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ESSENTIALS Bone is made up of (1) cells—osteoblasts, osteoclasts, and osteocytes; and (2) extracellular mineralized matrix—roughly one-third organic (90% type 1 collagen) and two-thirds inorganic (mainly hydroxy- apatite). Bone modelling occurs during growth and remodelling throughout life due to the constant processes of osteoclastic bone resorption and osteoblastic bone formation, which are closely linked and regulated within bone multicellular units. In adults, the replace- ment of old bone with new occurs at an annual turnover rate of 25% in trabecular bone, and 2–3% in cortical bone. Common presentations of bone disease include (1) deformity and short stature; (2) bone pain and fracture; (3) myopathy—in osteomal- acia and rickets; (4) features of underlying disease (e.g. renal failure, myeloma). A full general medical history, carefully taken family his- tory, and thorough physical examination—with particular emphasis on the musculoskeletal system—may be crucial in making the cor- rect diagnosis. Many generalized disorders of the skeleton, such as osteoporosis, have entirely normal routine biochemical values. Radiographic imaging can be diagnostic in some cases, but mag- netic resonance imaging and computed tomography are increas- ingly employed in addition to conventional (‘plain’) radiographs and bisphosphonate-labelled isotope scans. Bone biopsy is required for diagnosis in some circumstances. This chapter emphasizes those disorders in which impact on the skeleton is a substantial feature of the underlying condition. Introduction Classic metabolic bone diseases Osteomalacia and rickets—most frequently result from a lack of vitamin D or a disturbance of its metabolism, with the main histo logical feature of osteomalacia being defective mineralization of bone matrix. Causes are (1) lack of intake—either low dietary in take or ineffective ultraviolet (UV) B exposure; (2) malabsorptive (e.g. coeliac disease); (3) renal—including renal tubular disorders (e.g. inherited hypophosphataemias), and chronic kidney disease; (4) miscellaneous (e.g. anticonvulsant drugs). Dominant symp toms are bone pain and tenderness, skeletal deformity, and prox imal muscle weakness, often accompanied by the features of the underlying disorder and by

those of hypocalcaemia. Biochemical changes depend on the cause, but in vitamin D deficiency or malabsorption there are low urinary calcium excretion, low plasma phosphate, elevated PTH (secondary hyperparathyroidism) and an increase in plasma alkaline phosphatase; a low plasma 25(OH) D level is a good indication of vitamin D deficiency that has largely obviated the need for bone histology in the diagnosis of nutritional rickets. Frank hypocalcaemia is uncommon. The radiological hall mark of active osteomalacia is the Looser zone, a ribbon-like area of defective mineralization that is most often seen in the long bones, pelvis, ribs, and around the scapulae. Where there is doubt about the diagnosis, a bone biopsy examined before and after decalcification will demonstrate failure of mineralization and wide osteoid seams. Rickets and osteomalacia should respond rapidly to parent vitamin D (or one of its metabolites) in appro priate doses, and the response may be a useful way of confirming the diagnosis. Paget’s disease of bone—a common disorder (3–4% of people

> 40 years of age), characterized by excessive and disorganized resorption and formation of bone. It is predominantly of genetic cause, with the most frequent mutation being in the gene coding for the ubiquitin-binding protein sequestosome. The condition is often asymptomatic, but symptoms of Paget’s disease include pain, deformity, fracture, secondary osteoarthritis, deafness, and nerve compression; bone sarcoma arises in 1% or less of symptomatic patients. There is a marked increase in the level of plasma alkaline phosphatase, and the most characteristic radiological appearance is an increase in size of the affected bone. Many patients do not require any treatment. Bone pain should initially be treated with simple an algesics. If these are ineffective, or there are pagetic complications, treatment with a bisphosphonate is indicated. Zolendronic acid can induce almost complete long-term suppression of disease without significant side effects. (For further details on parathyroid bone disease and hyperpara thyroidism, see Chapters 13.4 and 21.6, respectively; for hypopara thyroidism, see Chapter 13.4; for osteoporosis, see Chapter 20.4.)
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> and clinical conditions B. Paul Wordsworth and M.K. Javaid

SECTION 20 Disorders of the skeleton 4616 Synthetic defects in the major components of the organic bone matrix and connective tissue Osteogenesis imperfecta—involves those tissues that contain the main fibrillar collagen, type 1. Manifest as a spectrum of disease, including (1) type 2, the most severe; commonly arises from single base changes in COL1A1 or COL1A2 genes; nearly always lethal; to (2) type 3, causes severe and progressive disability; patients rarely walk and have very short stature; sclerae may be blue in infancy but may take on a normal colour in childhood; to (3) type 1—the com monest and least serious form; appears to be caused by a null allele for collagen 1, so that only 50% of collagen is produced, but this is of normal composition; fractures occur in childhood but then remit during adulthood until the menopause; other features can include hypermobility and dislocation of joints, dentinogenesis imperfecta, and cardiac valve disease (e.g. aortic incompetence); blueness of the sclerae is characteristic. In the first few years of life nonaccidental injury, ‘battered baby syndrome’, is the main dif ferential diagnosis. Cyclic intravenous pamidronate may alleviate symptoms, increase bone density, and reduce fracture rate

in se vere disease but definitive evidence of effectiveness in adulthood is lacking. Skeletal dysplasias is a term used to cover a variety of general ized disorders of the skeleton affecting both cartilage and bone. It can be classified into families on the basis of (1) clinical fea tures (e.g. bodily proportions) achondroplasia is the prototype of the short-limbed, short-stature phenotype; spondyloepiphyseal dysplasias have prominent spinal involvement and short stature is partly due to shortness of the trunk; or (2) biochemical features/ genetic analysis. (For more on inherited defects of connective tissue—see Chapter 20.2.) Skeletal disorders caused by enzyme defects Homocystinuria—caused by cystathionine β-synthase deficiency; ocular, skeletal, central nervous, and vascular manifestations; skel etal features similar to Marfan syndrome and include long, thin body habitus, pectus excavatum, scoliosis, and gene values (see Chapter 12.2). Alkaptonuria—caused by decreased activity of homogentisate 1,2-dioxygenase; should be suspected when there is premature disc degeneration and/or early degenerative arthritis; characteristic fea tures include abnormal dark pigmentation of the cartilage of the ear and nose, the sclerae, and of the urine (see Chapter 12.2). Hypophosphatasia—caused by reduction in tissue nonspecific alkaline phosphatase; varies from a lethal perinatal disorder to an asymptomatic disease in adults, but adults may present with progres sive stiffness, pain in the bones, and apparent ‘stress’ fractures. Early painless loss of primary dentition and extensive chondrocalcinosis are characteristic. Lysosomal storage diseases—a large group of conditions due to various inborn errors that affect the function of specific lysosomal enzymes normally responsible for the breakdown of a variety of complex molecules. Can cause a variety of musculoskeletal prob lems, including some with devastating consequences (e.g. odontoid hypoplasia can lead to atlantoaxial instability, compression of the long spinal tracts, and paraplegia in Morquio syndrome; see Chapter 12.8). Intrinsic disorders of bone cells Osteopetrosis (‘marble bone disease’)—a group of disorders with a range of severity that best-known cause is of increased bone density. (1) Severe osteopetrosis —widespread increased density of the bones without modelling or remodelling, producing Erlenmeyer-flask de formity of the metaphyses; other features include leucoerythroblastic anaemia and hepatosplenomegaly, nerve compression, blindness, and deafness. (2) Mild osteopetrosis—affected individuals may be asymptomatic or affected by increased number of fractures affecting both the long bones and the small bones of the hands and feet. (3) Carbonic anhydrase 2 deficiency—features include mental re tardation, growth failure, dental malocclusion, osteopetrosis, renal tubular acidosis, and cerebral calcification. Fibrous dysplasia—a postzygotic activating mutation in GNAS1, the gene for the α subunit of the G-protein signalling system, leads to areas of immature fibrous tissue, either mono or poly-ostotic, within the skeleton. Radiology reveals a smooth-walled translucent area within the bone, often with thinning of the cortex and sometimes with associated deformity. (1) Monostotic fibrous dysplasia—lesions may occur in any bone; the most frequent presenting symptom is bone pain; fracture may occur. (2) Polyostotic fibrous dysplasia— multiple bone lesions; frequently associated with Café au Lait skin pigmentation and sexual precocity, especially in females (McCune– Albright syndrome). Ectopic ossification—this may be acquired at the site of injury, surgery, or in tumours and in a variety of other disorders. Inherited ectopic ossification is a major and disabling feature of two condi tions: fibrodysplasia ossificans progressiva and progressive osseous heteroplasia. Physiology of bone The past decade has seen fundamental advances in our under standing of bone-cell biology and in the noncollagen as well as the collagen components of the organic matrix of bone and the associ ated soft tissues. This is reflected in major discoveries in bone dis eases such as osteoporosis, osteopetrosis, osteogenesis imperfecta, and Paget’s disease. Outstanding discoveries in bone physiology include the identification and elucidation of the functions of the parathyroid-

hormone-related protein (PTHrP) and the bone mor phogenetic proteins (BMP). The causes of many rare skeletal dis orders have also now been discovered (Table 20.1.1). Examples are Marfan syndrome (mutations in fibrillin), vitamin D-dependent rickets type 2 (mutations in the 1,25-dihydroxycholecalciferol re ceptor), pseudohypoparathyroidism and fibrous dysplasia (ab normalities in the G-protein signalling system), osteogenesis imperfecta (mutations in type 1 collagen and numerous genes in volved in its metabolism), chondrodysplasias (some with similar mutations in type 2 collagen and other components of the car tilage matrix), the osteopetroses with mutations in the osteoclast acidification pathway, and fibrodysplasia ossificans progressiva (due to activating mutations in the BMP receptor, ALK2). The identification of the calcium-sensing receptor in the parathyroid and other tissues explains many rare disorders of mineral metab olism. Important new bone-cell signalling systems continue to be

20.1 Skeletal disorders—general approach and clinical conditions 4617 Table 20.1.1 Molecular basis of some metabolic disorders of bone and related tissues Disorder Affected gene protein Familial high bone density LRP5/lipoprotein receptor-related protein 5 X-linked hypophosphataemia PHEX Autosomal dominant hypophosphataemic osteomalacia FGF23/fibroblast growth factor 23 X-linked nephrolithiasis (Dent disease) CLCN5/chloride channel 5 Vitamin D-dependent rickets type 1 CYP27B1/25OHD 1α-hydroxylase Vitamin D-dependent rickets type 2 1,25(OH)2D receptor Oncogenic rickets (OM) FGF23 Paget’s disease SQSTM1/sequestosome Familial expansile osteolysis TNFRSF11A/RANK Expansile skeletal hyperphosphatasia TNFRSF11A/RANK Juvenile Paget’s disease TNFRSF11B/OPG Multiple endocrine neoplasia type 1 MEN1 Multiple endocrine neoplasia type 2 RET Familial hypocalciuric hypocalcaemia CASR/calcium-sensing receptor Neonatal hyperparathyroidism CASR Pseudohypoparathyroidism GNAS1 Jansen metaphyseal dysplasia PTH/PTHrP receptor Blomstrand chondrodysplasia PTH/PTHrP receptor Osteogenesis imperfecta COL1A1, COL1A2 Osteoporosis pseudoglioma LRP5 Marfan syndrome FBN1/fibrillin 1 Congenital contractural arachnodactyly FBN2/fibrillin 2 Loeys–Dietz syndrome TGFBR1/2 Ehlers–Danlos syndrome (EDS) EDS type 1 COL5A1 EDS type 4 COL3A1 EDS type 6 PLOD1/lysyl hydroxylase EDS type 7A and B COL1A1, COL1A2 Other EDS Tenascin-X, Lamin A Homocystinuria Cystathionine β-synthase Hypophosphatasia TNAP/alkaline phosphatase Alkaptonuria HGD/homogentisate 1,2-dioxygenase Menke syndrome ATP7A/copper transporting ATPase Gaucher disease β glucosidase Mucopolysaccharidoses Multiple lysosomal enzymes Achondroplasia FGFR3/fibroblast growth factor receptor 3 Thanatophoric dysplasia FGFR3 Hypochondroplasia FGFR3 Spondyloepiphyseal dysplasia (SED) congenital COL2A1 Spondyloepiphyseal dysplasia tarda, (X-linked) TRAPPC2/tracking protein particle complex subunit 2 (involved in intracellular residue trafficking) Stickler syndrome COL2A1, COL11A1 Kniest dysplasia COL2A1 Achondrogenesis COL2A1 Multiple epiphyseal dysplasia COL9A1, 2, 3, COMP, SLC26A2 (DTDST), MATN3 (matrilin 3) Pseudoachondroplasia COMP/cartilage oligomeric matrix protein Metaphyseal chondrodysplasia (type Schmid) COL10A1 (continued)

