific diseases causing hypercalcaemia Primary hyperparathyroidism—due to excessive secretion of PTH by parathyroid

tumour(s); of unknown cause in most instances, but 10% of cases are associated with hereditary disorders, for example, multiple endocrine neoplasia type 1 (MEN1, with combined occurrence of parathyroid, pancreatic islet cell and anterior pituitary tumours) and type 2 (MEN2, with association of medullary thyroid carcinoma, phaeochromocytoma and parathyroid tumours); biochemical diagnosis typically achieved by finding an elevated PTH concentration in the presence of hypercalcaemia; parathyroidectomy is the definitive cure, but cinacalcet—an allosteric activator of the calcium-sensing receptor—can be effective. Tertiary hyperparathyroidism—secondary hyperparathyroidism arises in the context of chronic kidney disease, but eventually the parathyroid cells become autonomous, secreting excessive PTH despite hypercalcaemia, which is known as tertiary hyperparathyroidism. Malignancy—hypercalcaemia is usually due to increased bone resorption, which may either be directly due to skeletal metastases (most commonly from breast, lymphoma, or multiple myeloma) or indirectly due to tumour production of a humoral factor (usu- ally parathyroid hormone-related peptide, PTHrP, secreted from squamous carcinomas or other cancers) that stimulates osteoclastic bone resorption. Aside from measures just described, management involves reducing the tumour load by surgery, radiotherapy, and/or chemotherapy. Granulomatous disorders—hypercalcaemia is due to extrarenal synthesis of 1,25-dihydroxy vitamin D; most common diagnosis is sarcoidosis, when hypercalcaemia should respond within 10 days to treatment with glucocorticoids. Familial benign hypocalciuric hypercalcaemia—autosomal dominant due to heterozygous inactivating mutations of the calcium- sensing receptor, G-protein subunit α11, or adaptor protein 2 sigma subunit; causes (usually) asymptomatic hypercalcaemia in asso- ciation with an inappropriately low urinary calcium excretion and normal serum PTH. Hypocalcaemia Clinical presentation—this is variable, including (1) a mild, asymp- tomatic, biochemical abnormality; (2) in chronic cases with ectopic calcification, subcapsular cataract, papilloedema, and abnormal dentition; and (3) in severe cases with neuromuscular irritability. Aetiology—may be associated with (1) low serum PTH— hypoparathyroidism, most often caused by autoimmune disease, surgical removal of the parathyroid glands, or hypomagnesaemia; 13.4 Parathyroid disorders and diseases altering calcium metabolism R.V. Thakker

 or (2) high serum PTH—secondary hyperparathyroidism, most com- monly due to vitamin D deficiency and/or renal failure. Management—aside from appropriate treatment of the underlying condition, management of acute hypocalcaemia depends on its se- verity, rapidity of onset, and the degree of neuromuscular irritability. Patients with seizures or tetany may require intravenous calcium gluconate, as do asymptomatic patients with serum calcium below 1.90 mmol/litre as well as oral vitamin D. Specific diseases causing hypocalcaemia Pluriglandular autoimmune hypoparathyroidism—characterized by hypoparathyroidism, Addison's disease, and candidiasis in the pres- ence of other organ-specific autoimmune diseases; autosomal re- cessive inheritance due to mutation of an autoimmune regulator gene, with antibodies directed against the adrenal, thyroid, and para- thyroid glands sometimes present. Hypomagnesaemia—may be caused by malabsorption or renal tubular disorder; leads to functional hypoparathyroidism because magnesium is required for the release of PTH from the parathyroid gland and also for PTH action via adenyl cyclase. A variety of rare syndromes may cause hypoparathyroidism, and similar functional consequences can be caused by resistance to the effects of PTH (e.g. pseudohypoparathyroidism, of which there are five variants, some with somatic features such as shortening of one or more metacarpals). Introduction Calcium plays an important role in many physiological pathways that include muscle contraction, the secretion of neurotransmitters and hormones, and coagulation. The control of body calcium

involves a balance between the amounts that are absorbed from the gut, depos- ited into bone and cells, and excreted from the kidney (Fig. 13.4.1). This fine balance, involving all these organs, is chiefly under the control of parathyroid hormone (PTH), which is synthesized and secreted by the parathyroid glands. Thus, hypocalcaemia will lead to an increased secretion of PTH, whereas hypercalcaemia will result in diminished PTH secretion. Abnormalities of the parathyroid glands themselves will cause derangements of calcium homeostasis and several clinical disorders. PTH oversecretion due to parathyroid tumours, which af- fect 3 in 1000 of the population, is a major cause of hypercalcaemia which may be associated with kidney stones, osteoporosis, and peptic ulcers. PTH deficiency, which results in hypocalcaemia and occurs in 1 in 4000 live births, may be associated with epilepsy, tetany, cataracts, skeletal malformations, and abnormal dentition. This chapter will re- view the physiological and biochemical mechanisms underlying extra- cellular calcium homeostasis, the clinical features of hypercalcaemia and hypocalcaemia, the clinical disorders associated with abnormal calcium homeostasis and their management, and the genetic basis for disorders of calcium metabolism. Historical perspective The discovery of the parathyroids in the latter part of the 19th century and their function in regulating calcium homeostasis has evolved over 150 years and has involved studies in humans and other mammals (Table 13.4.1). In the past few decades with the advent of the advances in molecular biology, several cellular and molecular mechanisms involving G-protein-coupled receptors, intracellular second messengers, and transcription factors have been shown to be involved in calcium homeostasis and in the aetiology of parathyroid disorders (Fig. 13.4.2). These advances have elucidated the roles of the parathyroids and PTH in regulating calcium. Moreover, these advances have helped in defining new treatments for patients. For example, cinacalcet, which is an allosteric modulator of the calcium-sensing receptor (CaSR), is now used in the treatment of secondary hyperparathyroidism in dialysis patients with end stage renal dis- ease and for the treatment of hypercalcaemia in parathyroid car- cinoma, and PTH, which has been shown to reduce the incidence of vertebral and nonvertebral fractures, has now been approved as the first anabolic agent for the treatment of osteoporosis. Calcium homeostasis Most of the total of 1 kg of calcium in the healthy adult is present within the crystal structure of bone mineral and less than 1% is in sol- uble form in the extracellular and intracellular fluid compartments. In the extracellular fluid compartment about one-half of the total Dietary Ca2+, Vitamin D Vitamin D PARATHYROID ECF PTH INTESTINE UV LIGHT 7-Dehydro-cholesterol LIVER KIDNEY 1,25(OH)2Vitamin D 25(OH) Vitamin D 1α S K I N + + + B O N E Ca2+ + + Ca2+ Ca2+ Ca2+ Fig. 13.4.1 Regulation of extracellular fluid (ECF) calcium (Ca2+) by parathyroid hormone (PTH) action on kidney, bone, and intestine. A decrease in ECF Ca2+ is sensed by the calcium-sensing receptor (CaSR) (Fig. 13.4.2), and this leads to an increase in PTH secretion which predominantly acts directly on kidney and bone that possess the PTH receptor (PTHR, Fig. 13.4.2). The skeletal effects of PTH are to increase (+) osteoclastic bone reabsorption, but as osteoclasts do not have PTHRs, this action is mediated via the osteoblasts, which do have PTHRs and in response release cytokines and factors that activate osteoclasts. In the kidney, PTH stimulates (+) the 1α-hydroxylase (1α) to increase the conversion of 25-hydroxyvitamin D (25(OH)D) to the active metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D). In addition, PTH increases (+) the reabsorption of Ca2+ from the renal distal tubule and inhibits the reabsorption of phosphate from the proximal tubule, thereby leading to hypercalcaemia and hypophosphataemia. PTH also inhibits Na+–H+ antiporter activity and bicarbonate reabsorption, thereby causing a mild hyperchloraemic acidosis. The elevated 1,25(OH)2D acts on the intestine to increase (+) absorption of dietary calcium and phosphate, and it is important to note that PTH does not appear to have a direct action on the gut. Thus, in response to hypocalcaemia and the increase in

PTH secretion, all of these direct and indirect actions of PTH on the kidney, bone, and intestine will help to increase ECF Ca2+, which in turn will act via the CaSR to decrease PTH secretion.

13.4 Parathyroid disorders and diseases altering calcium metabolism 2315 calcium is ionized and the rest is principally bound to albumin or complexed with counterions. Ionized calcium concentrations range from 1.17 to 1.33 mmol/litre, and the total serum calcium concentra- tion ranges from 2.12 to 2.62 mmol/litre. Measurements of free ion- ized calcium are not often undertaken because they are difficult; most laboratories report total serum calcium concentration for routine clinical use. However, the usual 2:1 ratio of total to ionized calcium may be disturbed by disorders such as metabolic acidosis, which re- duces calcium binding by proteins, or by changes in protein concen- tration caused by cirrhosis, dehydration, venous stasis, or multiple myeloma. In view of this, total serum concentrations are adjusted or ‘corrected’ to a reference albumin concentration; thus, the corrected serum calcium may be related to a reference albumin concentration of 41 g/litre and for every 1 g/litre of albumin above or below the ref- erence value the calcium is adjusted by 0.016 mmol/litre up or down, respectively. For example, a total serum calcium of 2.70 mol/litre with an albumin concentration of 47 g/litre would be equivalent to a cor- rected serum calcium of 2.60 mmol/litre, thereby correcting the ini- tial apparent hypercalcaemic value to a normal value. The extracellular concentration of calcium is closely regulated within the narrow physiological range that is optimal for those cel- lular functions that are affected by calcium (Fig. 13.4.1). Indeed, both hypercalcaemia and hypocalcaemia impair the function of many different organ systems. Regulation of extracellular cal- cium takes place through complex interactions at the target or- gans of the major calcium-regulating hormone PTH (Fig. 13.4.2) and by vitamin D and its active metabolite 1,25-dihydroxyvitamin D. The parathyroid glands secrete PTH at a rate that is appro- priate to and depending on the prevailing extracellular calcium ion concentration. Aetiology and genetics Parathyroid gland disorders cause either hypercalcaemia or hypo- calcaemia, and these can be classified according to whether they arise from an excess of PTH, its deficiency, or an insensitivity to its effects (Table 13.4.2 and Fig. 13.4.2). Table 13.4.1 Some historical landmarks elucidating the role of the parathyroids in calcium homeostasis Date Discovery 1852 Sir Richard Owen, curator of the Natural History Museum (London) discovers the parathyroids when dissecting a rhinoceros that had died in London Zoo 1880 Sandstrom, in Uppsala, describes parathyroids in man 1881 Weiss in Billroth’s clinic (Vienna) reports tetany following thyroidectomy 1891 Gley shows that parathyroidectomy alone can cause tetany and death 1891 Von Recklinghausen reports first case of osteitis fibrosis cystica 1906 Erdheim describes parathyroid ‘overgrowth’ in calcium-deficient state of osteomalacia 1909 McCallum and Voegtlin demonstrate that postparathyroidectomy tetany and hypocalcaemia can be corrected by administration of parathyroid extract or calcium 1925 Collip establishes the role of parathyroids as endocrine glands that secrete PTH 1925 Mandl operates on a patient with severe bone demineralization and fractures and removes an enlarged parathyroid, resulting in a dramatic improvement of the patient’s condition; this represents the first successful parathyroidectomy 1939 Drake et al. report six cases of idiopathic hypoparathyroidism 1942 Albright et al. report three cases of pseudohypoparathyroidism 1959 Aurbach, and Rasmussen and Craig independently isolate PTH 1978 Keutmann et al. report complete amino acid sequence of human PTH 1983 Vasicek et al. characterize nucleotide sequence of human PTH gene 1987 Mosely et al. Suva et al. and Strewler et al. independently identify PTHrP as the humoral factor causing the hypercalcaemia of malignancy 1991 Juppner et al. identify a G-protein-coupled receptor that mediates actions of PTH and PTHrP 1993 Brown et al. identify the CaSR, a G-protein-coupled receptor, and that CaSR