SECTION 20 Disorders of the skeleton 4618 identified, particularly that involving Wnt, an important controller of bone mass, and low-density lipoprotein receptor-related protein 5 (LRP5). Further advances have been made in our understanding of the development of the osteoblast from stromal cell precursors and the ways in which the osteoblast controls osteoclast develop ment and function (see next). The mammalian skeleton serves three main functions, the de mands of which sometimes conflict. The first is to provide a rigid structure; the second is to act as an accessible mineral/protein store and thirdly as an endocrine organ through secretion of FGF23. Both depend on the activities of specialized bone cells, which are con trolled by genetic, mechanical, nutritional,

and hormonal influ ences, and by a host of short-acting messengers produced by cells, collectively known as cytokines. Structure Bone tissue consists of cells and an extracellular mineralized matrix (35% organic and 65% inorganic). Some 90% of the or ganic component is type 1 collagen. The remainder includes many noncollagen products of the osteoblast, such as osteocalcin, osteonectin, and proteoglycans. The mineral is present mainly as a complex mixture of calcium and phosphate in the form of hydroxyapatite. Two anatomical types of bone may be defined: trabecular (cancellous) and cortical. The proportion of these differs from one bone to another (e.g. vertebral bodies are predominantly trabecular and the shafts of the long bones are cortical). Such variation is related both to the functions of the bones and to the development of disorders of them, such as osteoporosis. Trabecular bone contains more metabolically active surfaces in a given volume than cortical bone. Cellular activities take place on the surfaces of trabecular bone and through resorbing channels (cutting cones) in cortical bone. The fine structure of bone is dealt with in anatomical texts. Bone is often assumed to be inert because of its structural rigidity and persistence after death, and to be composed entirely of mineral because it contains 99% of the calcium in the body. These assump tions are superficially reasonable, but neither is correct.
Bone cells Conventional histological sections of bone demonstrate three types of bone cell which are clearly different (Fig. 20.1.1): (1) osteoblasts, which may be plump and apparently active, or flat and apparently inactive—otherwise called bone-lining cells; (2) multinucleate osteoclasts, which most often occupy areas of resorption; and (3) osteocytes within lacunae in the mineralized bone, apparently in contact with other osteocytes and bone cells through their exten sions in the canaliculi. All these cells are in close contact with the bone marrow, which contains their precursors and brings them into close relationship with the immune system. Bone cells are at the centre of an information system of as tonishing complexity. All bone cells communicate with each other to control bone modelling during growth and remodel ling throughout life. The constant processes of osteoclastic bone resorption and osteoblastic bone formation that achieve this are closely linked and take place in bone multicellular units. The cel lular cycle of such units begins with the activation of multinucleate osteoclasts from their macrophage-like mononuclear cell pre cursors; these produce resorption (Howship) lacunae on the sur face of trabecular bone or cutting cones in cortical bone. These are identical processes; in trabecular (cancellous) bone, the bone multicellular unit may be looked upon as a sagittal section of a cortical bone multicellular unit. Resorption is followed by a re versal phase, during which a cement line is deposited, and new bone matrix is formed by osteoblasts, which is subsequently min eralized. In the young adult, when the bone mass is constant and there may be several million resorbing sites in the skeleton at any one time, the amount of newly formed bone equals that resorbed. In childhood, more bone is formed than is resorbed and in later years there is an imbalance favouring resorption which eventually leads to osteoporosis. Estimates of the time scale of the remodelling cycle are only approximate. In the adult, the replacement of old bone with new occurs at an annual turnover rate of 25% in trabecular bone and from 2% to 3% in cortical bone. In the bone multicellular unit, resorption takes from one to two weeks and new bone forma tion about seven weeks. A complete cycle, including reversal and Disorder Affected gene protein Diastrophic dysplasia SLC26A2 (DTDST) Campomelic dysplasia SOX 9 Apert syndrome FGFR2 Osteopetrosis (marble bone disease) TC1RG1, CLCN7, CA2 Pycnodysostosis CTSK/cathepsin K Camurati–Engelmann disease TGFB1 Sclerosteosis SOST/sclerostin Fibrous dysplasia GNAS1 G s α-protein subunit Familial hyperphosphataemic tumoural calcinosis FGF23, GALNT3 Fibrodysplasia ossificans progressiva ACVR1/activin receptor-like kinase 2 (ALK2) Familial chondrocalcinosis/craniometaphyseal dysplasia ANKH/transmembrane pyrophosphate transporter Progressive osseous heteroplasia GNAS1 Modified from Smith R,

Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission. Table 20.1.1 Continued

20.1 Skeletal disorders—general approach and clinical conditions 4619 mineralization, takes several months. The turnover of bone at a given site is determined by the frequency with which bone multi cellular units are activated and the rates of function of individual cells. Bone loss and gain depend on both factors and the mech anism of bone loss varies between different disorders. Although the existence of the bone multicellular unit system is widely ac cepted, it is far from understood; for example, what factors lead to activation of the osteoclasts to initiate the resorbing cycle as well as the role of clastokines such as Sphingosine 1-phosphate linking osteoblast and osteoclast activity? It is clear that osteoblasts occupy a central position in bone physiology (Fig. 20.1.2a). They are derived from the mesenchymal– stromal cell system within the bone marrow. This system is multi potential and the stromal cells can give rise to osteoblasts, fibro blasts, chondrocytes, myocytes, and adipocytes. Under the influence of the differentiation factor RUNX2 (runt-related tran scription factor 2, also known as CBFA1), osterix (transcription factor Sp7) and LRP5, stromal cells develop into osteoblasts. Osteoblasts respond to humoral factors, both systemic and local (cytokines), and to mechanical stress. They synthesize the organic bone matrix (mainly collagen) and noncollagen proteins and they control bone mineralization. Importantly, they also appear to direct the activity of other cell types, particularly the osteo clasts. In this respect they may also activate the bone-resorbing cycle. One of the main factors that controls osteoclast differenti ation has been identified as RANKL, the ligand for the receptor activator of NF-κB (RANK), found on the surface of osteoclast precursors. RANKL, also variously known as osteoclast differen tiation factor, osteoprotegerin ligand (OPGL), tumour necrosis factor (TNF) related activation-induced cytokine (TRANCE), and TNF ligand superfamily member 11 (TNFSF11) is a soluble factor produced by osteoblasts, which plays an important role in controlling the formation and activation of osteoclasts through its effect on the osteoclast receptor RANK (Fig. 20.1.2b). It is possible that these many functions are divided between different osteoblasts. The bone-lining cells—resting osteoblasts—may not be as inactive as they appear since they may provide a cellular barrier separating the so-called bone fluid from the general extracellular compartment. Osteocytes, also derived from osteoblasts, occupy lacunae within the mineralized bone and communicate with each other through gap junctions via their processes within the canaliculi (Fig. 20.1.1). They probably have an important function in the de tection of mechanical forces and the resultant response of bone to them and have been identified as an important source of RANKL for influencing osteoclast function as well as FGF23. In contrast to osteoblasts osteoclasts are multinucleated cells derived from the haemopoietic system. The osteoclasts re sorb bone after attaching themselves to its surface via integrins (vitronectin receptor) and forming a seal to isolate their area of activity (Fig. 20.1.3). Within this sealed zone they produce a very acid environment, with the aid of an osteoclast-specific proton pump linked to the enzyme carbonic anhydrase 2, to en able digestion of whole bone by lysosomal enzymes, including cathepsin K. The absence of carbonic anhydrase 2 is linked to a rare form of osteopetrosis (see next). Other inherited defects of the acidification machinery, such as the chloride channel CLCN7, lead to different forms of osteopetrosis. Osteoclasts have receptors to calcitonin that, when occupied, directly sup press their activity; the existence of any other hormone receptors is controversial. However, they are activated by prostaglandins. The osteoclastic resorptive effects of parathyroid hormone and of 1,25-dihydroxycholecalciferol are probably mediated through the osteoblast. Bone lining cells Unmineralized bone matrix (osteoid) Osteoblasts Osteocytes Gap junctions Mineralized bone

Canaliculi Osteoclast Ruffled border Oc (a) (b) Ob Howship’s resorption lacuna Fig. 20.1.1 Bone cells: (a) the histological appearance: a multinucleated osteoclast (centre, arrow) is present on a Howship’s resorption lacuna along one surface of a bone trabecula; a row of plump osteoblasts lie on the opposite surface (right, arrows) (haematoxylin and eosin, magnification ×400); and (b) a diagram to show the main connections of the osteocyte. Ob, osteoblast; Oc, osteoclast. From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission.

SECTION 20 Disorders of the skeleton 4620 Bone formation The factors that control bone formation are complex and not fully understood, but they act largely through the osteoblast. The stromal precursors of osteoblasts are found in the periosteum and the endosteal surfaces close to the bone marrow. The local remod elling stimulus for new bone formation appears to come from some product or products of bone resorption (e.g. BMPs and/or transforming growth factor β (TGFβ) sequestered in the bone ma trix). Such substances are included in the category of cytokines. Many such cytokines affect which act in an autocrine, paracrine, or endocrine manner on the metabolism of bone and cartilage. Many cytokines have alternative names and multiple actions, featuring both synergism and antagonism. They include interleu kins (IL-1 and IL-6), TNF, γ-interferon, platelet-derived growth factor, fibroblast growth factors (FGFs), insulin-like growth fac tors, TGFβ, and BMPs. Since bone cells contain, synthesize, and respond to many cyto kines, they are part of a complex network. As an example, TGFβ appears to comprise a family of multifunctional regulatory pep tides and bone is probably their most abundant source. Not only do osteoblasts synthesize TGFβ, but they also have high-affinity receptors for it and are mitogenically stimulated by it. Strikingly, most of the BMPs belong to the TGFβ superfamily. Bone resorption Osteoclasts are controlled by systemic and local factors but there is no direct evidence that they are influenced by mechanical stress. Calcitonin directly inhibits the osteoclast, temporarily abolishes the active ruffled border, and suppresses the generation of new osteoclasts. Bone resorption is increased by parathyroid hormone and 1,25-dihydroxycholecalciferol. Since the osteoclast contains no receptors for either of these hormones it is proposed that their Activated osteoclasts (b) Osteoclast progenitors Mononuclear osteoclasts Differentiation m-CSF 1 ,25(oH)2D3 PTH PGE2 IL-11 c-Fms RANK OPG Fusion Activation Osteoclasts Osteoblasts/ stromal cells RANKL RANKL RANKL (a) Endocrine Nutrition Cytokines Lining cells Osteocytes Apoptosis Control of osteoclast Noncollagen proteins Type I collagen Alkaline phosphatase Mineralization Osteoblast Genetic Mechanical Stromal cell Preosteoblast Chondrocyte Fig. 20.1.2 The osteoblast (a) The central position of the osteoblast in bone physiology. Broad arrows show the origin of the osteoblasts from preosteoblasts, themselves derived from stromal cells, and of the lining cells and osteocytes. Endocrine influences include calciotropic hormones, oestrogen, and cortisol. Cytokines and hormones all act through specific receptors. The way in which mechanical forces and nutrition affect the osteoblast is not well defined. Most cytokines influence the activity of the osteoclast via the osteoblasts. Others bypass the osteoblasts and have a direct effect on osteoclasts. (b) The close interactions between the osteoblast and the origin and function of the osteoclast. Together, macrophage colony-stimulating factor (M-CSF) and RANKL act throughout osteoclast differentiation. Osteoprotegerin strongly inhibits all the effects of RANKL. Note that 1,25(OH)2D, parathyroid hormone, PGE2 (prostaglandin E2), and IL-11 (part of the IL-6 family) are shown to act via the osteoblasts, but there is evidence of direct cytokine effects on the osteoclasts. (a) From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission. (b) From Takahashi N et al. (2002). Cells of

Bone: Osteoclast Generation, In: Bilezikian JP et al. (eds) Principles of Bone Biology, 2nd edn. San Diego: Academic Press, with permission from Elsevier.

20.1 Skeletal disorders—general approach and clinical conditions 4621 resorbing effect is mediated via the osteoblast. It is now realized that the balance between osteoprotegerin and RANKL is central to osteoblast–osteoclast interaction. The number and activity of the osteoclasts are also increased by various cytokines produced by lymphocytes and monocytes (lymphokines and monokines, re spectively) and by peptide growth factors such as epidermal growth factor. In myeloma, the malignant plasma cells release IL-1, IL-6, and TNF, all of which stimulate osteoclastic destruction of bone. Bone mass (see also osteoporosis) The development of the skeleton and its eventual size and density are greatly influenced by genetic factors modified by mechanical stress, nutrition, the systemic effects of endocrine hormones, and local factors produced by the bone cells themselves. These determine the balance between resorption and formation and their relative con tribution varies with age. Recent research emphasizes the importance of the genetic con tribution to bone mass. Apart from the obvious differences in bone mass between races, the heritability of bone mass is demonstrated by the relative similarities between monozygotic twins compared to dizygotic twins. Clearly, mutations in the structural type 1 col lagen genes have a considerable effect on bone mass, as in osteogen esis imperfecta (see next). The contribution of vitamin D receptor gene polymorphisms and genetic changes in the promoter region of the type 1 collagen gene has been widely discussed (see osteopor osis). Mutations in LRP5 can cause both low and high bone density, and this protein—which is involved in Wnt signalling—is also important in the control of bone mass in the general population. (b) CO2+H2O H2CO3 CO2 Cl− Cl− H+ H+ K+ K+channel HCO3− + H+ H CO3− Chloride channel ATP ADP+Pi Proton pump Ruffled border Vitronectin receptor Calcified bone Lysosomal enzyme Proton Bicarbonate/Chloride exchanger Carbonic anhydrase II M M M M Clear zone Cathepsin K Calcitonin receptor Sodium/Proton antiporter H+ Na+ (a) conductance Fig. 20.1.3 The osteoclast (a) The appearance of damaged bone under the scanning electron microscope: the osteoclast has removed part of the mineralized surface and is presumed to be moving on to digest further bone; and (b) the cellular events and ion exchanges that Boccur within it. M, positions of gene mutations described in human osteopetrosis for carbonic anhydrase II
(CA II), vacuolar ATP’ (ATPase), chloride channels (Cl–), and cathepsin K (cysteine proteinase). Adapted from Rouselle A-V, Heymann D (2002). Osteoclastic acidification pathways during bone resorption. Bone, 30, 533–40, with permission from Elsevier.

SECTION 20 Disorders of the skeleton 4622 There is growing evidence to support the development origins of adult bone mass with the tracking of bone mass across the life course. This highlights the potential importance of the uterine en vironment, such as vitamin D status, in programming the offspring’s bone trajectory, and ultimately bone mass in later adulthood and fracture risk. The main function of the skeleton is mechanical and bone is laid down along lines of stress. Although the way in which this occurs is obscure, early in vitro experiments showed that osteo blasts may respond to mechanical stress by an increase in levels of cAMP and phosphoinositol, partly mediated by prostaglandins. It is also common sense that the size and density of the skeleton should be related to nutritional intake, particularly of calcium, protein, and energy. This has been difficult to prove, but twin studies in growing children demonstrate significantly greater bone density (which may be temporary) in those taking calcium sup plements, and the starvation associated with anorexia nervosa reduces bone mineral content. The latter may also be due to oes trogen deficiency and

emphasizes the important effect of repro ductive hormones on the skeleton. The sex hormones testosterone and oestrogen encourage new bone formation. Oestrogen-defi cient men have osteoporosis, and the skeleton depends on a full complement of sex steroids for its integrity. Growth hormone is also an important anabolic skeletal agent during the early years of life, partly through the local production of somatomedins (insulin-like growth factors). Several hormones that influence bone resorption may also have anabolic actions mediated by osteo blasts. One is parathyroid hormone, which under certain circum stances increases the proliferation of osteoblast precursors. This is relevant to the treatment of osteoporosis. Collagen Collagen is the principal extracellular protein in the body, more than half of which is contained within the skeleton, and it is the main product of the osteoblast. There are many different molecular types, with different functions, each encoded by distinct genes (Table 20.1.2). Collagen in bone is type 1. This heterotrimer is composed of two α-1(I) chains and one α-2(I) chain. The general structure of the α-1(I) chain is (Gly–X–Y)338, where X and Y are often pro line or hydroxyproline. The α-chains are synthesized as precursors within the osteoblasts and undergo several synthetic modifications, including posttranslational hydroxylation of proline and lysine residues; certain hydroxylysine residues are further modified into aldehydes and are also glycosylated (Fig. 20.1.4). After removal of their terminal propeptide extensions, the triple- helical molecules form an exact structure with a quarter-stagger overlap that is subsequently cross-linked. The so-called ‘hole zones’ within this structure provide a template for early mineralization. Mutations in the collagen genes and defects in posttranslational modification cause inherited disorders of connective tissue, of which osteogenesis imperfecta (type 1 collagen) and the vascular form (type 4) of Ehlers–Danlos syndrome (type 3 collagen) are ex amples (Table 20.1.1). The fibrillar collagens are quantitatively the most important, but many other minor collagens exist, playing im portant roles in regulating fibre diameter and interactions with other matrix proteins. Renal excretion of hydroxyproline peptides is an indicator of bone collagen turnover. Excretion of pyridinium com pounds is a measure of bone resorption (see next). Noncollagen proteins Many such proteins may be extracted from bone, although their abundance differs according to the starting material and the methods used. They include osteocalcin (bone Gla protein, see next), sialoproteins, various phosphoproteins, such as osteonectin and osteopontin, the bone morphogenetic proteins, and bone- specific proteoglycans. The nature of noncollagen substances sequestered in bone ma trix is complex and most are synthesized by the osteoblasts. Few, if any, are unique to bone, and to date, no unambiguous func tion has been determined for any of these proteins. Osteonectin Table 20.1.2 The vertebrate collagens Type α-chains Most common molecular form Tissue distribution 1 α-1(I), α-2(I) [α-1(I)]2 α-2(I) Most connective tissues, e.g. bone, tendon, skin, lung, cornea, sclera, vascular system 2 α-1(II) [α-1(II)]3 Cartilage, vitreous humour, embryonic cornea 3 α-1(III) [α-1(III)]3 Extensible connective tissues, e.g. lung, vascular system 4 α-1(IV), α-2(IV), α-3(IV), α-4(IV), α-5(IV) [α-1(IV)]2 α-2(IV) Basement membranes 5 α-1(V), α-2(V), α-3(V) [α-1(V)]2 α-2(V) Tissues containing collagen type 1, quantitatively minor component 6 α-1(VI), α-2(VI), α-3(VI) α-1(VI) α-2(VI) α-3(VI) Most connective tissues, including cartilage 7 α-1(VII) [α-1(VII)]3 Basement-membrane-associated anchoring fibrils 8 α-1(VIII), α-2(VIII) [α-1(VIII)]2 α-2(VII)? Product of endothelial and various tumour cell lines 9 α-1(IX), α-2(IX), α-3(IX) α-1(IX) α-2(IX) α-3(IX) Tissues containing collagen type 2, quantitatively minor component 10 α-1(X) [α-1(X)]3 Hypertrophic zone of cartilage 11 α-1(XI), α-2(XI), α-3(XI)a α-1(XI) α-2(XI) α-3(XI) Tissues containing collagen type 3, quantitatively minor component 12 α-1(XII) [α-1(XII)]3 Tissues containing collagen type 1, quantitatively minor component 13 α-1(XIII) [α-1(XIII)]3? Quantitatively minor collagen, found, e.g. in skin, intestine 14 α-1(XIV) [α-1(XIV)]3? Tissues containing collagen type 1, quantitatively minor component aClosely

related to α-1(II). From Smith R (1998). Bone in health and disease. In: Maddison PJ, et al. (eds) Oxford Textbook of Rheumatology, 2nd edn, pp. 421–40. Oxford: Oxford University Press, with permission.

20.1 Skeletal disorders—general approach and clinical conditions 4623 is the major noncollagen protein produced by human osteoblasts. It binds strongly to calcium ions, hydroxyapatite, and native col lagen, but it is not limited to mineralizing tissue, being also found in human platelets. Although osteonectin mRNA is widely distrib uted in developing tissues, it is most abundant in bone. Two bone sialoproteins, BSP1 and BSP2, are now recognized. Their relative amounts vary with the species studied (e.g. BSP1 is a minor com ponent of human bone but a major contributor to total sialoprotein in rat bone). The protein contains an RGD (Arg–Gly–Asp) cell- attachment motif and is therefore called osteopontin. The major human sialoprotein is BSP2. There are two Gla-containing proteins in bone: osteocalcin (bone Gla protein; BGP) (osteocalcin) and matrix Gla protein. The term Gla refers to the γ-carboxylated glutamic acid residues, formed by the vitamin K-modulated, posttranslational carboxyl ation of peptide-bound glutamic acid. These proteins have some sequence homology but are products of different genes. Matrix Gla protein is also a cartilage protein and is found at an earlier developmental stage than osteocalcin. The function of osteocalcin is unknown. Osteocalcin biosynthesis is regulated by 1,25- dihydroxycholecalciferol (1,25(OH)2D) (and no other hormone), which enhances its nuclear transcription and eventual secretion from bone cells. Plasma osteocalcin has been linked to the rate of bone formation or, less specifically, bone turnover. Proteoglycans are proteins with one or more attached glycosa minoglycan chains. They vary widely in form and function. Those of bone, which include decorin and biglycan, have been studied less extensively than those of cartilage and differ in their small overall Synthesis and modification of procollagen α-chains NH2 NH2 NH2 NH2 NH2 N N N -OH -OH OH OH -OH -OH -OH -OH -OH Triple-helix formation Chain association and nucleation Cell membrane Assembly and cross-linking of fibrils Intracellular Extracellular Cleavage of N- and C-propeptides CCC Fig. 20.1.4 Collagen: the synthetic pathways. The individual polypeptide chains are synthesized on the ribosomes of the rough endoplasmic reticulum. They undergo complex enzymic modifications before chain association and triple helix formation. The newly formed procollagen molecules are secreted into the extracellular space and proteinases remove the N- and C-propeptides. In the fibril, collagen molecules overlap (in a quarter-staggered array) and form specific covalent cross-links. From Kielty CM and Grant ME (2002). The Collagen Family: Structure, Assembly, and Organization in the Extracellular Matrix. In: Royce PM and Steinmann B (eds) Connective Tissue and its Heritable Disorders, 2nd edn, New York: Wiley- Liss, pp. 159–221, with permission.