mutations cause familial hypocalciuric hypercalcaemia type 1 (FHH1) 1996 Winer et al. report that administration of synthetic human PTH to patients with hypoparathyroidism, maintains normocalcaemia and reduces urinary calcium excretion 2001 Neer et al. report that administration of PTH reduces the occurrence of osteoporotic vertebral and nonvertebral fractures in postmenopausal women 2004 Block et al. show that cinacalcet, a calcimimetic agent that acts on the CaSR, lowers PTH levels, and improves calcium and phosphate homeostasis in patients on dialysis and with uncontrolled secondary hyperparathyroidism 2005 Peacock et al. report that cinacalcet reduces serum calcium and PTH in patients with primary hyperparathyroidism, thereby providing a potential medical therapy for this condition 2013 Nesbit et al. show that mutations of Gα11 cause FHH2 2013 Nesbit et al. report that mutations of AP2σ cause FHH3 2015 FDA approves use of human recombinant PTH (1-84) for management of refractory hypoparathyroidism 2016 Howles et al. report that cinacalcet can reduce the symptoms of hypercalcaemia in patients with FHH3 CaSR, calcium-sensing receptor; Gα11, G-protein subunit alpha 11; AP2σ, adaptor protein 2 sigma subunit; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide.

SECTION 13 Endocrine disorders 2316 Fig. 13.4.2 Schematic representation of some of the components involved in calcium homeostasis. Alterations in extracellular calcium are detected by the calcium-sensing receptor (CaSR), which is a 1078 amino acid G-protein-coupled receptor. The PTH/PTH-related peptide (PTHrP) receptor, which mediates the actions of PTH and PTHrP, is also a G-protein-coupled receptor. Thus, Ca2+, PTH, and PTHrP involve G-protein-coupled signalling pathways, and interaction with their specific receptors can lead to activation of Gs, Gi, and Gq, respectively. Gs stimulates adenyl cyclase (AC) which catalyses the formation of cAMP from ATP. Gi inhibits AC activity. cAMP stimulates protein kinase A which phosphorylates cell-specific substrates. Activation of Gα11/Gq stimulates phospholipase C (PLC), which catalyses the hydrolysis of the phosphoinositide (PIP2) to inositol triphosphate (IP3), which increases intracellular calcium, and diacylglycerol (DAG), which activates protein kinase C (PKC). These proximal signals modulate downstream pathways, which result in specific physiological effects. Abnormalities in several genes, which lead to mutations in proteins in these pathways, have been identified in specific disorders of calcium homeostasis (Table 13.4.1). ADH1 and ADH2, autosomal dominant hypocalcaemia types 1 and 2; AIRE, autoimmune regulator protein; AP2σ, adaptor protein 2 sigma subunit; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome; CCND1, cyclin D1; CDC73, cell division cycle protein 73; FAMIIIA, family with sequence similarity 111A; FHH1–3, familial hypocalciuric hypercalcaemia types 1–3; GATA3, GATA binding protein 3; GCM2, glial cells missing homologue 2; HDR, hypoparathyroidism, deafness, and renal dysplasia syndrome; HPT-JT, hyperparathyroidism–jaw tumour syndrome; KSS, Kearns–Sayre syndrome; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MEN1, multiple endocrine neoplasia type 1 syndrome; MTPDS, mitochondrial trifunctional protein deficiency syndrome; NSHP, neonatal severe primary hyperparathyroidism; Rb, retinoblastoma; TBCE, tubulin-specific chaperone. Adapted from Thakker RV (2000). Parathyroid disorders. Molecular genetics and physiology. In: Morris PJ, Wood WC (eds) Oxford textbook of surgery, 2nd edition, pp. 1121–9. Oxford University Press, Oxford.

13.4 Parathyroid disorders and diseases altering calcium metabolism 2317 Table 13.4.2 Parathyroid diseases and their chromosomal locations Metabolic abnormality Disease Inheritance Gene/gene product Chromosomal location Hypercalcaemia MEN1 (OMIM 131100) Autosomal dominant Menin 11q13 MEN2 and MEN3 (OMIM 171400) Autosomal dominant RET 10q11.2 MEN4

(OMIM 610755) Autosomal dominant CDNK1B 12p13.1 HPT-JT (OMIM 145001) Autosomal dominant CDC73/Parafibromin 1q31.2 Sporadic hyperparathyroidism (OMIM 145000) Sporadic CCND1 11q13 Retinoblastoma 13q14 Unknown 1p32-pter Parathyroid carcinoma (OMIM 608266) Sporadic Parafibromin 1q31.2 Retinoblastoma 13q14 FHH1 (OMIM 145980) Autosomal dominant CASR 3q21.1 FHH2 (OMIM 139313) Autosomal dominant Gα11 19p13 FHH3 (OMIM 600740) Autosomal dominant AP2S1/AP2σ 19q13 NSHP (OMIM 239200) Autosomal recessive CASR 3q21.1 Autosomal dominant Jansen's disease (OMIM 156400) Autosomal dominant PTHR/PTHrPR 3p21.3 William's syndrome (OMIM 194050) Autosomal dominant ELN, LIMK1 (and other genes) 7q11.23 Infantile hypercalcaemia (OMIM 143880) Autosomal recessive CYP24A 20q13.2-q13.3 McCune–Albright syndrome (OMIM 174800) Mutations during early embryonic development? Gsα 20q13.3 Hypocalcaemia Isolated hypoparathyroidism (OMIM 146200) Autosomal dominant PTH 11p15a Autosomal recessive PTH, GCM2 11p15a, 6p24.2 X-linked recessive SOX3 Xq26–27 ADH1 (OMIM 601198) Autosomal dominant CaSR 3q21.1 ADH2 (OMIM 615361) Autosomal dominant Gα11 19p13 Hypoparathyroidism associated with polyglandular autoimmune syndrome (APECED) (OMIM 240300) Autosomal recessive AIRE1 21q22.3 Hypoparathyroidism associated with Kearns–Sayre (OMIM 530000) and MELAS (OMIM 540000) syndromes Maternal Mitochondrial genome Hypoparathyroidism associated with complex congenital syndromes DiGeorge syndrome type 1 (OMIM 188400) Autosomal dominant TBX1 22q11.2/10p DiGeorge syndrome type 2 (OMIM 601362) Autosomal dominant NEBL 10p14-p13 HDR syndrome (OMIM 146255) Autosomal dominant GATA3 10p15 Blomstrand lethal chondrodysplasia (OMIM 215045) Autosomal recessive PTHR/PTHrPR 3p21.3 Kenney–Caffey type 1 (OMIM 244460), and
Sanjad–Sakati syndromes Autosomal dominant TBCE 1q42.3 Kenney–Caffey type 2 (OMIM 127000) Autosomal recessive FAM111A 11q12.1 Barakat syndrome Autosomal recessiveb Unknown ? Lymphoedema Autosomal recessive Unknown ? Nephropathy, nerve deafness Autosomal dominantb Unknown ? Nerve deafness without renal dysplasia Autosomal dominant Unknown? ? PHP (type Ia) (OMIM 103580) Autosomal dominant parentally imprinted GNAS exons 1–3 20q13.2 PHP (type Ib) (OMIM 603233) Autosomal dominant parentally imprinted GNAS, upstream deletion 20q13.3 CDC73, cell division cycle protein 73; CDNK1B, cyclin-dependent kinase inhibitor 1B, GATA3, GATA binding protein 3; GCM2, glial cells missing homologue 2; HDR, hypoparathyroidism, deafness, and renal dysplasia; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; NEBL, nebulette; PTHR, parathyroid hormone receptor; PTHrPR, parathyroid hormone-related peptide receptor; ? location not known. a Mutations of PTH gene identified only in some families. b Most likely inheritance.

SECTION 13 Endocrine disorders 2318 The PTH gene is located on chromosome 11p15 and consists of three exons (transcribed regions) which are separated by two in- trons. Exon 1 of the PTH gene is 85 bp in length and is untranslated whereas exons 2 and 3 code for the 115 amino acid pre-proPTH peptide. Exon 2 is 90 bp in length and encodes the initiation (ATG) codon, the prehormone sequence, and part of the prohormone sequence. Exon 3 is 612 bp in length and encodes the remainder of the prohormone sequence, the mature PTH peptide, and the 3′ untranslated region. The 5′ regulatory sequence of the human PTH gene contains a vitamin D response element 125 bp upstream of the transcription start site, which down-regulates PTH mRNA tran- scription in response to vitamin D receptor binding. PTH gene transcription (as well as PTH peptide secretion) is also dependent on the extracellular calcium concentration, although the presence of a specific upstream 'calcium response element' has not yet been demonstrated. The mature PTH peptide is secreted from the parathyroid chief cell as an 84 amino acid peptide; however, when the PTH

mRNA is first translated it is as pre-proPTH peptide. The ‘pre’ sequence con- sists of a 25 amino acid signal peptide (leader sequence) which is responsible for directing the nascent peptide into the endoplasmic reticulum to be packaged for secretion from the cell. The ‘pro’ sequence is six amino acids in length and, although its function is less well defined than that of the ‘pre’ sequence, it is also essential for correct PTH processing and secretion. After the 84 amino acid ma- ture PTH peptide is secreted from the parathyroid cell, it is cleared from the circulation, with a short half-life of about 2 min, via non- saturable hepatic uptake and renal excretion. PTH shares a receptor with PTH-related peptide (PTHrP); this PTH/PTHrP receptor (Fig. 13.4.2) is a member of a subgroup of the G-protein-coupled receptor family. The PTH/PTHrP receptor gene is located on chromosome 3p21.3 and is expressed in kidney and bone, where PTH is its predominant agonist. Expression of the PTH/PTHrP receptor also occurs in the brain, heart, skin, lung, liver, and testis where it mediates the actions of PTHrP. Mutations involving the genes that encode these proteins and receptors in this calcium regulating pathway (Fig. 13.4.2) are associated with hypercalcaemic and hypocalcaemic disorders (Table 13.4.2). Hypercalcaemia Clinical features and investigations The clinical presentation of hypercalcaemia varies from a mild, asymptomatic, biochemical abnormality detected during routine screening to a life-threatening medical emergency. In general, the presence or absence of symptoms correlates with the severity and rapidity of onset of the hypercalcaemia. Thus, symptoms do not usu- ally develop when serum calcium is below 3.00 mmol/litre and are in- variably present when the hypercalcaemia exceeds 3.50 mmol/litre. However, there is a considerable variability and some patients may be symptomatic with mild hypercalcaemia (2.65–2.90 mmol/litre). Although there are many causes of hypercalcaemia (Box 13.4.1), the signs and symptoms of hypercalcaemia are similar, regardless of aetiology. Indeed, the clinical manifestations of hypercalcaemia in- volve several organ systems that include the renal, musculoskeletal, gastrointestinal, neurological, and cardiac systems (Box 13.4.2), and many of these have been referred to as ‘moans, groans, pains, and stones’. Investigations should be directed at confirming the presence of hypercalcaemia and establishing the cause (Box 13.4.1). The causes of hypercalcaemia can be classified according to whether serum PTH concentrations are elevated (i.e. primary hyperparathyr- oidism) or low (i.e. not due to a parathyroid tumour). Primary hyper- parathyroidism and malignancy are the most common causes and account for more than 90% of patients with hypercalcaemia. Detailed clinical history and examination will usually help to differentiate be- tween these two diagnoses. In primary hyperparathyroidism, the hypercalcaemia is often less than 3.00 mmol/litre, asymptomatic, and may have been present for months or years. If symptoms such Box 13.4.1 Causes of hypercalcaemia High PTH levels • Primary hyperparathyroidisma (adenoma, hyperplasia, or carcinoma): nonfamilial or familial (e.g. MEN1, MEN2, HPT-JT, FIHP) • Tertiary hyperparathyroidism (hyperplasia or adenoma in chronic renal failure) Low PTH levels Malignancya Primary • PTH-related protein, PTHrP (carcinoma of lung, oesophagus, renal cell, ovary, and bladder) • Excess production of 1,25-dihydroxyvitamin D (lymphoma) Secondary • Lytic bone metastasesa (multiple myelomaa and breast carcinomaa) • Other location, ectopic factors (e.g. cytokines) • Excess vitamin D • Exogenous vitamin D toxicity by parent D compound, 25-hydroxyvitamin D3, or 1,25-dihydroxyvitamin D3 in vitamin preparations, cod liver oil, herbal medicines • Endogenous production of 25-hydroxyvitamin D3—William’s syndrome • Endogenous production of 1,25-dihydroxyvitamin D3, for example, granulomatous disorders (sarcoidosis, HIV, tuberculosis, histo- plasmosis, coccidioidomycosis, leprosy), lymphoma, and infantile hypercalcaemia Drugs • Thiazide diuretics • Lithium • Total parenteral nutrition • Oestrogens/antioestrogens, testosterone • Milk-alkali syndrome • Vitamin A toxicity • Foscarnet • Aluminium intoxication (in chronic renal failure) • Aminophylline

Nonparathyroid endocrine disorders • Thyrotoxicosis • Phaeochromocytoma • Acute adrenal insufficiency • Vasoactive intestinal polypeptide hormone producing tumour (VIPoma) • Immobilization Inappropriate PTH levels due to altered set point • Familial benign hypocalciuric hypercalcaemia (FHH or FBH) types 1–3 a Most common causes.

13.4 Parathyroid disorders and diseases altering calcium metabolism 2319 as nephrolithiasis are present, then they have usually been present for several months. However, in malignancy the patients are usually acutely ill, often with neurological symptoms, the hypercalcaemia is more than 3.00 mmol/litre, and the cancer (e.g. lung, breast, or mye- loma) is often readily apparent. Hypercalcaemia from causes other than primary hyperparathyroidism or malignancy may also occur (Box 13.4.1) and a careful history (e.g. for vitamin D ingestion, drugs, renal disease) and examination (e.g. for thyrotoxicosis, adrenal dis- ease, granulomatosis diseases), together with appropriate investiga- tions (Box 13.4.3) are essential for establishing the diagnosis. Management of hypercalcaemia The management of hypercalcaemia depends on the severity of the hypercalcaemia and the presence of symptoms. Thus, asymptom- atic patients with mild hypercalcaemia (i.e. serum calcium below 3.00 mmol/litre), do not usually need urgent treatment. However, a patient with severe hypercalcaemia (i.e. a serum calcium above 3.50 mmol/litre), would require treatment regardless of symptoms, while a patient with moderate hypercalcaemia (i.e. a serum calcium in the range 3.00 to 3.50 mmol/litre), would require urgent treatment if symptomatic. Before instituting treatment, it is always important to consider the underlying causes (Box 13.4.1) and to initiate in- vestigations (Box 13.4.3). In addition, drugs such as thiazides and vitamin D compounds that cause hypercalcaemia should be discon- tinued and, if appropriate, dietary calcium restricted. The acute management of hypercalcaemia involves general meas- ures to enhance hydration and diuresis, and specific measures using drugs to lower serum calcium. Dehydration due to hypercalcaemic symptoms (e.g. anorexia, nausea, vomiting, and polyuria) because of defective urinary concentration, is very common and patients may require 5 to 10 litres of 0.9% sodium chloride over a 24- to 48-h period. This vigorous hydration with normal saline may lower serum calcium by 0.25 to 0.75 mmol/litre; it enhances urinary calcium ex- cretion by increasing glomerular filtration and reducing proximal and distal renal tubular reabsorption of calcium and sodium. The saline diuresis may need adjuvant therapy with a loop diuretic (e.g. furosemide 10 to 20 mg), as necessary, to control complications due to volume overload, especially in elderly people and those with im- paired cardiovascular and renal function. It is important to note that excessive use of furosemide before intravascular volume has been restored may worsen the hypercalcaemia by exacerbating volume depletion. Saline diuresis may lead to hypokalaemia, hypomagnes- aemia, and electrolyte imbalance, which will need correction. If saline diuresis is not successful, and particularly if the hypercalcaemia is very severe, then more specific measures (e.g. dialysis and/or drugs), will be required. The drugs of choice are pamidronate or zoledronic acid, which are potent bisphosphonates that are administered parenterally. Recommended regimens are to administer pamidronate (60–90 mg) or zoledronic acid (4 mg) intra- venously as a single infusion. Other bisphosphonates (e.g. etidronate and clodronate), and other agents such as mithramycin, calcitonin, and gallium nitrate have also been used in the past. Glucocorticoid therapy (e.g. hydrocortisone 120 mg/day in three divided doses) is particularly effective when the hypercalcaemia is mediated by the actions of 1,25-dihydroxyvitamin D, for example, in granulomatosis disease or lymphoma (Box 13.4.1), or myeloma. Dialysis using a low or zero calcium dialysate should be considered if these treatments are not effective or if the patient has renal failure. Once the acute management of hypercalcaemia has been completed, then appro-

priate treatment for the underlying cause (e.g. parathyroidectomy for primary hyperparathyroidism), needs to be undertaken. Box 13.4.2 Clinical features of hypercalcaemia Renal Stones (nephrolithiasis) and nephrocalcinosis Polyuria Polydipsia Musculoskeletal Bone pain Osteopenia Fractures Muscular weakness, especially proximal myopathy Gastrointestinal Nausea Vomiting Lack of appetite Constipation Peptic ulcers Pancreatitis Neurological Tiredness Lethargy Inability to concentrate Increased sleepiness Depression Confusion Coma Cardiac Bradycardia First-degree AV block Arrhythmias Shortened QT interval Box 13.4.3 Preliminary investigations for hypercalcaemia Blood Two or three estimations of serum calcium, phosphate, albumin, urea and electrolytes, creatinine, alkaline phosphatase, and liver function tests PTH Haemoglobin, full blood count, ESR Electrophoretic protein strip 25-hydroxyvitamin D3 (and, if indicated, 1,25-dihydroxyvitamin D3) Thyroid function tests Magnesium PTHrP (if malignancy suspected) Urine Two or three estimations of 24-h urinary calcium and creatinine, and clearance ratios Imaging Chest radiograph Radiograph of hands Ultrasound of kidneys

SECTION 13 Endocrine disorders 2320 Hypercalcaemic diseases Hypercalcaemia may arise through one or more of three mech- anisms: increased bone resorption, increased gastrointestinal absorption of calcium, and decreased renal calcium excretion (Fig. 13.4.1). For example, lytic bone metastases cause increased bone resorption, thiazide diuretics lead to a decrease in calcium excretion, and excessive PTH will either directly or indirectly, by increasing 1,25-dihydroxyvitamin D production, stimulate bone resorption and calcium absorption from the gut and renal tubules. The hypercalcaemic diseases may be classified according to whether serum PTH concentrations are elevated or reduced (Box 13.4.1). In addition, hypercalcaemia may be classified as being due to an excess of PTH (e.g. primary or tertiary hyperparathyroidism) from parathyroid tumours, an excessive production of PTHrP, a defect in the PTH receptor (i.e. the PTH/PTHrP receptor), an excess pro- duction of downstream mediators (e.g. 1,25-dihydroxyvitamin D), or an altered set point in the CaSR (Fig. 13.4.2). Hyperparathyroidism Hyperparathyroidism is characterized by high concentrations of serum immunoreactive PTH, and three types, referred to as pri- mary, secondary, and tertiary, are recognized. Primary and tertiary hyperparathyroidism are associated with hypercalcaemia (Box 13.4.1), whereas secondary hyperparathyroidism is associated with hypocalcaemia (see next). Primary hyperparathyroidism may arise as an isolated endocrinopathy or as part of a multiple endocrine neo- plasia (MEN) syndrome, and tertiary hyperparathyroidism usually arises in association with chronic renal failure. Primary hyperparathyroidism Primary hyperparathyroidism, which affects 3 in 1000 adults, is one of the two most common causes of hypercalcaemia and is due to an excessive secretion of PTH from one or more parathyroid tumours. Epidemiological studies have estimated that the global prevalence of parathyroid tumours is 4 million. In 80% of patients this tumour is a solitary parathyroid adenoma, and in 15 to 20% of patients hyperplasia involving all four parathyroids is present. Parathyroid carcinoma accounts for less than 0.5% of patients with primary hyperparathyroidism. Primary hyperparathyroidism usu- ally occurs between the ages of 40 to 65 years, and is three times more common in women than men. The underlying causes of pri- mary hyperparathyroidism are largely unknown, but abnormalities of several genes have been identified. Thus, abnormalities of the cyclin D1 (CCNDI), retinoblastoma, CaSR (CASR), parafibromin, MEN type 1 (MEN1), and MEN type 2 (MEN2) genes, together with other genes yet to be identified, for example, on chromosome 1p (Table 13.4.2), are associated with the development of some parathyroid tumours. Clinical features Many patients with primary hyperparathyr- oidism will be asymptomatic and the hypercalcaemia, which is usually mild, will have been detected by chance at the time of bio- chemical screening for other reasons.

However, it is important to note that nearly one-half of the patients will have subtle neuromus- cular symptoms such as fatigue and weakness and this becomes ap- parent only in retrospect after a successful parathyroidectomy. Symptomatic hypercalcaemia (Box 13.4.2) predominantly af- fects the skeletal, renal, and gastrointestinal systems; peptic ulcers and pancreatitis may develop. The skeletal changes of osteitis fibrosa cystica due to subperiosteal resorption of the distal phalanges (Fig. 13.4.3), tapering of the distal clavicles, a 'salt and pepper' ap- pearance of the skull, bone cysts, and brown tumours of the long bones are now identified in less than 5% of patients. However, osteopenia, as assessed by bone mineral density, occurs in 25% of patients. Renal stone disease (nephrolithiasis and nephrocalcinosis) occurs in 20% of patients and hypercalciuria occurs in 30% of pa- tients; renal impairment may complicate this disease. (f) (e) (d) (c) (b) (a) Fig. 13.4.3 Renal osteodystrophy over a 9-year period in a patient with chronic renal failure. Marked periosteal erosions were seen (a) despite treatment with 1α-hydroxycholecalciferol, and a resolution was observed following dialysis (b). Note the vascular calcification. One year later a relapse was noted with periosteal erosions (c) and the use of calcitriol resolved these (d). Unfortunately, a relapse occurred 2 years later (e), and following renal transplantation a marked resolution was observed (f).