 size and relatively larger amounts of protein. Such small proteogly cans are thought to interact with growing collagen fibrils in a precise manner and to regulate their growth, maturation, and interactions. Type 9 collagen, one of a family of fibril associated collagens with interrupted triple helices, is found on the surface of type 2 collagen fibrils in cartilage. It facilitates interactions between the collagen and proteoglycans in the cartilage matrix through the chondroitin sul phate glycosaminoglycan chain on the α-2(IX) chain. It has been known for many years that demineralized bone matrix contains substances capable of inducing ectopic bone formation. Because they are present in such small amounts, their extraction and isolation have presented great difficulties, but these bone mor phogenetic proteins have now been isolated and their corresponding genes cloned. Bone mineral and mineralization Mineralization occurs on bone matrix collagen. There is now good evidence that, in most mineralized tissues,

calcifying vesicles de rived from chondrocytes or osteoblasts provide the focus for min eralization. These vesicles are easily demonstrable in cartilage, but their function in the organized matrix of bone is controversial. The precipitation of calcium within these vesicles may be controlled by the action of a pyrophosphatase that locally destroys pyrophos phate, itself an inhibitor of mineralization. Alkaline phosphatase is the most important pyrophosphatase and is readily demonstrable both in osteoblasts and in mineralizing vesicles. Its deficiency in hypophosphatasia causes defective mineralization. It is possible, for the purpose of clarity, to consider two types of mineralization: (1) homogeneous nucleation from amorphous calcium phosphate to form crystalline hydroxyapatite, which occurs in the lumen of the matrix vesicles; and (2) heterogeneous nucleation, which is collagen-mediated and may partly rely on adsorbed noncollagen proteins as nucleators. After this first phase (mediated either by vesicles or collagen), there is a second phase of rapid spread of min eralization, initially in the hole zones and later the overlap regions of the collagen matrix. Abnormal calcification or ossification may occur in many patho logical states and as a consequence of ageing. Thus, abnormal cal cification of articular cartilage (chondrocalcinosis) may occur with increasing age, in inflammatory states, as a result of trauma, or due to perturbations of inorganic pyrophosphate levels. Such lesions are not exclusively limited to the musculoskeletal system and may be manifest, for example, as ectopic mineralization in blood vessels. Calcium and phosphorus balance The circulating level of plasma calcium is determined by the amount of calcium that is absorbed by the intestine, the amount that is ex creted by the kidney, and the exchange of mineral with the skeleton (see also section 12). The relative importance of these exchanges al ters during growth and in different pathological states. Total plasma calcium concentration is closely maintained between 2.25 and 2.60 mmol/litre, of which nearly half is in the ionized form (47% ionized, 46% protein bound, and the remainder complexed). The skeleton contains approximately 1 kg (25 000 mmol) of calcium. The main fluxes of calcium in the young adult are shown in Fig. 20.1.5. Phosphate balance is less well understood. 1000 PTH 1,25(OH)2D3 800 300 500 Plasma calcium 9−10.2 mg/100 ml PTH CT PTH 9 800 (12 000) 400 (12 000) 400 10 000 PTH 1,25 (OH)2D3 Prostaglandins PTHrP Exercise various hormones, GH, etc. bone morphogenetic phosphate Cortisol immobility Fig. 20.1.5 Calcium homeostasis in the adult. The main daily changes in external calcium balance (figures refer to mg Ca/day). The interrupted line around the bone suggests a bone envelope across which rapid calcium exchange (12 000 mg/day) may occur. The effects of cytokines and other molecules are not shown. From Smith R (1998). Bone in health and disease. In: Maddison PJ, et al. (eds) Oxford Textbook of Rheumatology, 2nd edition, pp. 421–40. Oxford: Oxford University Press, with permission.

20.1 Skeletal disorders—general approach and clinical conditions 4625 Parathyroid hormone (see also Chapter 13.4) The secretion of parathyroid hormone (PTH) is stimulated by a reduction in the plasma ionized-calcium concentration. Small changes in plasma calcium are detected by a G protein-coupled calcium-sensing receptor (CASR) in the parathyroid gland. CASR can cause hypocalcaemic and hypercalcaemic syndromes (Table 20.1.1). Increase in PTH secretion leads to an increase in calcium absorption through the gut, an increase in calcium resorption through the kidney, and an increase in bone resorp tion. Intestinal calcium absorption is mediated by the active me tabolite of vitamin D, 1,25(OH)2D, and the 1α-hydroxylation of 25-hydroxycholecalciferol (25OHD) in the kidney is stimulated by PTH, so that the effect of PTH on increasing intestinal cal cium absorption is indirect. In contrast, the renal effect of PTH on calcium resorption is direct. The cellular effects of PTH on kidney and bone involve two cellular systems, namely cAMP and inositol triphosphate. PTH encourages osteoclastic bone re sorption by its effects on the osteoblast (as

previously described). Peripheral resistance to the effect of PTH due to inherited loss-of- function mutations in the G-protein signalling system occurs in pseudohypoparathyroidism (see Chapter 13.4). Vitamin D Vitamin D is synthesized either as vitamin D3 (cholecalciferol) by the action of ultraviolet light from its precursor 7-dehydrocholesterol or taken in with food, either as vitamin D3 or D2 (ergocalciferol) (Fig. 20.1.6). It is transported to the liver by a binding protein where it undergoes 25-hydroxylation; 25-hydroxy-vitamin D (25OHD) is then hydroxylated in the 1α-position by the renal 1α-hydroxylase. 1,25(OH)2D is the active metabolite of vitamin D and has wide spread effects, the full extent of which are only just being appre ciated. These are mediated through a widely distributed vitamin D receptor that has DNA- and hormone-binding components. In addition to its classic effect on intestinal calcium transport, vitamin D is linked with the immune system and the growth and differenti ation of a wide variety of cells. Measurement of the plasma 25OHD concentration is a useful indicator of vitamin D status and work on 1,25(OH)2D and its receptors has illuminated the cause of the rarer forms of inherited rickets (see next). While the kidney is the main source of 1,25(OH)2D this metabolite can also be synthesized by macrophages in a variety of granulomas, providing an explanation for the hypercalcaemia of sarcoidosis, disseminated tuberculosis, and, occasionally, lymphomas. There is also evidence that some cell types, including myocytes, can synthesize 1,25(OH)2D locally without influencing the systemic concentrations of this metabolite. Calcitonin Calcitonin, a 32-amino-acid peptide, is just one product of the ex tensive calcitonin gene family. It is produced by alternative splicing of the primary gene transcript also responsible for the production of calcitonin gene-related peptide. The main effect of calcitonin is to reduce bone resorption by the direct and reversible suppression of osteoclasts and by inhibition of their production from precursors. Calcitonin is thought to protect the skeleton during physiological stresses such as growth and pregnancy and its receptor is widely distributed. Skin Provitamin D3 Vitamin D 25 OHD 1− Hydroxylase Liver Kidney 24-hydroxylase 24,25(OH)2D Decreased by Ca ↓ Increased by 1,25(OH)2D↑ Food Vitamin D3 Vitamin D2 (irradiated ergosterol) Vitamin D3 +vitamin D2 Previtamin D3 Increased by phosphate ↓ Ca ↓ PTH ↑ Oestrogen ↑ 1,25(OH)2D combines with widespread cell receptor Gene activation or repression Effects on Differentiation of cells Proliferation Calcium and phosphorus homeostasis Development Fig. 20.1.6 The origin, synthetic pathways, and molecular and cellular effects of 1,25(OH)2D. From Smith R (1998). Bone in health and disease. In: Maddison PJ, et al. (eds) Oxford Textbook of Rheumatology, 2nd edition, pp. 421–40. Oxford: Oxford University Press, with permission.

SECTION 20 Disorders of the skeleton 4626 Parathyroid-hormone-related protein (PRrP) This hormone was discovered through studies on patients with nonmetastatic hypercalcaemia of malignancy. PRrP has close sequence homology to PTH at the amino-terminal end of the mol ecule and has very similar effects. It has been detected in several tu mours, particularly of the lung. There is also evidence that it may have a role in fetal physiology, controlling the calcium gradient across the placenta to maintain the relatively higher concentra tions in the fetal circulation. PTH and PRrP use the same receptor. Activating mutations of this receptor can cause Jansen metaphyseal chondrodysplasia (MIM 156400) while inactivating mutations cause the Blomstrand chondrodysplasia (MIM 215045), highlighting its importance in the development of the skeleton. Fibroblast growth factor 23 (FGF23) This hormone has similar effects to PTH on reducing renal phos phate reabsorption but has an opposite effect by inhibiting 1-α activation of vitamin D. Overactivity of FGF23 causes rickets/ ostoemalacic condictions such as familial hypophosphataemia and oncogenic osteomalacia as well as reducing bone strength in severe polyostotic fibrous dysplasia. Other hormones Apart from the recognized calciotropic hormones,

the skeleton is influenced by corticosteroids, sex hormones, thyroxine, and growth hormones. The main effect of excess corticosteroids (either thera peutic or in Cushing's syndrome) is to suppress osteoblastic new bone formation, although there is also an element of secondary hyper parathyroidism. Androgens and oestrogens promote and maintain skeletal mass. Osteoblasts have receptors for oestrogens, although they are not abundant. Thyroxine increases bone turnover and pref erentially increases resorption over formation; thyrotoxicosis thus leads to bone loss. Excess growth hormone leads to gigantism and acromegaly (according to the age of onset) with enlargement of the bones. Absence of growth hormone will lead to proportional short stature; where there is general pituitary failure, the reduction in gonadotropins will also induce bone loss. Biochemical measures of bone turnover These include plasma bone-derived alkaline phosphatase, osteocalcin, collagen-derived propeptides, and the urinary total hydroxyproline and cross-linked collagen-derived peptides (Table 20.1.3). Since for mation and resorption are closely linked, such measurements are also related to each other and to overall bone turnover. Total plasma alkaline phosphatase (largely derived from osteo blasts) provides a crude but readily accessible index of bone forma tion, being increased during periods of rapid growth and particularly when bone turnover is greatly increased, as in Paget's disease. Early measurements of serum osteocalcin gave widely variable results and depended on the origin, sensitivity, and stability of the antibodies used. Total urinary hydroxyproline excretion is influenced by dietary collagen (gelatin) and reflects both resorption and new collagen syn thesis. The development of methods for the measurement of urinary collagen-derived pyridinium cross-links gives a reliable indication of bone resorption rate, unrelated to new collagen formation and uninfluenced by diet. There are two forms of cross-linked peptide— pyridinoline and deoxypyridinoline, depending on whether they originate from oxidized hydroxylysine or lysine residues. Previous assays were dependent on high-pressure liquid chromatography of urinary peptides after hydrolysis with acid. Simple and more direct immunoassays have now been developed to measure collagen- derived fragments, both in the urine and plasma. Correct interpretation of collagen-derived fragments depends on knowledge of collagen metabolic pathways (Fig. 20.1.4). Soon Table 20.1.3 Biochemical measurements used to assess the rate of bone turnover Measurement Comment Formation indicators Alkaline phosphatase (S) Bone-specific isoenzyme useful when total not greatly increased or origin uncertain Osteocalcin (S) Variable methods and ranges Unstable on storage Collagen propeptides (S) P1CP and P1NP Resorption indicators Hydroxyproline (U) Useful if considerably increased Influenced by gelatine in diet Pyridinium compounds (S, U) Pyridinoline and deoxypyridinoline; HPLC tedious but still gold standard Cross-linked telopeptides of collagen type 1 N-terminal (NTX-1) (S, U) Osteomark: very variable C-terminal (CTX-1) (S, U) Crosslaps: very variable C-terminal (CTX-MMP; ICTP) (S) Hydroxylysine glycosides (U) Galactosyl hydroxylysine from skeletal collagens Tartrate-resistant acid phosphatase (S) Bone sialoprotein (S) HPLC, high performance liquid chromatography; S, serum; U, urine. From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission.

 after export from the cell, the amino and carboxypropeptide ex tensions are cleaved from the helical central part of the collagen chain. Measurement of these fragments in the plasma indicates the collagen formation rate. Once the collagen chains are cross-linked, measurement of different cross-linked fragments in the urine and plasma indicate (mainly bone) collagen resorption (Table 20.1.3). Current international guidelines recommend the use of procollagen type I propeptides and C-terminal

telopeptides. Diagnosis of bone disease The diagnosis of bone disorders increasingly depends on specialized investigation, with the result that important clinical points tend to be forgotten. History Deformity, pain, and fracture are common features. To these may be added proximal myopathy (in osteomalacia and rickets), dentition, hearing, and the symptoms of any underlying systemic disease. The family history is often relevant. Deformity and short stature Deformity suggests an underlying skeletal disorder or previous skel etal disease, especially if there is also disturbance of growth. Short stature and disproportion are more frequent than excessive height. In children, knowledge of the normal growth patterns is essential: in the normal adult, height and span are approximately equal and the crown to pubis measurement is roughly equal to the pubis to heel length; but in children under the age of 10 years, the upper body segment is typically greater than the lower body segment. Short stature (defined as below the 0.4th centile) can be divided into pro portionate and disproportionate forms, of which the most frequent is caused by short limbs. Proportionate short stature may occur in children who appear to be otherwise normal, whereas subjects with disproportionate short stature usually (but not always) appear ab normal from birth. Children below the 0.4th centile for height or who have sequential measurements of height that cross successive centile bands should be further investigated. About three-quarters of children exhibiting short stature either have familial short stature or constitutional delay of growth and puberty; others have chronic disease (10%), syndromic short stature (6%), chromosomal abnor malities (5%), skeletal dysplasias (1%), or growth hormone or other hormone deficiencies (1–2%). Some causes of short stature are given in Table 20.1.4. Skeletal dysplasias are dealt with further next. Kyphosis, with loss of trunk height, as in osteoporosis and osteo malacia, is the commonest acquired deformity of adult life. It may be noticed because clothes no longer fit. During childhood, vertebral collapse will slow the growth rate. Other deformities are character istic of the underlying disease (e.g. active childhood rickets pro duces knock knees, bowed legs, enlarged epiphyses, and bossing of the skull); Paget’s disease produces asymmetric thick limb bones and an enlarged skull vault; and severe osteogenesis imperfecta produces very short limbs and deformity. Bone pain and fracture The cause of bone pain is not well understood. In osteomalacia it may be generalized and associated with tenderness on pressure. It may be due to excessive vascularity, with stretching of the perios teum; certainly, it can be rapidly relieved by appropriate treatment, such as bisphosphonates for Paget’s disease or parathyroidectomy for parathyroid bone disease. Fractures of different sorts occur, for example partial, multiple, and painful microfractures (fissure frac tures) on the convexity of pagetic bone, the Looser zones on medial borders of osteomalacic bones, and the multiple vertebral compres sion fractures of osteoporosis. Myopathy The cause of proximal muscle weakness in osteomalacia and rickets remains unknown. The signs include a waddling gait and inability to rise from a chair, to lift objects off high shelves, or to climb stairs. Limbs may be described as stiff rather than weak. In contrast, myop athy does not occur in subjects with inherited hypophosphataemia. Underlying disease It is necessary to be alert for the symptoms of the underlying disease, such as renal failure, steatorrhoea, or myeloma, and to enquire par ticularly about previous abdominal operations, including hysterec tomy and oophorectomy. Physical signs It is important to see the patient out of bed so that an abnormal gait or stature is not missed. The appearance may give vital clues; for ex ample, the large skull vault of Paget’s disease; the coarse features, large nose, big lower jaw, and widely spaced teeth of acromegaly; and the round face, simplicity, and cataracts of pseudohypoparathyroidism.
Table 20.1.4 Some examples of short stature Description Disorder Proportionate Genetic Familial Endocrine Growth hormone deficiency Hypothyroidism Metabolic Lysosomal storage diseases Renal glomerular failure Cystic fibrosis Nutritional Coeliac disease Starvation Chronic disease Cyanotic

heart disease Intrauterine Low birth weight dwarfism Chromosomal Turner’s syndrome Social Emotional deprivation Disproportionate Short limbs Lethal Type 2 osteogenesis imperfecta Thanatophoric dwarfism Achondrogenesis Nonlethal Achondroplasia Inherited hypophosphataemia Metaphyseal dysplasias Short spine Spondyloepiphyseal dysplasia

SECTION 20 Disorders of the skeleton 4628 Endocrine disorders affecting the skeleton, such as hypogonadism and hypopituitarism, are readily recognizable. Special facial fea tures should receive attention; these include the eyes for such signs as corneal calcification (hypercalcaemia), arcus juvenilis (osteo genesis imperfecta), and lens dislocation shown by the shimmering (iridodonesis) of the unsupported iris (Marfan syndrome). Other examples are corneal clouding (some mucopolysaccharidoses) and cystine crystals (cystinosis). Typically, the sclerae are blue in mild forms of osteogenesis imperfecta. In dentinogenesis imperfecta, often found with osteogenesis imperfecta, the teeth are abnormal in shape, tend to be opalescent, and vary in colour from yellow to grey. Enamel defects occur in hypoparathyroidism, teeth are lost early in hypophosphatasia, and dental abscesses are common in hypophosphataemic rickets. Hands and feet need particular attention. The fingers may be ab normally long and thin (Marfan syndrome) or excessively short and mobile (pseudoachondroplasia); alternatively, they may be short, wide, and stiff in some mucopolysaccharidoses or the hands may have short metacarpals (pseudohypoparathyroidism) or add itional digits (Ellis–van Creveld syndrome, MIM 225500). The monophalangic big toe (and, less often, short thumbs) is character istic of fibrodysplasia ossificans progressiva. Abnormal body pro portions are common: the spine is relatively short after vertebral collapse. Scoliosis often dates from adolescence and occasionally it may be a clue to an inherited connective tissue disorder. A thora columbar gibbus is a particular (though not exclusive) feature of the mucopolysaccharidoses. Spinal deformity produces secondary changes; thus, a young patient with severe osteoporosis will develop a prominent sternum with ribs that impinge on the iliac crest and a transverse crease across the front of the abdomen. Spontaneous tetany is a rare symptom, but there are two recognized bedside tests for latent tetany: of these, Chvostek’s sign is more convenient, but that of Trousseau more reliable. The first involves tapping the branches of the facial nerves as they spread out from within the parotid gland; a positive sign is twitching of the appropriate facial muscle. In the second, the forearm is made ischaemic with a sphygmomanometer cuff for up to three minutes; if positive, carpal spasm will occur. Investigations Biochemistry Plasma Many generalized disorders of the skeleton, such as postmenopausal osteoporosis, osteogenesis imperfecta, and the chondrodysplasias, have normal routine biochemical values; in others, changes are diag nostic (Table 20.1.5). In normal persons, the fasting plasma calcium remains virtually constant through life; the plasma phosphate, typ ically higher in children, declines in adolescence to adult levels; and the plasma alkaline phosphatase increases temporarily during rapid adolescent growth. Since total plasma calcium includes a protein- bound fraction, it is usual to relate it to the plasma albumin level and, if necessary, adjust it to a plasma albumin of 40 g per litre. Acceptable corrections include: for SI units: 0.02 mmol/litre for every 1 g/litre change of albumin from 40 g/litre or adjusted calcium (mg per 100 ml) = measured calcium –albumin (g per 100 ml) + 4. The fasting plasma calcium is normal in osteoporosis and in Paget’s dis ease unless the patient is immobilized. It is increased in primary hyperparathyroidism, vitamin D overdosage, various neoplasms (including humoral hypercalcaemia of malignancy), sarcoidosis, and, sometimes, several other states such as acromegaly and thyro toxicosis (Table 20.1.5). It is low in osteomalacia, but may be re stored towards normal by secondary hyperparathyroidism, and it is low in parathyroid insufficiency. Normal values are to be

expected in inherited untreated hypophosphataemia and in other forms of renal tubular rickets. Since the main determinant of the fasting plasma phosphate con centration is its renal tubular resorption, hypophosphataemia occurs in primary hyperparathyroidism and in the humoral hypercalcaemia of malignancy, and it is also low in inherited hypophosphataemic rickets and after a meal so fasting morning paired serum sample with second void urine phosphate and creatinine should be used to guide management. Both oral aluminium hydroxide and pro longed intravenous nutrition also lower plasma phosphate levels. Hyperphosphataemia occurs in hypoparathyroidism, in renal glom erular failure, and in the very rare, recessively inherited form of tumoural calcinosis (MIM 211900). Total plasma alkaline phosphatase and bone-derived alkaline phos phatase is normally increased in adolescence and in osteomalacia, particularly in the young, but it may be near normal in renal tubular osteomalacia. Increases occur in primary hyperparathyroidism, but only where there is demonstrable bone disease. The highest values for plasma alkaline phosphatase are found in young patients with active Paget's disease and in idiopathic hyperphosphatasia, and the lowest in hypophosphatasia. Other plasma measurements, which have application in par ticular circumstances and in research, include tartrate-resistant acid phosphatase (a product of the osteoclast and therefore an indica tion of bone resorption), osteocalcin (a product of the osteoblast and therefore sometimes useful as an indicator of bone formation), the N- and C-propeptide extensions of collagen (again indicators of bone formation rate), and fibroblast growth factor (FGF)23 which is responsible for several rare hyperphosphaturic states (next). Urine The amount of calcium excreted in the urine is related both to the plasma levels and to the percentage of the filtered load resorbed through the renal tubules, itself altered by parathyroid hormone. Hypocalcaemia therefore causes hypocalciuria, particularly in osteomalacia and rickets. Hypercalcaemia leads to hypercalciuria, especially when this is due to rapid bone loss as in neoplastic disease of the skeleton, leukaemia, myeloma, and immobilization. Since parathyroid hormone increases the renal tubular resorption of cal cium, the normal relationship between plasma and urine calcium is disturbed in parathyroid disease; however, most hypercalcaemic hyperparathyroid patients excrete more calcium than normal. Urine phosphate excretion is best measured with a second void fasting morning sample and is increased in hyperparathyroidism but is also increased in certain genetic disorders associated with renal tubular dysfunction. These include various forms of inherited phosphaturia and oncogenic rickets (see next). Total hydroxyproline in the urine (after acid hydrolysis of the pep tides) is a good indicator of bone breakdown and collagen turnover, provided the patient is ingesting a low-gelatine diet. The physio logical changes in hydroxyproline excretion are striking, with a par ticularly sharp peak in adolescence coinciding with the maximum height velocity. The highest values are seen in active Paget's disease,

20.1 Skeletal disorders—general approach and clinical conditions 4629 Table 20.1.5 The main symptoms, biochemical findings, and other features of disorders of the skeleton Disorder Most common symptoms Plasma concentrations Urine concentrations Other biochemical features Comments Ca P ALPa Ca THPb Osteoporosis Fracture N N N N N or H Usually none but depends on cause Hypercalciuria if immobilized Osteomalacia (and rickets) Bone pain; proximal muscle weakness; deformity N or L L N or H L N or H Depends on cause Plasma P increased in renal glomerular failure Inherited hypophosphataemia Short; limb deformity; fracture N L N or H N L Raised FGF23 PHEX or FGF23 mutation Oncogenic osteomalacia Fractures; bone pain; muscle weakness N L H N L Raised FGF23 Often mesenchymal tumour Paget's disease Pain; deformity N N H N H Hypercalcaemia if immobilized; some have mutations in SQSTM1 gene Idiopathic

hyperphosphatasia:
‘juvenile Paget’s disease’ Large head; bowing of long bones; occurs in childhood N N Very high N Very high Similar to Paget’s disease; very rare; osteoprotegerin deficiency; mutation in TNFRSF11B Hyperparathyroidism (with bone disease) Bone pain; hypercalcaemic symptoms H L H H H Aminoaciduria AP and THP normal if clinical bone disease absent Hypoparathyroidism Tetany; ectopic calcification L H N N N May be acute or chronic Pseudohypoparathyroidism` Simple; short metacarpals; subcutaneous ossification L H N N N Some are biochemically normal
(see text) Neoplastic bone disease Bone pain; fracture N or H N or L N or H N or H N or H Biochemistry depends on metastases
and/or effects of PTHrP Osteogenesis imperfecta Brittle bones; blue sclerae N N N N N Hypercalciuria may occur; most mutations in COL1A1, COL1A2 Ca P ALPa Ca THPb Osteoporosis pseudoglioma syndrome Blind; fracture N N N N N Mutation in LRP5 Marfan syndrome Tall with scoliosis; dislocated lenses; aortic dissection N N N N N or H Dominant inheritance; clinically variable; mutations in FBN1 usually Homocystinuria Intellectual disability; look like Marfan syndrome N N N N N Homocystine in urine Venous thrombosis may occur; variable deficiency of cystathionine synthase Alkaptonuria Back pain; early arthritis; dark urine N N N N N Homogentisic acid in the urine Calcified intervertebral discs Mucopolysaccharidosis Short stature; thoracolumbar gibbus; intellectual disability (depends on type) N N N N N Characteristic mucopolysaccharide in urine Varies with type (see text) (continued)