 Investigations In the presence of hypercalcaemia, the finding of elevated circulating PTH concentrations establishes the diag- nosis, as the PTH will be elevated in approximately 90% of pa- tients with primary hyperparathyroidism who will invariably have hypercalcaemia. However, it is important to make sure that the immunoradiometric and immunochemiluminometric as- says for PTH are used to measure the intact molecule, rather than the older radioimmunoassays which are not as reliable. The only other hypercalcaemic disorders in which PTH may occasion- ally be elevated are those related to familial benign hypocalciuric hypercalcaemia (FBH), immobilization, or lithium or thiazide use (Box 13.4.1), and a careful history and a cessation of drug use will help to exclude these possibilities. About one-third of patients with primary hyperparathyroidism will have a low serum phosphate and in the others, it will be in the lower range of normal. In addition, some patients will have a small increase in serum chloride concen- tration and a concomitant decrease in bicarbonate concentration. Serum alkaline phosphatase activity may be elevated in some pa- tients, and urinary calcium excretion is increased in 30% of pa- tients. The circulating 1,25-dihydroxyvitamin D concentration is elevated in some patients with primary hyperparathyroidism, al- though it is not of diagnostic value as it is also elevated in other hypercalcaemic disorders such as sarcoidosis and lymphomas. The serum 25-hydroxyvitamin D concentration is within the normal range. Densitometric scanning is of use in detecting early skeletal changes. Patients with primary hyperparathyroidism develop re- duced bone mineral densities (osteopenia) primarily of the cortical bone (e.g. distal one-third of forearm) rather than the cancellous bone (e.g. lumbar spine). The hip bones, which are an equal mix- ture of cortical and cancellous bone, show intermediate reductions in bone mineral density. Overall, the risk of bone fractures in pa- tients with mild primary hyperparathyroidism is similar to those in matched, normal controls. However, successful parathyroidectomy does lead to an increase in bone mineral density over a 6- to 12- month period and this continues for up to 10 years. Indeed, bone mineral density measurements are used in the evaluation of pa- tients with primary hyperparathyroidism and in deciding on con- servative as opposed to surgical management (Box 13.4.4). Preoperative localization to define the site(s) of the parathy- roid tumours may be undertaken. The noninvasive tests consist of ultrasonography, CT, MRI, and scintigraphy with technetium-99m sestamibi. Sestamibi scintigraphy has now become established as the best and most convenient localization test; this can be performed with CT

techniques (single photon emission CT, SPECT) to give a three-dimensional image with greater anatomical resolution. It is important to note that there is an appreciable incidence of false-positive rates with all the noninvasive localization procedures and so a confirmation using two methods is preferable. Invasive local- ization tests consist of arteriography and selective venous sampling for PTH in the veins draining the thyroidal region. These tests are time-consuming, expensive, difficult, and dependent on the skill of the radiologist. It is generally accepted that these preoperative local- ization tests are indicated in those patients who have had previous neck surgery. However, their role in patients who have not had prior surgery remains to be established and at present the preferences and expertise of the local medical, radiology, and surgery teams usually determine the use of venous sampling procedures. Management and treatment Parathyroidectomy, which is the de- finitive cure, is a generally successful and safe procedure if under- taken by an experienced surgeon. There have also been major advances in surgery that have facilitated a surgical approach to be undertaken under local, as opposed to general, anaesthesia. An ex- ample of this is the use of minimally invasive parathyroidectomy in the patient with single gland disease that has been successfully lo- calized by the combined use of sestamibi scintigraphy and ultrason- ography. Surgery is recommended for symptomatic patients and for those who have skeletal and renal complications. However, the de- cision to recommend surgery, which does have a small risk, may be difficult in asymptomatic patients, who may constitute over 50% of patients with primary hyperparathyroidism. The natural history of primary hyperparathyroidism in most patients is to progress slowly or not at all. For example, among asymptomatic patients only 25% will have progressive disease, which is usually manifested as a de- crease in bone mineral density during a 10-year period. This has led to a controversy regarding the indications for surgery, and guidelines have been provided by the Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism (Box 13.4.4). However, these guidelines may not exclusively influ- ence the decision for or against surgery, and a careful evaluation and assessment of the risks and benefits is considered by most medical and surgical teams in conjunction with the patient. Clearly, some patients will not wish to continue living with a curable disease and will prefer surgery despite the guidelines (Box 13.4.4), while other patients will decline surgery, despite having guideline indications for it, because they may have coexisting medical conditions that make them feel that the risks of surgery are too great. Patients who do not undergo parathyroidectomy (e.g. those with asymptomatic primary hyperparathyroidism) should be evaluated clinically, and also monitored for serum calcium, creatinine, and es- timated glomerular filtration rate (eGFR), annually; bone mineral density at three sites, 1–3 year intervals with X-ray, or vertebral frac- ture assessment of spine if there has been height loss or back pain; and if nephrolithiasis is suspected then appropriate assessments of 24 hour urine collections and renal imaging. In addition, the fol- lowing medical guidelines are recommended. First, they should Box 13.4.4 Guidelines for the management of primary hyperparathyroidism, recommended by the Fourth International Workshop (2013) Surgery is recommended if the patient meets any one of the following criteria: • Serum calcium is more than 0.25 mmol/litre above upper limit of normal • Any complication of primary hyperparathyroidism (e.g. nephrolithiasis, nephrocalcinosis, bone erosions of osteitis fibrosa cystica) • An episode of acute primary hyperparathyroidism with life-threatening hypercalcaemia • Marked hypercalciuria (>10 mmol/litre per 24 h or >400 mg/24 h) and increased stone risk by biochemical stone risk analysis • Significant reduction in creatinine clearance (i.e. <60 ml/min) • Reduction in bone mineral density (BMD) (i.e. T score <–2.5 at spine, total hip, femoral neck, or distal third of radius; and/or vertebral frac- ture shown by X-ray, CT, MRI, or vertebral fracture assessment) • Age less

than 50 years

SECTION 13 Endocrine disorders 2322 avoid dehydration and remain ambulant. Second, vitamin D defi- ciency should be corrected, and the serum 25-hydroxy vitamin D should be maintained above 50 nmol/litre. Third, dietary intake of calcium should be normal; limiting calcium intake is not recom- mended. Fourth, thiazide diuretics, herbal and tonic remedies that may contain vitamin D or vitamin A, should be avoided. These meas- ures may help. Drugs that have been used include oral phosphate, oestrogens, or selective oestrogen receptor modulators (SERMs) in postmenopausal women, and bisphosphonates. Phosphate is not used because of concerns related to soft tissue ectopic calcification. Oestrogens and SERMs such as raloxifene do increase bone density in postmenopausal women with primary hyperparathyroidism but they have only small effects on the serum calcium and PTH con- centrations. The bisphosphonates (e.g. alendronate) inhibit bone re- sorption, improve bone mineral density (BMD) at the lumbar spine without altering serum calcium and PTH concentrations. However, these effects are not sustained. The calcimimetic drug, cinacalcet, which increases the sensitivity of the parathyroid CaSR (see next) to extracellular calcium and thereby reduces PTH secretion, is effective in lowering serum calcium concentrations to normal values with modest reductions in PTH levels in patients with primary hyperpara- thyroidism. However, bone mineral density in the treated patients remained unchanged. The use of cinacalcet is approved for adult (i.e. over the age of 18 years) patients, who are on dialysis with uncon- trolled secondary hyperparathyroidism, have hypercalcaemia due to inoperable parathyroid carcinoma, or have severe hypercalcaemia due to primary hyperparathyroidism and are unable to undergo parathyroidectomy. The use of these drugs should be dictated by the aims of the treatment. For example, bisphosphonate therapy should be chosen if the aim is to increase BMD, and cinacalcet should be chosen if the aim is to reduce serum calcium concentrations. Combined use of cinacalcet and alendronate has been reported, by one study, to normalize hypercalcaemia and improve BMD in pa- tients with primary hyperparathyroidism. Uraemic hyperparathyroidism Serum PTH levels rise in response to hypocalcaemia and this sec- ondary hyperparathyroidism usually resolves with treatment of the underlying cause of hypocalcaemia (Box 13.4.5). However, in chronic renal failure the secondary hyperparathyroidism may persist for a longer time, and eventually the parathyroid cells gain an autono- mous function, secreting excessive PTH despite hypercalcaemia; this state is referred to as tertiary hyperparathyroidism (Box 13.4.1). The cause of progression from the early, presumably polyclonal, secondary hyperplasia of the parathyroids to the later, presumably monoclonal, tumours is not understood and appears to involve genes other than those involved in the aetiologies of the sporadic and familial forms of primary hyperparathyroidism (Table 13.4.2). Clinical features and treatment In chronic renal failure, the ensuing phosphate retention and decreased production of 1,25- dihydroxyvitamin D result in hypocalcaemia and secondary hyper- parathyroidism. This combination of biochemical abnormalities results in a severe bone disease that shows combined features of hyper- parathyroidism and vitamin D deficiency (i.e. osteomalacia). Thus in renal osteodystrophy, bone erosions (Fig. 13.4.3) and osteomal- acia are simultaneously observed. Treatment is based on correcting the hypocalcaemia (e.g. with oral administration of calcium salts), which also ameliorates the hyperphosphataemia by chelating phos- phate in the intestines, and with calcitriol (1,25-dihydroxyvitamin D). The use of the most appropriate phosphate binder is not well established, but it is clear that aluminium-containing compounds are to be avoided. Aluminium in these preparations and as a con- taminant of dialysis solutions contributed in the recent past to the osteomalacic osseous disease and other aspects of metal toxicity in patients with renal failure (e.g.

hypochromic anaemia and enceph- alopathy). Early treatment of the metabolic disturbance will prevent or delay the onset of severe secondary hyperparathyroidism and tertiary hyperparathyroidism, which requires parathyroidectomy. For patients who have end stage renal failure and are on dialysis, Box 13.4.5 Causes of hypocalcaemia Low PTH levels (hypoparathyroidism) Parathyroid agenesis • Isolated or part of complex developmental anomaly (e.g. DiGeorge's syndrome) Parathyroid destruction • Surgerya • Radiation • Infiltration by metastases or systemic disease (e.g. haemochromatosis, amyloidosis, sarcoidosis, Wilson's disease, thalassaemia) • Autoimmune • Isolated • Polyglandular (type 1)a Reduced parathyroid function (i.e. PTH secretion) • PTH gene defects • Hypomagnesaemiaa • Neonatal hypocalcaemia (may be associated with maternal hypercalcaemia) • Hungry bone disease (postparathyroidectomy) • CaSR or Gα11 mutations High PTH levels (secondary hyperparathyroidism) Vitamin D deficiencya • As a result of nutritional lacka, malabsorptiona, liver disease, or vitamin D receptor defects Vitamin D resistance (rickets) • As a result of renal tubular dysfunction (Fanconi's syndrome) or vitamin D receptor defects PTH resistance • (e.g. pseudohypoparathyroidism, hypomagnesaemia) Drugs • Calcium chelators (e.g. citrated blood transfusions, phosphate; cow's milk is rich in phosphate) • Inhibitors of bone resorption (e.g. bisphosphonates, calcitonin, plicamycin) • Altered vitamin D metabolism (e.g. phenytoin, ketoconazole) • Foscarnet Miscellaneous • Acute pancreatitis • Acute rhabdomyolysis • Massive tumour lysis • Osteoblastic metastases (e.g. from prostate or breast carcinoma) • Toxic shock syndrome • Hyperventilation a Most common causes.

 cinacalcet—the allosteric activator of the CaSR—can be used to treat the severe secondary hyperparathyroidism. Cinacalcet will re- duce the PTH concentrations and may also have an antiproliferative effect. Familial primary hyperparathyroidism Primary hyperparathyroidism is most frequently encountered as a nonfamilial disorder. However, approximately 10% of patients with primary hyperparathyroidism will have a hereditary form which may either be part of the MEN type 1 (MEN1) and type 2 (MEN2) syndromes, or part of the hereditary hyperparathyroidism–jaw tu- mour (HPT-JT) syndrome. In addition, hereditary primary hyper- parathyroidism may develop as a solitary endocrinopathy and this has also been referred to as familial isolated hyperparathyroidism (FIHP). Investigations of these hereditary and sporadic forms of primary hyperparathyroidism have helped to identify some of the genes and chromosomal regions that are involved in the aetiology of parathyroid tumours (Table 13.4.2). FIHP has been reported in several kindreds, and some have been shown to harbour muta- tions of the MEN1 gene or the gene encoding parafibromin. These familial syndromes associated with parathyroid tumours will be briefly reviewed. MEN1 MEN1 is characterized by the combined occurrence of tu- mours of the parathyroids, pancreatic islet cells, and anterior pi- tuitary. Parathyroid tumours occur in 95% of MEN1 patients, and the resulting hypercalcaemia is the first manifestation of MEN1 in about 90% of patients. Pancreatic islet cell tumours occur in 40% of MEN1 patients, and gastrinomas, leading to the Zollinger–Ellison syndrome, are the most common type and also the important cause of morbidity and mortality in MEN1 patients. Anterior pituitary tumours occur in 30% of MEN1 patients, with prolactinomas rep- resenting the most common type. Associated tumours that may also occur in MEN1 include adrenal cortical tumours, carcinoid tumours, lipomas, angiofibromas, and collagenomas. The gene causing MEN1, which is located on chromosome 11q13 and repre- sents a putative tumour suppressor gene, consists of 10 exons that encode a 610 amino acid protein, known as menin. Menin is pre- dominantly a nuclear protein in nondividing cells, but in dividing cells it is found in the cytoplasm.

Menin has been shown to interact with many proteins that are involved in transcriptional regulation, genome stability, and cell division. The majority (>80%) of the germ- line MEN1 mutations in families are inactivating. Mutational ana- lysis of the MEN1 gene is helpful in the diagnosis and management of patients and their families. MEN2 and MEN3 MEN2 describes the association of medullary thyroid carcinoma (MTC), phaeochromocytomas, and parathyroid tumours. Three clinical variants of MEN2 are recognized: MEN2a, MEN2b (also referred to as MEN3), and MTC-only. MEN2a is the most common variant, where the development of MTC is associ- ated with phaeochromocytomas (50% of patients), which may be bilateral, and parathyroid tumours (20% of patients). MEN2b, which represents 5% of all MEN2 cases, is characterized by the oc- currence of MTC and phaeochromocytoma in association with a marfanoid habitus, mucosal neuromas, medullated corneal fibres, and intestinal autonomic ganglion dysfunction leading to multiple diverticulae and megacolon. Parathyroid tumours do not usually occur in MEN2b. MTC-only is a variant in which MTC is the sole manifestation of the syndrome. The gene causing all three MEN2 variants was mapped to chromosome 10q11.2, a region containing the c-RET proto- oncogene which encodes a tyrosine kinase re- ceptor with cadherin-like and cysteine-rich extracellular domains and a tyrosine kinase intracellular domain. Specific mutations of c-RET have been identified for each of the three MEN2 variants. Thus in 95% of patients, MEN2a is associated with mutations of the cysteine-rich extracellular domain and mutations in codon 634 (Cys→Arg) account for 85% of MEN2a mutations. MTC-only is also associated with missense mutations in the cysteine-rich extracel- lular domain and most mutations are at codon 618. MEN2b is asso- ciated with mutations in codon 918 (Met→Thr) of the intracellular tyrosine kinase domain in 95% of patients. Mutational analysis of c-RET to detect mutations in codons 609, 611, 618, 634, 768, and 804 in MEN2a and MTC-only, and codon 918 in MEN2b, has been used in the diagnosis and management of patients and families with these disorders. MEN4 Approximately 5% to 10% of MEN1 patients do have muta- tions of the MEN1 gene, and about 3% of these may have mutations involving the gene encoding a cyclin-dependent kinase inhibitor (CDNK1B) and are referred to as having MEN4. MEN4, an auto- somal dominant disorder, is characterized by occurrence of parathy- roid adenomas in association with pituitary adenomas, pancreatic neuroendocrine tumours, and tumours of the gonads, adrenals, kid- neys, and thyroid. HPT-JT The HPT-JT syndrome is an autosomal dominant dis- order characterized by the occurrence of parathyroid tumours that may be carcinomas in approximately 15% of patients and ossifying fibromas that usually affect the maxilla and/or mandible. In addition, some patients may also develop Wilms' tumours, renal cysts, renal hamartomas, renal cortical adenomas, papillary renal cell carcinomas, uterine tumours that may be malignant, pancre- atic adenocarcinomas, testicular mixed germ cell tumours with a major seminoma component, and Hürthle cell thyroid adenomas. It is important to note that the parathyroid tumours may occur in isolation and without any evidence of jaw tumours, and this may cause confusion with other hereditary hypercalcaemic disorders such as MEN1, familial hypocalciuric hypercalcaemia (FHH), and FIHP. HPT-JT can be distinguished from FHH, as in FHH serum calcium concentrations are elevated from the early neonatal or in- fantile period whereas in HPT-JT such elevations are uncommon in the first decade. In addition, HPT-JT patients, unlike those with FHH, will have associated hypercalciuria. The distinction between HPT-JT patients and MEN1 patients, who have only developed the usual first manifestation of hypercalcaemia (>90% of patients), is more difficult and is likely to be influenced by the operative and histological findings and the occurrence of other characteristic le- sions in each disorder. It should be noted that HPT-JT patients will usually have single adenomas or a carcinoma, while MEN1 patients will often have multiglandular parathyroid disease. The distinc- tion between FIHP and HPT-JT in the absence of jaw

tumours is difficult but important as HPT-JT patients may be at a higher risk of developing parathyroid carcinomas. These distinctions may be helped by the identification of additional features, and a search for jaw tumours and renal, pancreatic, thyroid, and testicular abnor- malities may help to identify HPT-JT patients. The jaw tumours in HPT-JT are different from the brown tumours observed in some

 patients with primary hyperparathyroidism, and do not resolve after parathyroidectomy. Indeed, ossifying fibromas of the jaw are an important distinguishing feature of HPT-JT from FIHP, and the occurrence of these may occasionally precede the development of hypercalcaemia in HPT-JT patients by several decades. The gene causing HPT-JT is CDC73, located on chromosome 1q31.2 and consisting of 17 exons that encode a ubiquitously ex- pressed 531 amino acid protein, parafibromin. This gene is also re- ferred to as HRPT2 (i.e. hyperparathyroidism type 2). Parafibromin has been shown to be associated with the human homologue of the Paf1 protein complex which interacts with RNA polymerase II, and, as part of this protein complex, parafibromin may regu- late post-transcriptional events and histone modification. The ma- jority (>80%) of the germ-line mutations in HRPT-JT families are inactivating and are predicted to result in a functional loss of the parafibromin protein because of premature truncation. In addition, patients with nonfamilial parathyroid carcinomas may harbour germ-line mutations, and mutational analysis of the gene encoding parafibromin is now undertaken in patients who have nonfamilial parathyroid carcinoma, FIHP, and HPT-JT. Malignancy Hypercalcaemia may occur in c.25% of patients with a malignancy and this is usually due to increased bone resorption, which may be either directly due to skeletal metastases or indirectly due to tumour production of a humoral factor that stimulates osteoclastic bone re- sorption. The cancers that typically metastasize to produce lytic bone lesions are from the breast, lymphomas, or multiple myeloma (Box 13.4.1). The associated osteolysis, mediated by recruitment and ac- tivation of osteoclasts, involves cytokines. Denosumab, which a hu- manized neutralizing monoclonal antibody to RANKL may be used to prevent the recruitment and activation of osteoclasts. The cancers that are typically associated with the humoral hypercalcaemia of ma- lignancy (HHM) are squamous carcinomas of the lung, oesophagus, cervix, vulva, skin, head, or neck, but other types from the kidney, bladder, ovary, and breast may also occur. HHM accounts for up to 80% of patients with malignancy-associated hypercalcaemia. The most common factor causing HHM is PTHrP, which can be meas- ured in the serum by immunoassay. However, these assays may be relatively insensitive and the failure to detect serum PTHrP does not exclude the diagnosis of HHM. Patients with HHM generally have hypercalcaemia associated with lower or undetectable serum PTH levels, marked hypercalcaemia, and a reduced plasma 1,25- dihydroxyvitamin D level. Therapy of HHM is aimed at: (1) reducing the tumour load by surgery, radiotherapy, and/or chemotherapy; (2) reducing osteoclastic bone resorption by use of bisphosphonates or calcitonin; and (3) increasing renal calcium clearance by a saline diuresis. Granulomatous disorders Several granulomatous disorders are associated with hypercalcaemia (Box 13.4.1) and this is invariably associated with elevated circu- lating concentrations of 1,25-dihydroxyvitamin D, which is due to extrarenal synthesis. Sarcoidosis is the most frequently encountered granulomatous disorder associated with hypercalcaemia, and 10% of patients with sarcoidosis will have hypercalcaemia and about one-half will become hypercalciuric. The finding of raised serum angiotensin-converting enzyme activity may help in confirming the diagnosis. Glucocorticoids (e.g. 40–60 mg prednisolone) de- crease 1,25-dihydroxyvitamin D production and restore the calcium concentration to normal. Failure to achieve normal serum calcium concentrations within 10 days of glucocorticoid therapy (e.g. hydro-