SECTION 20 Disorders of the skeleton 4630 Disorder Most common symptoms Plasma concentrations Urine concentrations Other biochemical features Comments Hypophosphatasia Lethal short-limbed dwarfism; bone disease like rickets Chondrocalcinosis N N L N N Phosphoethanolamine increased in urine Sometimes hypercalcaemia in infancy; fractures in adult; multiple ALP mutations Chondrodysplasias Short-limbed; short stature; many types N N N N N Hypercalcaemia in Jansen metaphyseal dysplasia Different biochemical families (see text and tables) Osteopetrosis (marble bone disease) Anaemia; deafness (extreme form); fractures; variable phenotype N N N L N Increase in acid phosphatase in some forms Mild form fractures only; rarely carbonic anhydrase lack with systemic acidosis; mutations in chloride channel and H+ATPase genes Fibrous dysplasia Fracture; sexual precocity in girls; pigmentation N N or L Slight increase N Slight increase Biochemical changes in polyostotic form only Raised FGF23 Mutations in GNSA1; occasional hypophosphataemic osteomalacia due to FGF23 Fibrogenesis imperfecta ossium Fracture N N Increased N Slight increase Monoclonal proteinuria Excessively rare; nonbirefringent osteoid Fibrodysplasia ossificans progressive Pain and swelling in muscles; fixation of joints N N Increased during acute episodes N N Mutation in ACVR1 monophalangic big toe; other patterning defects Progressive osseous heteroplasia Progressive soft-tissue ossification/calcification, often asymmetrical N N N N N Mutation in GNSA1 ALP, alkaline phosphatase; H, high; L, low; N, normal; PTHrP, parathyroid-hormone-related protein; THP, total hydroxyproline. a The changes in alkaline phosphatase refer to total alkaline phosphatase; bone-specific measurements are useful where changes in total alkaline phosphatase are minor. The changes in osteocalcin are usually in the same direction but not always. b THP = total hydroxyproline. The same changes occur in cross-linked collagen-derived peptides (CTX-1, NTX-1; see Table 20.1.3). Table 20.1.5 Continued

20.1 Skeletal disorders—general approach and clinical conditions 4631 where the excretion may be increased 50-fold. Hydroxyproline ex cretion correlates well with plasma alkaline phosphatase and is therefore increased in some forms of osteomalacia and in hyper parathyroidism with bone

disease. Since thyroxine increases col lagen turnover, urinary hydroxyproline is also abnormally high in thyrotoxicosis and abnormally low in myxoedema (either primary or secondary). Hydroxyproline excretion can be most usefully expressed as the amount in a 24-hr urine sample in a patient on a gelatine-free diet or in a fasting urine sample in relation to creatinine. However, hydroxyproline peptide excretion is related both to newly formed and mature collagen and is not, therefore, a direct measure of bone resorption. The urinary excretion of pyridinium compounds from the lysyl- and hydroxylysyl-derived cross-links of mature collagen is a direct measure of bone resorption, irrespective of dietary col lagen. These cross-linked peptides may now be conveniently meas ured in the serum (Table 20.1.3). Finally, glucose in the urine of a patient with inherited rickets suggests multiple renal tubular defects (as in Fanconi syndrome) and proteinuria is an important clue to myelomatosis. Radiology The diagnosis of bone disease often depends on the radiographic appearances, especially where there are no demonstrable biochem ical changes. A particular example is in the differential diagnosis of perinatal lethal dwarfism. Conventional radiographs demon strate structural changes such as fractures, deformity, areas of resorption, and alteration in size, but they are unreliable for the assessment of bone density. As radiographic techniques develop, increasing use is made of isotope bone scans, computed tomog raphy (CT) scans, and magnetic resonance imaging (MRI) scans. Bisphosphonate-labelled scanning agents are selectively taken up in areas of increased vascularity or turnover. They are very useful in demonstrating the skeletal extent of Paget’s disease of bone, the presence of bony metastases, the pathological fractures of osteo porosis, and Looser zones in osteomalacia. An isotope scan is pref erable to multiple radiographs to assess the distribution (but not the structure) of abnormal bone. CT scanning can also be very useful in bone disease. Examples include the delineation of ectopic ossification, of spinal cord com pression, and of bone tumours. MRI is very effective at defining soft- tissue abnormalities but is also usually the investigation of choice in detecting bony pathology. Methods for measuring bone mass are considered under the section on osteoporosis (see next). Bone biopsy Direct examination of bone is a valuable but underused investiga tion. Its use in the routine diagnosis of osteomalacia has been largely supplanted by the widespread availability of reliable laboratory measurements of serum vitamin D. Bone can be taken by a transiliac trephine (using a local anaesthetic) and sections should be exam ined with and without decalcification. Ideally the bone should be labelled with tetracycline to allow an estimate of formation rates. In the various metabolic bone diseases, the appearances are char acteristic: the excess osteoid of osteomalacia; the disorganized mo saic pattern, excessive cellular activity, and fibrosis of Paget’s disease; and osteitis fibrosa cystica of hyperparathyroid bone disease. In mild osteogenesis imperfecta, there is typically an apparent increase in the number of osteocytes (due to the reduced amount of matrix synthesized), and, in the more severe form, a considerable increase in the amount of woven bone. A normal biopsy will exclude these diseases except where the pathological changes are patchy. Where possible, histological examination should now include transmission and scanning electron microscopy and the report should include quantitative histomorphometry. More details are given in the litera ture (see Further reading). Further investigations There are many measurements available for specific problems. Important examples (in the plasma) are intact PTH assays (to in vestigate hyper and hypocalcaemia), parathyroid hormone-related peptide (PTHrP; particularly for suspected hypercalcaemia of ma lignancy), and 25OHD and 1,25(OH)2D, and FGF23 (for the inves tigation of rickets and osteomalacia). In inherited disorders, analysis of DNA or biochemical studies of cultured skin fibroblasts can be diagnostic but require specialist facilities. Concluding remarks on diagnosis The diagnosis of a skeletal disorder is not difficult where there are clear biochemical disturbances (Table 20.1.5), although, as in osteo

malacia, the causes may be many. An exact diagnosis may be im possible when the standard biochemical results are normal, and this is particularly so in some of the rare heritable disorders. Guidance based on the age of the patient and frequency of the disorder is given in Table 20.1.6. Osteomalacia and rickets Osteomalacia most frequently results from a lack of vitamin D or a disturbance of its metabolism; in the growing skeleton it is re ferred to as rickets and the terms are often used interchangeably (Table 20.1.7). Very rarely, severe calcium deficiency can lead to rickets. Inherited hypophosphataemia and several other renal tubular disorders may also cause rickets without clear evidence of abnormal vitamin D metabolism. The causal mutations in inherited hypophosphataemia have now been identified. The main histological feature of osteomalacia is defective min eralization of bone matrix (Fig. 20.1.7). Our present understanding of osteomalacia relies on advances in knowledge of vitamin D me tabolism (Fig. 20.1.8). For clinical purposes, two aspects of the physiology of vitamin D require emphasis. The first is the quanti tative importance of vitamin D synthesis in the skin in comparison with that in the diet and the second concerns the relative role of different vitamin D metabolites. The measurement of circulating concentrations of 25OHD as an index of vitamin D status has identi fied those groups (Asian immigrants and older people) most at risk from vitamin D deficiency; importantly it has also shown the large amounts of vitamin D that can be synthesized in the human skin when exposed to ultraviolet light. The causes of osteomalacia can now be partly understood in terms of its metabolites and the major importance of 1,25(OH)2D is established. The effects of giving vitamin D can probably not be ascribed solely to the actions of 1,25(OH)2D alone and may include other biologically active deriva tives such as 25OHD and, possibly, 24,25-dihydroxycholecalciferol (24,25(OH)2D).

SECTION 20 Disorders of the skeleton 4632 Pathophysiology The features of osteomalacia can be predicted largely from the known calciotropic effects of vitamin D. Examination of undecalcified bone shows wide osteoid seams with many birefringent lamellae of col lagen (Fig. 20.1.7b) covering more of the bone surface than normal and absence of the ‘calcification front’. The absence of this front is important since excessive osteoid may also be found in conditions other than osteomalacia, such as hypophosphatasia, Paget’s disease of bone, and thyrotoxicosis, where the calcification front is normal; in these disorders, the increase tends to be in the amount of bone surface covered rather than in the thickness of osteoid. Excess osteoid also occurs when etidronate or aluminium accumulate in the skeleton. In rickets the main change is disorganization of the growth plate. Since there is intestinal malabsorption of calcium in vitamin D deficiency, both the plasma and urine calcium levels are lower than normal; absorption of phosphorus is also defective, with resultant hypophosphataemia. As hypocalcaemia stimulates the secretion of parathyroid hormone, this will correct the low plasma calcium level and exaggerate hypophosphataemia. In osteomalacia, osteoblastic activity is increased, and the plasma alkaline phosphatase is therefore also increased. There appears to be no difficulty in laying down bone matrix collagen, but it cannot be properly mineralized. One should recall that the effects of vitamin D are not confined to the skeleton, although they are clinically most obvious in this tissue: thus vitamin D has important effects on cellular differentiation, on the immune system, and on striated muscle. Table 20.1.6 Diagnosis of disorders of the skeleton Age Main presenting symptom Most likely diagnosis Frequency Exclude Over 50 years Pain in the back; loss of height; fracture Osteoporosis, most common in women Common Myeloma (especially in men); secondary deposits; coexistent osteomalacia Deformity of long bones; pain in hips; pathological fracture; deafness Paget’s disease of bone; most common in men Common Osteomalacia; hyperparathyroid bone disease; skeletal

metastases Bone pain and tenderness; difficulty in walking; unable to climb stairs; pathological fracture Osteomalacia Uncommon, especially in the adult Carcinoma; polymyalgia rheumatica Bone pain and deformity; thirst; nocturia; depression; vomiting; constipation Osteitis fibrosa cystica; most common in women Rare Carcinoma with hypercalcaemia; myeloma 20–50 years Loss of height; bone pain Probably secondary deposits; or myeloma Rare Osteomalacia; accelerated osteoporosis Muscle weakness; loss of height; bone pain Osteomalacia Rare Late muscular dystrophy; neoplastic neuromyopathy; Cushing's syndrome 0–20 years Bowing of bones; deformity; weakness 'Nutritional' rickets Most common Asian immigrants in northern cities Other causes of rickets; hypophosphatasia Multiple fractures; bruising at different times Nonaccidental injury Not uncommon Osteogenesis imperfecta Bone pain; ill health Leukaemia Uncommon Osteomyelitis; rickets Pain in back; difficulty in walking; pain in ankles; less rapid growth Juvenile osteoporosis Rare Leukaemia; osteogenesis imperfecta Failure to grow (short stature) Many causes (Table 20.1.4) Common Particularly hypothyroidism; Turner syndrome; coeliac disease Excessive or disproportionate growth Several causes, often familial Less common than short stature Particularly pituitary tumour; Marfan syndrome; homocystinuria; hypogonadism and chromosomal abnormalities Fracture and deformity at birth (often lethal) Severe osteogenesis imperfecta Uncommon Hypophosphatasia; achondrogenesis; thanatophoric dwarfism Table 20.1.7 The main causes of osteomalacia and rickets Cause Effect Lack of vitamin D Defective synthesis in the skin Low dietary intake Increased requirement Malabsorption Gluten-sensitive enteropathy (coeliac disease) Gastric surgery Bowel resection Intestinal bypass surgery Biliary cirrhosis Pancreatic insufficiency Renal disease Renal tubular disorders X-linked inherited hypophosphataemia (vitamin D-resistant rickets) Others (see Table 20.1.9) Renal glomerular failure Renal osteodystrophy Bone disease with dialysis and transplantation Others Tumour rickets (oncogenic osteomalacia) Vitamin D-dependent rickets (types 1 and 2) Phosphate-deficiency rickets Anticonvulsant osteomalacia Calcium deficiency rickets From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission.