cortisone 40 mg, three times per day), which is referred to as the steroid suppression test, should suggest the coexistence of another cause for the hypercalcaemia (e.g. primary hyperparathyroidism) or malignancy. Endocrine causes of hypercalcaemia other than hyperparathyroidism Several nonparathyroid disorders (Box 13.4.1) are associated with hypercalcaemia and these include thyrotoxicosis, phaeochromo- cytoma, Addison's disease, VIPomas, FHH (also referred to as fa- milial benign hypercalcaemia (FBH)), Jansen's disease, and William's syndrome. Thyrotoxicosis Mild hypercalcaemia (<3.00 mmol/litre) frequently accompanies thyrotoxicosis, which leads to increased bone turnover and re- sorption. The hypercalcaemia may respond to treatment with β- adrenergic blockers. FHH and NHPT FHH is an autosomal dominant disorder with a high degree of pene- trance. It is characterized by lifelong asymptomatic hypercalcaemia in association with an inappropriately low urinary calcium excretion (i.e. ratio of calcium clearance to creatinine clearance (CCR) <0.01), and normal circulating PTH concentrations in 80% of patients. Mild hypermagnesaemia is also typically present. Although most patients with FHH are asymptomatic, chondrocalcinosis and acute pancreatitis have occasionally been observed. Patients with FHH have been mis-diagnosed as having primary hyperparathyroidism, as 20% of FHH patients may have elevated plasma PTH concentra- tions. In addition, 20% of FHH patients may have a CCR more than 0.01, and therefore be indistinguishable from patients with primary hyperparathyroidism. Moreover, low CCR are observed in patients with primary hyperparathyroidism who have vitamin D deficiency, or renal insufficiency, or are of an African-American origin. It is important to distinguish FHH patients from those with primary hyperparathyroidism, as the hypercalcaemia in FHH is generally benign and does not result in sequelae (Table 13.4.3). Moreover, parathyroidectomy does not correct the hypercalcaemia in FHH. Mutational analysis may help in identifying FHH patients from those with primary hyperparathyroidism. FHH is genetically heterogenous, with three reported variants FHH1, FHH2, and FHH3, whose loci are on chromosomes 3q21.1, 19p, and 19q13, respectively (Table 13.4.1). FHH1 is due to heterozy- gous loss-of-function mutations of the CaSR, which is a G-protein- coupled receptor (GPCR) that signals via Gαq and Gα11. The human CaSR, a 1078 amino acid cell surface protein encoded by the CaSR gene located on chromosome 3q21.1, is expressed in parathy- roids, thyroid cells, and kidney (Fig. 13.4.2), and is a member of the family of G-protein-coupled receptors. Approximately two-thirds of FHH kindreds will have unique heterozygous loss-of-function mu- tations of the CaSR. FHH2 is due to loss-of-function mutations in the G-protein subunit α11 (Gα11) (Fig. 13.4.2), and these may occur in less than 5% of FHH patients. FHH3 is due to loss-of-function

 mutations of the adaptor protein 2 (AP-2) sigma subunit (AP2σ) (Fig. 13.4.2). AP2 is a central component of clathrin-coated vesicles (CCVs) and is pivotal in clathrin-mediated endocytosis, which in- ternalizes plasma membrane constituents such as GPCRs. AP2 is a heterotetramer of α, β, μ and σ subunits and links clathrin to vesicle membranes and binds to tyrosine- and dileucine-based motifs of membrane-associated cargo proteins. The FHH3-associated AP2σ mutations, which all involve an Arg15 residue that forms key con- tacts with the dileucine-based motifs of CCV cargo proteins, reduce CaSR endocytosis, whose disruption likely decreases intracellular signalling. Such AP2σ loss-of-function mutations occur in more than 5% of FHH patients. FHH1, FHH2, and FHH3 have similar clinical features, and thus genetic analysis may help to identify the relevant mutations. However, the hypercalcaemia in FHH3 patients may be more severe and symptomatic than that in FHH1 patients, and cinacalcet can correct the hypercalcaemia of FHH3 patients with an improvement in

the symptoms. Some patients, who have the clinical features of FHH1, but not CaSR mutations, may have autoimmune hypocalciuric hypercalcaemia (AHH). Such patients may have multiple clinical autoimmune manifestations, including antithyroid antibodies, antigliadin, or antiendomyseal antibodies. These patients were shown to have cir- culating antibodies to the extracellular domain of the CaSR, and these antibodies stimulated PTH release from dispersed human parathyroid cells in vitro, probably by inhibiting the activation of the CaSR by extracellular calcium. The effects of treatment with gluco- corticoids have been variable, with the hypercalcaemia responding in one patient but not in another. Thus, AHH is a condition of extra- cellular calcium-sensing that should be considered in FHH1 pa- tients who do not have CaSR mutations. NSHP Neonatal severe primary hyperparathyroidism (NSHP) is defined as symptomatic hypercalcaemia with skeletal manifestations of hyperparathyroidism in the first 6 months of life. NSHP children often present in the first few days or weeks of life with failure to thrive, dehydration, hypotonia, constipation, rib cage deformities, and multiple fractures due to bony undermineralization. Children with NSHP often have life-threatening hypercalcaemia and require urgent parathyroidectomy, which corrects the PTH-dependent hypercalcaemia and bone demineralization. FHH is due to heterozy- gous inactivating mutations of the calcium-sensing receptor (CaSR) and NSHP is often associated with inactivating homozygous CaSR mutations when the children are from consanguineous parents with FHH1 (Fig. 13.4.2). However, NSHP has also been observed in chil- dren where only one parent had clinically apparent FHH, and many other NSHP patients appear to be sporadic, that is both parents have normal serum calcium concentrations. In such NSHP patients with heterozygous CaSR mutations, the mutant CaSR may exert a dom- inant negative action on the normal CaSR. Jansen's disease Jansen's disease is an autosomal dominant disease that is characterized by short-limbed dwarfism, due to metaphyseal chondrodysplasia, and severe hypercalcaemia and hypophosphataemia, despite normal or undetectable serum levels of PTH. These abnormalities are asso- ciated with activating mutations of the PTH receptor (Fig. 13.4.2) and thus this represents a PTH-independent activation of the PTH receptor. William's syndrome William's syndrome is an autosomal dominant disorder character- ized by supravalvular aortic stenosis, elfin-like facies, psychomotor retardation, and infantile hypercalcaemia. The underlying abnor- mality of calcium metabolism remains unknown but abnormal 1,25-dihydroxyvitamin D3 metabolism or decreased calcitonin pro- duction have been implicated, although no abnormality has been consistently demonstrated. Hemizygosity due to a microdeletion at the ELN locus on chromosome 7q11.23 in over 90% of patients with the classic William's phenotype has been demonstrated. This microdeletion has been reported to involve another gene, desig- nated LIMK1, that is expressed in the central nervous system. The

Table 13.4.3 Clinical, biochemical, and genetic features of hypoparathyroid and pseudohypoparathyroid disorders Hypoparathyroidism Pseudohypoparathyroidism PHPIa PPHP PHPIb PHPIc PHPII AHO manifestations No Yes Yes No/Rarely Yes No Serum calcium ↓ ↓ N ↓ ↓ ↓ Serum PO4 ↑ ↑ N ↑ ↑ ↑ Serum PTH ↓ ↑ N ↑ ↑ ↑ Response to PTH: Urinary cAMPa (Chase–Aurbach test) ↑ ↓ ↑ ↓ ↓ ↑ Urinary PO4 (Ellsworth–Howard test) ↑ ↓ ↑ ↓ ↓ ↓ Gsα activity N ↓ ↓ N N N Inheritance AD/AR/X AD AD AD/Sporadic AD Sporadic Molecular defect PTH/CaSR/GATA3/GCM2/others GNAS1 GNAS1 GNAS1b GNAS1 ?cAMP targets Other hormonal resistance No Yes No No (Usually) Yes No AD, autosomal dominant; AHO, Albright's hereditary osteodystrophy; AR, autosomal recessive; CaSR, calcium-sensing receptor; GATA3, GATA binding protein 3; GCM2, glial cells missing homologue 2; N, normal; PHP, pseudohypoparathyroidism; PPHP, pseudopseudohypoparathyroidism; X, X-linked; ↓, decreased; ↑, increased; ?, presumed, but not proven. a Plasma cAMP responses are similar to those of urinary cAMP. b Involves deletions

located upstream of GNAS1

SECTION 13 Endocrine disorders 2326 calcitonin receptor gene has been localized to chromosome 7q21 and close to the region deleted in William's syndrome. However, the calcitonin receptor gene was not involved in the deletion found in four patients with William's syndrome, indicating that it is un- likely to be implicated in the hypercalcaemia of such children. While the involvement of the ELN and LIMK1 genes in the deletions of William's syndrome patients can explain the respective cardiovas- cular and neurological features of this disorder, it seems possible that another, as yet uncharacterized gene that is within this contigu- ously deleted region is likely to be involved to explain the abnormal- ities of calcium metabolism. Infantile hypercalcaemia Infantile hypercalcaemia is associated with failure to thrive and is characterized by: severe hypercalcaemia; hypercalciuria; nephrocalcinosis; and elevated circulating 1,25(OH)2D concen- trations. Some infants with this disorder have homozygous or compound heterozygous mutations of the gene encoding the 24- hydroxylase (CYP24A1) enzyme which metabolizes the active 1,25(OH)2D to the inactive 1,24,25(OH)3D form (Fig. 13.4.1). Drugs Several drugs (Box 13.4.1) can cause hypercalcaemia by different mechanisms. Compounds containing vitamin D and vitamin A are common and frequently associated with hypercalcaemia. The use of thiazide diuretics is often associated with hypercalcaemia. The hypercalcaemia appears to be largely renal in origin, as thiazides enhance distal renal tubular calcium reabsorption. Hypercalcaemia reverses rapidly with discontinuation of the drug. The milk-alkali syndrome was first described in the 1930s, gen- erally in the context of ulcer treatment with large quantities of milk together with sodium bicarbonate. Today, the responsible agent is usually calcium carbonate, although consumption of large quantities of dairy products (milk, cheese, and yoghurt) may still contribute. Classic features include moderate to severe hypercalcaemia with al- kalosis and renal impairment. The amount of calcium ingested by patients with this syndrome is usually 5 to 15 g/day. Treatment con- sists of: (1) discontinuing the ingestion of the calcium-containing compound(s) and antacids, (2) rehydration, and (3) saline diuresis. Hypocalcaemia Clinical features and investigations The clinical presentation of hypocalcaemia (serum calcium <2.12 mmol/litre) ranges from an asymptomatic biochemical ab- normality to a severe, life-threatening condition. In mild hypo- calcaemia (serum calcium 2.00–2.12 mmol/litre), patients may be asymptomatic. Those with more severe (serum calcium <1.9 mmol/ litre) and long-term hypocalcaemia may develop acute symptoms of neuromuscular irritability (Box 13.4.6), ectopic calcification (e.g. in the basal ganglia, which may be associated with extrapyramidal neurological symptoms), subcapsular cataract, papilloedema, and abnormal dentition. Investigations should be directed at confirming the presence of hypocalcaemia and establishing the cause. Hypocalcaemia (Box 13.4.5) can be classified by cause, according to whether serum PTH concentrations are low (i.e. hypoparathyroid disorders) or high (i.e. disorders associated with secondary hyperparathyr- oidism). Hypocalcaemia is most commonly caused by hypopara- thyroidism, a deficiency or abnormal metabolism of vitamin D, acute or chronic renal failure, or hypomagnesaemia. In hypopara- thyroidism, serum calcium is low, phosphate is high, and PTH is undetectable; renal function and concentrations of the 25-hydroxy and 1,25-dihydroxy metabolites of vitamin D are usually normal. The features of pseudohypoparathyroidism are similar to those of hypoparathyroidism except for PTH, which is markedly increased. In chronic renal failure, which is the most common cause of hypo- calcaemia, phosphate is high and alkaline phosphatase, creatinine, and PTH are elevated; 25-hydroxyvitamin D3 is normal and 1,25- dihydroxyvitamin D3 is low. In vitamin D deficiency and osteomal- acia, serum calcium and phosphate are low, alkaline phosphatase and PTH are elevated, renal function

is normal, and 25-hydroxyvitamin D3 is low. The most frequent artefactual cause of hypocalcaemia is hypoalbuminaemia, such as occurs in liver disease or the nephrotic syndrome. Management of acute hypocalcaemia The management of acute hypocalcaemia depends on the severity of the hypocalcaemia, the rapidity with which it developed, and the degree of neuromuscular irritability (Box 13.4.6). Treatment should be given to symptomatic patients (e.g. with seizures or tetany) and asymptomatic patients with a serum calcium of less than 1.90 mmol/litre who are at high risk of developing compli- cations. The preferred treatment for acute symptomatic hypocal- caemia is calcium gluconate, 10 ml 10% weight per volume (w/v) (2.20 mmol calcium), diluted in 50 ml of 5% dextrose or 0.9% so- dium chloride and given by slow intravenous injection (>5 min); this can be repeated as required to control symptoms. Serum calcium concentrations should be assessed regularly. Persistent hypocalcaemia may be managed acutely by administration of a calcium gluconate infusion as follows. Dilute 10 ampoules of cal- cium gluconate, 10 ml 10% w/v (22.0 mmol calcium), in 1 litre of 5% dextrose or 0.9% sodium chloride, start the infusion at 50 ml/ h, and titrate to maintain serum calcium concentrations in the normal range. Generally, 0.3 to 0.4 mmol/kg elemental calcium in- fused over 4 to 6 h increases serum calcium by 0.5 to 0.75 mmol/ Box 13.4.6 Hypocalcaemic clinical features of neuromuscular irritability • Paraesthesia, usually of fingers, toes, and circumoral regions • Tetany, carpopedal spasm, muscle cramps • Chvostek's signa • Trousseau's signb • Seizures of all types (i.e. focal or petit mal, grand mal, or syncope) • Prolonged Q–T interval on ECG • Laryngospasm • Bronchospasm a Chvostek's sign is twitching of the circumoral muscles in response to gentle tapping of the facial nerve just anterior to the ear; it may be present in 10% of normal individuals. b Trousseau's sign is carpal spasm elicited by inflation of a blood pressure cuff to 20 mm Hg above the patient's systolic blood pressure for 3 min.

 litre. If hypocalcaemia is likely to persist, oral vitamin D therapy (see next) should also be administered. In hypocalcaemic patients who are also hypomagnesaemic, the hypomagnesaemia must be corrected before the hypocalcaemia will resolve. This may occur in the postparathyroidectomy period or in patients with severe malabsorption (e.g. those with established coeliac disease). Management of persistent hypocalcaemia The two main agents available for the treatment of hypocalcaemia are supplemental calcium (c.10–20 mmol calcium every 6–12 h), and vitamin D preparations. Patients with hypoparathyroidism seldom require calcium supplements after the early stages of sta- bilization with vitamin D. A variety of vitamin D preparations have been used. These include vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol), 25 000 to 100 000 IU (1.25–5 mg/ day); dihydrotachysterol (now seldom used), 0.25 to 1.25 mg/ day; alfacalcidol (1α-hydroxycholecalciferol), 0.25 to 1.0 µg/day; and calcitriol (1,25-dihydroxycholecalciferol), 0.25 to 2.0 µg/day. In children, these preparations are prescribed in dosages based on body weight. Cholecalciferol and ergocalciferol are the least expensive preparations but have the longest durations of action and may result in prolonged toxicity. The other preparations, which do not require renal 1α-hydroxylation, have the advantage of shorter half-lives and thereby minimize the risk of prolonged toxicity. Calcitriol is probably the drug of choice because it is the active metabolite and, unlike alfacalcidol, does not require hepatic 25-hydroxylation. Close monitoring (at about 1- to 2-week inter- vals) of the patient's serum and urine calcium concentrations are required initially, and at 3- to 6-month intervals once stabilization is achieved. The aim is to avoid hypercalcaemia, hypercalciuria, nephrolithiasis, and renal failure. It should be noted that hypercalciuria may occur in the absence of hypercalcaemia. The use of PTH replacement, using

recombinant human PTH 1-84 (rhPTH) by subcutaneous injections, in patients with hypoparathyroidism has been reported to: decrease the requirements of supplemental calcium and calcitriol; and to restore serum cal- cium concentrations to within the normal range without producing hypercalciuria. The use of rhPTH has been approved by the Food and Drug Administration (FDA) for treatment of refractory hypoparathyroidism. Hypocalcaemic diseases Hypocalcaemic diseases (Box 13.4.5) may arise because of destruc- tion of the parathyroid glands, failure of parathyroid gland develop- ment, or reduced PTH secretion or PTH-mediated actions in target tissues. Thus, these diseases may be classified as being due to a de- ficiency of PTH, a defect in the PTH receptor (i.e. the PTH/PTHrP receptor), or an insensitivity to PTH caused by defects downstream of the PTH/PTHrP receptor (Fig. 13.4.2). The diseases may also be classified as being part of the hypoparathyroid disorders, of the CaSR abnormalities, or of the pseudohypoparathyroid disorders. Hypoparathyroidism Hypoparathyroidism is characterized by hypocalcaemia and hyperphosphataemia, which are the result of a deficiency in PTH secretion or action. Serum concentrations of immunoreactive PTH are low or undetectable and the concentrations of 1,25-dihydroxyvitamin D3 are usually in the low normal to low range, but alkaline phosphatase activity is unchanged. The daily urinary excretion of calcium is reduced, although the fractional excretion of calcium is increased. Nephrogenous cAMP excretion is low and renal tubular reabsorption of phosphate is elevated. Urinary cAMP, plasma cAMP, and urinary phosphate excretion increase markedly after administration of exogenous bioactive PTH (Chase–Aurbach and Ellsworth–Howard tests). Hypoparathyroidism may result from agenesis (e.g. DiGeorge’s syndrome) or destruction of the parathyroid glands (e.g. following neck surgery, in autoimmune diseases), from reduced secretion of PTH (e.g. neonatal hypocal- caemia or hypomagnesaemia), or resistance to PTH (which may occur as a primary disorder (e.g. pseudohypoparathyroidism) or secondary to hypomagnesaemia). In addition, hypoparathyroidism may occur as an inherited disorder (Table 13.4.2) that may either be part of a complex congenital defect (e.g. DiGeorge’s syndrome), or as part of a polyglandular autoimmune disorder, or as a solitary endocrinopathy, which has been referred to as isolated or idiopathic hypoparathyroidism. Hypoparathyroidism may also complicate iron storage disease, especially secondary haemochromatosis in children and adolescents. In thalassaemic children, destruction of the parathyroids is associated with ill health and frank tetany, which may elude diagnosis and effective treatment unless hypoparathyr- oidism is suspected. Isolated hypoparathyroidism Isolated hypoparathyroidism may either be inherited, or it may be acquired by damage to the parathyroids at surgery, by infiltrating metastases, or following systemic disease (Box 13.4.5). Inherited hypoparathyroidism Patients with inherited forms of hypoparathyroidism may develop hypocalcaemic seizures in the neonatal or infantile periods and require lifelong treatment with oral vitamin D preparations (e.g. calcitriol). Autosomal dominant, autosomal recessive, and X-linked recessive inheritances for hypo- parathyroidism have been observed (Table 13.4.2). Some of the autosomal forms are due to mutations of the PTH gene, the CaSR and Gα11 (see next), and the transcriptional factor GCM2 (glial cells missing homologue 2). CaSR and Gα11 mutations causing ADH1 and ADH2 ADH1 and ADH2 are due to gain-of-function mutations of the CaSR and Gα11, respectively (Table 13.4.1, Fig. 13.4.2). ADH1 is character- ized by lifelong mild or severe hypocalcaemia in association with normal serum PTH concentrations in c.40% of patients or low serum PTH concentrations in c.60% of patients. Serum phosphate and magnesium concentrations may be elevated or low, respectively. Approximately 50% of ADH1 patients have asymptomatic hypo- calcaemia, and the remaining 50% may experience paraesthesia, muscle cramps, carpo-pedal spasms, and seizures, which may be associated with a febrile illness. In addition, about 10% of ADH1 patients may have absolute hypercalciuria which

may be associated with nephrocalcinosis and kidney stones in 35% of patients. Vitamin D preparations and calcium supplementation to correct the hypo- calcaemia may worsen the hypercalciuria and lead to renal impair- ment. Basal ganglia or ectopic calcification may be found in more than 35% of patients. About 20% of ADH1 patients do not have a previously reported family history, as they have de novo mutations. ADH2 patients appear to have clinical features that are similar to those in ADH1 patients.

SECTION 13 Endocrine disorders 2328 Acquired forms of hypoparathyroidism Hypoparathyroidism may occur after neck surgery, irradiation, or because of infiltration by metastases or systemic disease, for example, haemochroma- tosis, amyloidosis, sarcoidosis, Wilson's disease, or thalassaemia (Box 13.4.5). Surgical damage to the parathyroids occurs most com- monly after a radical neck dissection; for example, laryngeal or oe- sophageal carcinoma treatment, a total thyroid resection, or after repeated parathyroidectomies for multiglandular disease (e.g. in MEN1 or MEN2, see earlier). Hypocalcaemic symptoms begin 12 to 24 h postoperatively and may need treatment with oral or intra- venous calcium. Parathyroid function often returns, but persistent hypocalcaemia requires treatment with vitamin D preparations. Neonatal hypoparathyroidism resulting in hypocalcaemia may occur in the baby of a mother with hypercalcaemia caused by pri- mary hyperparathyroidism. Maternal hypercalcaemia results in in- creased calcium delivery to the fetus, and this fetal hypercalcaemia suppresses fetal PTH secretion. Postpartum, the infant's suppressed parathyroids are unable to maintain normocalcaemia. The disorder is usually self-limiting, but occasionally therapy may be required. In addition, the feeding to babies of cow's milk, which has a high phos- phate content, may also result in hypocalcaemia in some infants. Functional hypoparathyroidism may result from severe hypomag- nesaemia (<0.40 mmol/litre), which may be due to a severe intestinal malabsorption disorder (e.g. Crohn's disease) or a renal tubular dis- order. It is associated with hypoparathyroidism because magnesium is required for the release of PTH from the parathyroid gland and also for PTH action via adenyl cyclase. Magnesium chloride, 35 to 50 mmol intravenously in 1 litre of 5% glucose or other isotonic so- lution given over 12 to 24 h may be repeatedly required to restore normomagnesaemia. Complex syndromes associated with hypoparathyroidism Hypoparathyroidism may occur as part of a complex syndrome which may either be associated with a congenital developmental anomaly or with an autoimmune syndrome. The congenital devel- opmental anomalies associated with hypoparathyroidism, which occurs in 1 in 4000 live births, include the DiGeorge, the HDR (hypoparathyroidism, deafness, and renal anomalies), the Kenney– Caffey, and the Barakat syndromes, and also syndromes associ- ated with either lymphoedema or dysmorphic features and growth failure (Table 13.4.2). DiGeorge's syndrome types 1 and 2 Patients with DiGeorge's syn- drome (DGS) have neonatal hypoparathyroidism, T-cell immuno- deficiency, congenital heart defects, and deformities of the ear, nose, and mouth (e.g. cleft lip and/or palate). Children with DGS often die from infections related to the immunodeficiency. The disorder arises from a congenital failure in the development of the deriva- tives of the third and fourth pharyngeal pouches with resulting ab- sence or hypoplasia of the parathyroids and thymus. Most cases of DGS are sporadic but an autosomal dominant inheritance of DGS has been observed, and an association between the syndrome and an unbalanced translocation and deletions involving chromosome 22q11.2 have also been reported. Such patients with the 22q11.2 deletions are referred to as DGS type 1 (DGS1), and studies of the DGS1 deleted region have revealed four genes (RNEX40, NEX2.2- NEX3, UDFIL, and TBX1) to be involved. However, point muta- tions in DGS1 patients have been detected only in the TBX1 gene, and TBX1 is now considered to be the gene causing DGS1. TBX1 encodes a DNA-binding