20.1 Skeletal disorders—general approach and clinical conditions 4633 Causes There are many causes of osteomalacia (and rickets), some of which are very rare. They may conveniently be divided into three main groups: nutritional, malabsorptive, and renal (Table 20.1.7). Most can be understood in terms of vitamin D metabolism (Fig. 20.1.8). In older people and immigrant populations, the UVB mediated cu taneous conversion or food intake of vitamin D are often deficient and the requirements may be increased; the absorption of vitamin D is poor in coeliac disease, after partial gastrectomy, intestinal re section, or bypass, and in biliary disease. The intestinal absorption of calcium is reduced by phytate, as in chapattis, which may also increase vitamin D requirements (see next). Endogenous synthesis of vitamin D in the skin is reduced, especially in town and city com munities in high northern latitudes; it is further reduced by skin pigmentation. The 25-hydroxylation of calciferol may be impaired in some chronic liver diseases and anticonvulsants may induce hepatic enzymes that degrade vitamin D. The 1α-hydroxylation of 25OHD is reduced or absent in renal failure, after nephrectomy, in hyperphosphataemia (which suppresses the activity of the en zyme 1α hydroxylase), parathyroid insufficiency, in type 1 vitamin D-dependent rickets, by raised levels of FGF23, and, probably, in some bone tumours. Many patients have more than one cause for their osteomalacia; older people often have poor vitamin D intake, limited exposure to sunlight, and progressive renal glomerular failure. Reduced exposure to sunlight is an indirect consequence of physical immobility and may contribute to osteomalacia in rheuma toid arthritis and other chronic diseases. The effects of chronic kidney disease on the

skeleton are com plex (Chapter 21.6). Two main events occur: one is an increase in the plasma phosphate level, which leads to a fall in plasma calcium and secondary hyperparathyroidism with excessive bone resorp tion; the other is the reduced renal formation of 1,25(OH)2D, with (a) (b) Fig. 20.1.7 (a) Bone from a patient with osteomalacia showing the appearance of excessive osteoid under polarized light; excessive unmineralized osteoid is arrowed. (b) There are regular lamellae of double refractile collagen fibres. Vitamin D Malabsorption Biliary obstruction (2) Precursor 25 (OH)D 25OHD 1,25(OH)2D Vitamin D dependent rickets Type II (13) Food Renal failure (7) Nephrectomy (8) High P (9) Low PTH (10) Vitamin D dependent rickets Type I (11) X -linked hypophosphataemia (12) (1) Elderly Immigrant (3) Phytate Chapattis (4) Sunlight Pigment (5) Sunscreen (6) Anticonvulsants Fig. 20.1.8 The causes of rickets and osteomalacia in relation to vitamin D physiology. (1–5) Reasons for vitamin D deficiency; (6) anticonvulsants may reduce hepatic 25 hydroxylation of vitamin D; (7–11) some causes for reduced 1α-hydroxylation of 25OHD, which do not always cause rickets; (12) formation of 1,25(OH)2D is inappropriately low in X-linked hypophosphataemia, due to raised FGF23 secondary to mutations in PHEX; and (13) resistance to 1,25(OH)2D in type 2 vitamin D-dependent rickets.

SECTION 20 Disorders of the skeleton 4634 defective intestinal absorption of calcium and defective bone min eralization. The combination of these events rapidly produces severe deformity, especially in the growing skeleton. In patients receiving dialysis, renal osteodystrophy may be complicated by aluminium intoxication. Clinical features The main symptoms of osteomalacia are bone pain and tenderness, skeletal deformity, and proximal muscle weakness, often accom panied by the features of the underlying disorder and of hypocal caemia. In severe osteomalacia, all the bones are painful and tender (sometimes sufficient to disturb sleep). The tenderness can be par ticularly marked in the lower ribs and may also be accentuated over Looser zones. Deformity is most often seen in rickets when the ef fects of vitamin D deficiency are superimposed on a growing skel eton; the linear growth rate is reduced, there is bowing of the long bones, enlargement of the costochondral junctions (‘rickety rosary’) and bossing of the frontal and parietal bones. Later, osteomalacia may produce a triradiate pelvis, a gross kyphosis, and corresponding deformities of the chest. Proximal muscle weakness is an important symptom. Its cause is unknown, although myoblasts require 1,25(OH)2D in vitro and the development of myofibrils in animals without the vitamin D re ceptor may be abnormal. It is more marked in some forms of osteo malacia than in others. Most commonly, there is a waddling gait and difficulty in getting up and down stairs, out of low chairs, and in and out of small cars. In older people, weakness may make walking impossible thereby suggesting paraplegia. In younger subjects, mus cular dystrophy may be simulated. Examination of the patient with osteomalacia or rickets confirms the main symptoms. Measurement of the body proportions is useful. Thus, patients with inherited hypophosphataemia and rickets have relatively short limbs, whereas those with late-onset osteomalacia may have a relatively short trunk due to vertebral collapse. It is im portant to look for clues as to the cause of the osteomalacia, such as the scars of previous gastric or intestinal surgery. Investigations Biochemistry There are many causes of osteomalacia and the detailed biochem ical changes differ from one to another (Table 20.1.8). In vitamin D deficiency or malabsorption, there are low plasma calcium and phosphate levels, low urine calcium, and increased plasma alkaline Table 20.1.8 Biochemical changes in rickets and osteomalacia Disorder Plasma concentrations Comments Main groups Ca P ALP Vitamin D deficient ↓/N ↓ ↑ 25OHD low; PTH increased Malabsorption ↓ ↓ ↑ If severe may also have magnesium deficiency Renal tubular Inherited hypophosphataemia N ↓ ↑ X-linked most frequent; ↑ FGF23 Renal tubular acidosis ↓ ↓ ↑ Systemic acidosis Fanconi syndrome ↓

↓ ↑ Generalized aminoaciduria; glycosuria Renal glomerular osteodystrophy Renal glomerular ↓ ↑ ↑ Biochemistry of renal failure (1,25(OH)2D low) Dialysis and transplantation ? ? ↑ Very variable; aluminium excess important Oncogenic osteomalacia N ↓ ↑ 1,25(OH)2D ↓, FGF23 ↑, lTMP/GFR for age ↓, Vitamin D dependent Type 1 ↓ ↓ ↑ 1,25(OH)2D ↓ Type 2 ↓ ↓ ↑ 1,25(OH)2D ↑ Phosphate deficiency N ↓ ↑ 1,25(OH)2D ↑ Disorder Plasma Urine Plasma 1,25(OH)2D Hypophosphataemic syndromes Ca P ALP FGF23 Ca XLH N ↓ ↑or N ↑ ↓ (↓) HHRH N ↓ ↑ or N * ↑ ↑ ADHR N ↓ ↑ or N ↑ ↓ (↓) Dent disease N ↓ or N ↑ or N * ↑ (↓) Oncogenic osteomalacia N ↓ ↑ or N ↑ ↓ ↓ ADHR, autosomal dominant hypophosphataemic rickets; ALP, alkaline phosphatase; HHRH, hereditary hypophosphataemic rickets and hypercalciuria; N, normal; PTH, parathyroid hormone; XLH, X-linked hypophosphataemia. Note that the serum 25OHD concentration is normal in all these disorders. (↓) indicates that the 1,25(OH)2D concentration is decreased relative to serum phosphorus. Features of the underlying disorder include anaemia, tiredness, and steatorrhoea (coeliac disease), and pigmentation, thirst, and nocturia in renal failure. Occasionally, hypocalcaemia may cause spontaneous tetany; the manifestations of carpopedal spasm, stridor, and fits are more dramatic in the child than the adult.

20.1 Skeletal disorders—general approach and clinical conditions 4635 phosphatase. However, these may vary with the stage of the dis ease. Initially, hypocalcaemia may be the only abnormality. Later, with secondary hyperparathyroidism, the plasma calcium level returns towards normal, the plasma phosphate level falls, and the alkaline phosphatase level increases. In inherited X-linked hypophosphataemia (vitamin D-resistant rickets), plasma phos phate is low, but the plasma calcium is normal, and the alkaline phosphatase may also be normal. Renal glomerular failure causes an increase in plasma phosphate, urea, and creatinine, and hypo calcaemia, and, in the rare renal tubular syndromes, there may be a marked systemic acidosis. In patients with osteomalacia, the urine should always be examined for the presence of glucose and protein. If these are present, it is important to check for the amino acid and low molecular weight proteinuria characteristic of renal tubular disorders. Some of these are associated with specific tubular de fects, such in the chloride channel CLCN5 in Dent disease (MIM 300009) and related disorders (Chapters 21.15 and 21.16). The measurement of vitamin D metabolites is now routine and a low plasma 25OHD level is a good indication of vitamin D de ficiency. Estimation of plasma 1,25(OH)2D is important to eluci date the very rare causes of rickets and particularly to distinguish between type 1 (low 1,25(OH)2D) and type 2 (high 1,25(OH)2D) vitamin D-dependent rickets. Radiology The radiological appearances differ according to whether growth has ceased or not. In rickets, the main abnormalities are at the ends of the long bones, where the width of the growth plate is increased, and the metaphysis is widened, cupped, and ragged (Fig. 20.1.9). Osteomalacia may show the deformities previously described, but the radiological hallmark of active osteomalacia is the Looser zone (Fig. 20.1.10). This is a ribbon-like area of defective mineraliza tion, which may be found in almost any bone but is seen particu larly in the long bones, the pelvis, and the ribs, and also around the scapulae. Looser zones may be bilateral and symmetrical; in bones such as the femur, they occur on the medial border of the shaft or neck and are usually single, which contrasts with the multiple fis sure fractures on the lateral convexity of the bone in Paget’s disease. In osteomalacia, the vertebral bodies are often uniformly biconcave, to produce an appearance likened to a ‘cod fish’ spine. Additionally, in renal glomerular osteodystrophy, the endplates may become relatively more dense than the rest of the vertebral body, to pro duce the so-called ‘rugger jersey’ spine. In the adult with inherited hypophosphataemia, the bones may become increasingly deformed, buttressed, and dense; in this disorder, calcification/ossification of the tendons and

ligaments at their insertions (enthesopathy) and of the vertebral ligaments can produce an appearance reminiscent of ankylosing spondylitis. Ossification of the ligamenta flava narrows the spinal canal and compresses the spinal cord and its roots. This is well shown on CT scans or MRI. In patients with osteomalacia and hypocalcaemia, the radiological features of secondary hyperpara thyroidism appear with subperiosteal bone resorption that affects the phalanges, the pubic symphysis, and the outer ends of the clav icles. In rickets, periostitis of the distal ends of the long bones, such as the radius and ulna, often occur. The most extreme effects of parathyroid overactivity are seen in the skeleton of the child with renal osteodystrophy, where the region of the growth plate and metaphyses may fracture (an appearance likened to a rotting stump). Bone scintigraphy and/or MRI may be very useful in cases of osteomalacia, demonstrating multiple patho logical fractures often not seen on the plain films. The appearance is similar to that of bony metastases, for which it may be readily mistaken. Bone biopsy The diagnosis of osteomalacia is often clear without examining the bone, particularly with widespread access to serum vitamin D meas urements. Where doubt exists, a transiliac biopsy examined before and after decalcification will demonstrate the failure of mineral ization and the wide osteoid seams. It is important to use surgical opportunities to examine bone histologically, particularly during operations on fractured femurs in older people. Other investigations Further investigation is not usually needed to diagnose osteo malacia but may be necessary to identify its cause. Thus, patients with vitamin D-deficient rickets and osteomalacia will have a low plasma 25OHD (<30 nmol/litre), but not all subjects with such low levels have osteomalacia. In the very rare condition of vitamin D-dependent rickets (VDDR), measurement of circulating Fig. 20.1.9 The radiological appearance of rickets in a child with inherited hypophosphatemia. The growth plates are widened and the metaphyses are cupped and ragged. Fig. 20.1.10 Osteomalacia due to adult Fanconi syndrome. Bilateral Looser zones (arrowed) on the medial border of the femora in a woman.