transcriptional factor of the T-box family that is known to have an important role in vertebrate and inverte- brate organogenesis and pattern formation. The TBX1 gene is de- leted in approximately 96% of all DGS1 patients, and some of those without deletions have been shown to harbour mutations of TBX1. In some other patients, deletions of another locus on chromosome 10p13–p14 have been observed in association with DGS and this is referred to as DGS type 2 (DGS2). The nebulette (NEBL) gene has been reported to be heterozygously deleted in cell lines from DGS2 patients, and may be the responsible gene. Hypoparathyroidism, deafness, and renal anomalies (HDR) syn- drome HDR is an autosomal dominant disorder in which patients often have asymptomatic hypocalcaemia with undetectable or in- appropriately normal serum concentrations of PTH, and normal brisk increases in plasma cAMP in response to the infusion of PTH. Bilateral, symmetrical, sensorineural deafness involving all frequen- cies occurs, and the renal abnormalities consist mainly of bilateral cysts that compress the glomeruli and tubules and lead to renal impairment. Cytogenetic abnormalities involving chromosome 10p14–10pter have been identified in HDR patients. HDR patients do not have immunodeficiency or heart defects, which are key fea- tures of DGS2, and indeed there are two nonoverlapping regions; thus, the DGS2 region is located on 10p13–14 and HDR on 10p14– 10pter. HDR patients have deletions or mutations of the zinc finger transcription factor GATA3. Mitochondrial disorders associated with hypoparathyr- oidism Hypoparathyroidism has been reported to occur in three disorders associated with mitochondrial dysfunction: the Kearns– Sayre syndrome (KSS), the mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS), and a mitochondrial trifunctional protein deficiency syndrome. Kearns– Sayre syndrome is characterized by progressive external ophthal- moplegia and pigmentary retinopathy before the age of 20 years, and is often associated with heart block or cardiomyopathy. The MELAS syndrome consists of a childhood onset of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes. In add- ition, varying degrees of proximal myopathy can be seen in both conditions. Both the Kearns–Sayre and MELAS syndromes have been reported to occur with insulin-dependent diabetes mellitus and hypoparathyroidism, and mitochondrial gene abnormalities have been identified in some patients. Mitochondrial trifunctional protein deficiency is a disorder of fatty acid oxidation that is associ- ated with peripheral neuropathy, pigmentary retinopathy, and acute fatty liver degeneration in pregnant women who carry an affected fetus. Hypoparathyroidism has been observed in one patient with trifunctional protein deficiency. Kenney–Caffey, Sanjad–Sakati, and Kirk-Richardson syn- dromes Hypoparathyroidism has been reported to occur in over 50% of patients with the Kenney–Caffey syndrome, which is as- sociated with short stature, osteosclerosis, and cortical thickening of the long bones, delayed closure of the anterior fontanel, basal ganglia calcification, nanophthalmos, and hyperopia. Parathyroid tissue could not be found in a detailed post-mortem examination of one patient and this suggests that hypoparathyroidism may be due to an embryological defect of parathyroid development. In the Kirk-Richardson and Sanjad–Sakati syndromes, which are similar, hypoparathyroidism is associated with severe growth failure and

 dysmorphic features. This has been reported in patients of Middle Eastern origin, whose parents were consanguineous, thereby indicating that these are autosomal recessive disorders. Molecular genetic investigations have identified mutations of the tubulin- specific chaperone (TBCE) to be associated with the Kenney–Caffey and Sanjad–Sakati syndromes. TBCE encodes one of several chap- erone proteins required for the proper folding of α-tubulin subunits and the formation of α-β tubulin heterodimers. Kenney–Caffey type 2 is due to mutations of the family with sequence similarity 111, member

A (FAM111A) gene, located on chromosome 11q12.1. Additional familial syndromes Single familial syndromes in which hypoparathyroidism is a component have been reported (Table 13.4.2). Thus, an association of hypoparathyroidism, renal insufficiency, and developmental delay has been reported in one Asian family in whom autosomal recessive inheritance of the dis- order was established. The occurrence of hypoparathyroidism, nerve deafness, and a steroid-resistant nephrosis leading to renal failure, which has been referred to as the Barakat syndrome, has been re- ported in four brothers from one family, and an association of hypo- parathyroidism with congenital lymphoedema, nephropathy, mitral valve prolapse, and brachytelephalangy has been observed in two brothers from another family. Molecular genetic studies have not been reported from these two families. Blomstrand's disease Blomstrand's chondrodysplasia is an auto- somal recessive disorder characterized by early lethality, dramat- ically advanced bone maturation, and accelerated chondrocyte differentiation. Affected infants, who usually have consanguin- eous unaffected parents, develop pronounced hyperdensity of the entire skeleton with markedly advanced ossification that results in extremely short and poorly modelled long bones. Mutations of the PTH/PTHrP receptor that impair its function are associated with Blomstrand's disease. Thus, it seems likely that affected infants will, in addition to the skeletal defects, have abnormalities in other or- gans, including secondary hyperplasia of the parathyroid glands, presumably due to hypocalcaemia. Polyglandular autoimmune hypoparathyroidism This syn- drome (Fig. 13.4.4) comprises hypoparathyroidism, Addison's disease, candidiasis, and two or three of the following: insulin- dependent diabetes mellitus, primary hypogonadism, autoimmune thyroid disease, pernicious anaemia, chronic active hepatitis, steatorrhoea (malabsorption), alopecia (totalis or areata), and viti- ligo. The disorder has also been referred to as either the autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome or the polyglandular autoimmune type 1 syndrome. Antibodies directed against the adrenal, thyroid, and parathyroid glands are detected in the sera of some patients. The polyglandular autoimmune type 2 syndrome is characterized by adrenal insuffi- ciency, insulin-dependent diabetes mellitus, and thyroid disease, and does not involve hypoparathyroidism. APECED syndrome, which has an autosomal recessive inheritance, has a high incidence in Finland and among Iranian Jews. The affected gene in APECED syndrome is the AIRE (autoimmune regulator) gene, which has been located to chromosome 21q22.3. It encodes a 545 amino acid protein that contains motifs suggestive of a transcriptional factor and includes a nuclear localization signal, two zinc finger motifs, a proline-rich region, and three LXXLL motifs. Four AIRE mutations are commonly found in APECED families: Arg257Stop in Finnish, German, Swiss, British, and Northern Ireland families; Arg139Stop in Sardinian families; Tyr85Cys in Iranian Jewish families; and a 13- bp deletion in exon 8 in British, Dutch, German, and Finnish fam- ilies. These mutations likely abolish the E3 ubiquitin ligase activity of the AIRE1 protein, which has been shown to regulate the elimin- ation of organ-specific T cells in the thymus. Thus, APECED is likely to be caused by a failure of this specialized mechanism for deleting forbidden T cells and establishing immunological tolerance. Autoimmune acquired hypoparathyroidism (AH) Twenty per cent (20%) of patients who had acquired hypopara- thyroidism in association with autoimmune hypothyroidism, were found to have autoantibodies to the extracellular domain of the CaSR (Table 13.4.1, Fig. 13.4.2). The CaSR autoantibodies did not persist for long; 72% of patients who had AH for less than 5 years had detectable CaSR autoantibodies; whereas only 14% of patients with AH for more than 5 years had such autoantibodies. The ma- jority of the patients who had CaSR autoantibodies were females, a finding that is similar to that found in other auto-antibody medi- ated diseases. Indeed a few acquired hypoparathyroidism patients have also had features of autoimmune polyglandular syndrome type

1. The epitopes for the anti-CaSR antibodies were localized to the N-terminal of the extracellular domain of the receptor. These findings establish that the CaSR is an autoantigen in acquired hypoparathyroidism. Pseudohypoparathyroidism (PHP) Patients with PHP, which may be inherited as an autosomal dominant disorder, are characterized by hypocalcaemia and hyperphosphataemia due to PTH resistance rather than PTH deficiency. Five variants are recognized on the basis of bio- chemical and somatic features (Table 13.4.3) and three of these—PHP type Ia (PHPIa), PHP type 1b (PHPIb), and pseudopseudohypoparathyroidism (PPHP)—will be reviewed in further detail.
Fig. 13.4.4 Candidiasis and hyperpigmentation of the hands, particularly over the knuckles, are seen in this 8-year-old patient with hypoparathyroidism and Addison's disease. The patient also had vitiligo, and thus had some of the features of the polyglandular autoimmune syndrome type 1. Reproduced with permission from Thakker RV (1997). Hypocalcaemic disorders. In: Thakker RV, Wass JAH (eds) Endocrine disorders, medicine, vol. 25, pp. 68–70. The Medicine Group (Journals), Abingdon.

 Patients with PHPIa exhibit PTH resistance (hypocalcaemia, hyperphosphataemia, elevated serum PTH, and an absence of an increase in serum and urinary cAMP and urinary phosphate following intravenous human PTH infusion), together with the features of Albright's hereditary osteodystrophy (AHO), which in- cludes short stature, obesity, subcutaneous calcification, mental re- tardation, round facies, dental hypoplasia, and brachydactyly (i.e. shortening of the metacarpals (Fig. 13.4.5), particularly the third, fourth, and fifth). In addition to brachydactyly, other skeletal ab- normalities of the long bones and shortening of the metatarsals may also occur. Patients with PHPIb exhibit PTH resistance only and do not have the somatic features of AHO, while patients with PPHP ex- hibit the somatic features of AHO in the absence of PTH resist- ance. The absence of a normal rise in urinary excretion of cAMP excretion after an infusion of PTH in PHPIa indicates a defect at some site of the PTH receptor–adenyl cyclase system (Fig. 13.4.2). This receptor system is regulated by at least two G proteins, one of which stimulates (Gsα) and another which inhibits (Giα) the ac- tivity of the membrane-bound enzyme that catalyses the forma- tion of the intracellular second messenger cAMP. Interestingly, patients with PHPIa may also show resistance to other hormones (e.g. thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone) that act via G-protein-coupled recep- tors. Inactivating mutations of the Gsα gene (referred to as GNAS1), which is located on chromosome 20q13.2, have been identified in PHPIa and PPHP patients. However, GNAS1 mutations do not fully explain the PHPIa or PPHP phenotypes, and studies of PHPIa and PPHP that occurred within the same kindred re- vealed that the hormonal resistance is parentally imprinted. Thus, PHPIa occurs in a child only when the mutation is inherited from a mother affected with either PHPIa or PPHP, and PPHP occurs in a child only when the mutation is inherited from a father affected with either PHPIa or PPHP. PHPIb is due to deletions that are located upstream of the GNAS1 gene. Moreover, in affected in- dividuals the deletion involved the maternal allele, whereas its occurrence on the paternal allele resulted in unaffected healthy carriers. This is consistent with parental imprinting of the GNAS1 abnormality causing PHPIb. FURTHER READING Bilezikian JP, et al. (2014). Guidelines for the management of asymp- tomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab, 99, 3561–9. Bilezikian JP, et al. (2016). Management of hypoparathyroidism: pre- sent and future. J Clin Endocrinol Metab, 101, 2313–24. Bollerslev J, et al. (2015). European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol, 173, G1–20. Brandi ML, et al. (2016). Management of hypoparathyroidism: sum- mary statement and guidelines. J Clin Endocrinol Metab, 101, 2273–83. Clarke BL, et al. (2016). Epidemiology and diagnosis of hypoparathyr- oidism. J Clin

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