 1,25(OH)2D will be necessary to distinguish the absence of 1α-hydroxylase (type 1 VDDR) from resistance to 1,25(OH)2D (type 2 VDDR). Further, CT and MRI may help to identify the presence of an FGF23-secreting mesenchymal tumour causing hypophosphataemic osteomalacia (oncogenic rickets, see next). Diagnosis Osteomalacia is not difficult to diagnose once it has been thought of. It should be distinguished from other forms of metabolic bone disease (Table 20.1.5), from other causes of proximal muscle weak ness, and from other disorders causing bone pain. In patients with proximal muscle weakness, polymyalgia rheumatica, thyrotoxic myopathy, muscular dystrophy, neoplastic neuropathy, dermato myositis, and polymyositis all need to be considered. Multiple myeloma and leukaemia should be excluded as causes of pain. Plasma calcium, phosphate, and alkaline phosphatase measured in patients with these symptoms, will usually identify osteomalacia, especially if coupled with measurement of serum 25OHD. Patients with psychological illness may have an abnormal gait and com plain of pain and weakness in their limbs, but the biochemistry will usually be normal. In practice, symptoms of pain and stiffness often first lead the patient with osteomalacia to a rheumatologist or orthopaedic surgeon. Treatment Rickets and osteomalacia should respond rapidly to vitamin D (or one of its metabolites) in appropriate doses and the re sponse may actually be a useful way of confirming the diagnosis. Increased mobility with an increase in muscle strength may be the first clinical response, despite a temporary increase in bone pain. Biochemically, plasma phosphate and urine hydroxyproline levels are the first to increase. The alkaline phosphatase level may show a temporary rise and then fall slowly to normal. As the plasma calcium and 25OHD concentrations increase towards normal, the parathyroid hormone concentration falls. The effective dose and the

particular vitamin D preparation de pends on the cause of the osteomalacia. That due to vitamin D defi ciency will respond to microgram doses (1 μg = 40 IU), but it is often useful to give considerably more than this, such as 2000–4000 IU per day for one or two months. Where there is doubt about com pliance, vitamin D may be injected intramuscularly in one large dose (up to 15 mg, 600, 000 units). Unfortunately, this may not be efficiently absorbed from the injection site. Lack of a response to microgram doses suggest that the osteomalacia is not due to simple vitamin D deficiency but, for example, to malabsorption or renal failure. It is particularly in the last group that the 1α-hydroxylated metabolites of vitamin D are effective (see Chapter 21.6). Clearly, underlying disorders must be treated at the same time (e.g. patients with coeliac disease will need a gluten-free diet). Particular forms of osteomalacia and rickets Nutritional osteomalacia In the United Kingdom and other northern European countries, so-called nutritional osteomalacia occurs particularly among older people and in Asian immigrants of all ages. In older people, the high incidence of osteomalacia is mainly due to their poor exposure to sunlight and a low intake of vitamin D; it may also be exacerbated by the effects of drugs such as anticonvulsants and by increasing renal glomerular failure. Since older people are often housebound, they may develop osteomalacia despite a sunny climate. The prevalence of osteomalacia in the older population is significant. The frequency of osteomalacia in patients with fractures of the femoral neck is also higher than previously suspected. It should always be excluded in older people with bone disease, and particularly in those with fem oral neck fractures. Where possible this should include histological examination of bone taken at operation or by biopsy. Vitamin D status should be assessed routinely in those with suspected rickets/ osteomalacia or those about to start potent osteoporosis therapies. In the geriatric population, the mean concentration of 25OHD is much lower than in younger patients; the usual seasonal variation, with lowest values in winter and early spring and highest values in late summer, may not occur in those who spend their time indoors. Asian immigrants to more northerly latitudes develop osteomal acia and rickets more often than the indigenous population for sev eral reasons. They tend to live in northern cities away from sunlight and, especially in women, do not expose their skin to the limited ultraviolet light. Where dermal synthesis of vitamin D is limited, dietary factors become more important and it is particularly those on a meat-free diet containing chapattis who develop osteomalacia. The role of chapattis and the phytates that they contain is not yet fully understood. Phytates bind to calcium so preventing its absorp tion and it can be shown, at least experimentally, that reduced cal cium absorption increases the vitamin D requirement by increasing its parathyroid-mediated breakdown. It has been suggested that such a mechanism of reduced calcium absorption may also con tribute to the osteomalacia of malabsorptive syndromes, such as that following partial gastrectomy. Pigmentation of the skin reduces vitamin D synthesis, but in practice this is of little significance. Since north European immi grants of Afro-Caribbean descent have a lower incidence of rickets than Asians in the same environment, it is clear that factors other than skin colour are important. As in older people, 25OHD levels can be very low, especially in Asian immigrants. They increase in the summer, when there may be spontaneous healing of rickets. Important work in Glasgow has shown that Asian rickets can be prevented by fortifying food such as chapatti flour with vitamin D, although the incidence of osteomalacia in Asian adults remains un affected. Other local lifestyle changes will also influence the diet of children. Osteomalacia and malabsorption Coeliac disease (gluten-sensitive enteropathy) (Chapter 15.10.3) is a relatively common cause of osteomalacia, approaching 1% in the United Kingdom. It should be suspected at any age and confirmed by the presence of circulating tissue transglutaminase antibodies and, if necessary, by a small intestinal biopsy showing an atrophic mucosa. Other causes of malabsorption vary in their frequency

according to surgical practice. Thus, it is well established that osteomalacia fol lows classic partial gastrectomy, but the actual incidence is debated and its cause is probably multifactorial. Postgastrectomy subjects tend to take little vitamin D in their diet and there is defective cal cium absorption. Available evidence suggests that clinical osteomal acia is rare after vagotomy and pyloroplasty. Osteomalacia can also follow the removal of long segments of small intestine for conditions such as Crohn’s disease and complicates some intestinal bypass op erations used for extreme obesity.

20.1 Skeletal disorders—general approach and clinical conditions 4637 Osteomalacia and liver disease Osteomalacia is uncommon in those with liver disease; in theory it may be due to several factors such as malabsorption of vitamin D and its defective 25-hydroxylation. Most research has concerned the osteomalacia of biliary cirrhosis, and osteomalacia in chronic liver disease appears to be a complication related to prolonged cholestasis. Osteomalacia and renal disease It is important to distinguish the osteomalacia and rickets of renal glomerular failure from that attributable to renal tubular disorders. Bone disease in chronic kidney disease (renal osteodystrophy) is dealt with elsewhere (see Chapter 21.6); this includes bone disease in the dialysis patient and the effects of aluminium. Renal glomerular osteodystrophy is a complex disease with excessive bone resorp tion, defective bone mineralization, and, in some cases, osteopor osis. Previously, it was treated with large doses of native vitamin D; more effective current therapy now includes the metabolites 1α- hydroxycholecalciferol or 1,25(OH)2D. Many renal tubular disorders lead to osteomalacia (Chapters 21.15 and 21.16; Tables 20.1.8 and 20.1.9). Of these, the most common is X-linked hypophosphataemia, so-called vitamin D-resistant rickets (MIM 307800), which is normally inherited as an X-linked dom inant trait; here, the main abnormality is hypophosphataemia due to a reduction in the maximum renal tubular resorption rate of phos phate. It exhibits substantial clinical heterogeneity; some patients in a family will have hypophosphataemia alone, whereas others will have hypophosphataemia with accompanying severe bone disease. It is now known that many cases of inherited hypophosphataemia are caused by mutations in the PHEX gene, the cognate protein of which has the features of an endopeptidase. Its effects may be me diated through one of the fibroblast growth factors (FGF23), levels of which are typically increased in X-linked hypophosphataemia. PHEX mutations alter the ability of this endopeptidase to cleave and inactivate the biologically active form of FGF23. In this regard, an other rare human autosomal dominant form of hypophosphataemia caused by FGF23 mutations is particularly interesting (MIM 193100); these mutations abolish the PHEX catabolic cleavage site in FGF23, thereby increasing the biological activity of this potent hypophosphataemic mediator (as is also seen with the raised FGF23 levels in oncogenic osteomalacia; see next). Since the 1,25(OH)2D levels are normal where the plasma phos phate is low, it is also proposed that the sensitivity of the 1α-hydroxylase enzyme is reduced. Children with hypophosphataemic rickets or osteomalacia are unlike patients with other forms of rickets. They present with deformity but are otherwise well and without muscle weakness; however, growth is defective, and their eventual height is usually less than 150 cm. Apart from hypophosphataemia, there may be no other abnormality in the biochemical values routinely avail able and the plasma alkaline phosphatase level can be normal for age. Radiographs show severe rickets and, later, the bones are often dense with buttressing and profound enthesopathy. Ossification of the ligamenta flava coupled with facet joint hypotrophy can cause spinal nerve root compression and even paraplegia. Spinal stiffness may be profound, mimicking spondyloarthropathy. There may be profound ossification of the joint capsules restricting movement. Total hip re placement can be very effective in such cases. Ligamentous

calcifi cation may also contribute to deafness. Finally, abnormal teeth in this disorder cause periapical translucencies and frequently lead to abscesses. The treatment of inherited hypophosphataemia is evolving. Early diagnosis is important to implement effective treatment promptly and to minimize growth retardation and deformity. For many years, its mainstay was large doses of vitamin D, but this posed a continuous danger of vitamin D poisoning and did not correct the eventual short stature. There is an improvement in growth rate when oral phosphate is given in addition to vitamin D, but the condition does not respond to phosphate alone. It has now been shown that Table 20.1.9 Renal tubular disorders, rickets, and osteomalacia Description Disorder MIM Vitamin D-resistant rickets X-linked hypophosphataemia 307800 Renal tubular acidosis (RTA) Inherited Proximal (bicarbonate wastage) 179830 Distal (H+ gradient defect) 179800 Acquired Ureterosigmoid anastomosis Some multiple renal tubular defects (Fanconi syndrome) Inherited Cystinosis 219800 Oculocerebrorenal syndrome (Lowe syndrome) 309000 Wilson disease 277900 Galactosaemia 230400 Acquired Multiple myeloma Cadmium poisoning Ifosfamide toxicity Other rare renal tubular defects X-linked hypercalciuric nephrocalcinosis (Dent disease) 300009 Hereditary hypophosphataemic rickets and hypercalciuria 241530 Autosomal dominant hypophosphataemic rickets 193100

SECTION 20 Disorders of the skeleton 4638 combined 1,25(OH)2D and oral phosphate (in up to five doses in 24 hr) produces healing of epiphyseal and trabecular bone and this is now the recommended treatment. This combination not only pro duces bone healing but also increases eventual stature. However, it is still unusual for affected patients to have an eventual height of much more than 1.5 m (5 feet). Accounts of the effects of medical treatment on deformity and height differ. Corrective osteotomy on the lower limbs is still required quite frequently but requires careful planning with an experienced orthopaedic surgeon because of the potentially complex nature of the deformities. It is also important that the parents should know the genetics of this condition. Because the defect in phosphate transport is in herited as a dominant on the X chromosome, an affected mother transmits the condition to 50% of her children regardless of their gender. All the daughters of an affected father will have the dis ease, but none of his sons. Affected sons may have more severe disease and some affected daughters may be asymptomatic. Clinical diagnosis can be made from birth, but this demands ac curate knowledge of the normal plasma phosphate level at that age. Prenatal diagnosis of X-linked hypophosphataemia is possible by identifying PHEX mutations. However, there is significant hetero geneity in hypophosphataemic rickets. Other forms include auto somal dominant (FGF23), autosomal recessive (DMP1 – MIM 21520; ENPP1 – MIM 173335) and X-linked recessive variants (CLCN5 – MIM 300008). Other renal tubular osteomalacic syndromes include hypopho sphataemic osteomalacia presenting in adult life, which may be due to a tumour (see next), inherited and acquired forms of renal tubular acidosis and rickets associated with multiple renal tubular defects, and generalized aminoaciduria (Fanconi syndrome). Renal tubular acidosis may be proximal or distal, with an inability to resorb bicarbonate or to acidify the urine. The osteomalacia may be cured by giving bicarbonate, alone or with vitamin D. A per sistent acidosis with resultant osteomalacia may also result from ureterosigmoid anastomosis. The commonest cause of Fanconi syndrome in childhood is nephropathic cystinosis, or cystine- storage disease, where there is a widespread deposition of cystine crystals throughout the tissues and in which thirst, polyuria, dehy dration, photophobia, and loss of weight begin at about the age of one year. The rickets will heal with correction of the acidosis and administration of phosphate and 1α-hydroxycholecalciferol; renal transplantation corrects the renal failure and prolongs survival but does not prevent nonrenal complications. Early diagnosis and treatment with

cysteamine can delay the onset of end-stage renal failure and hypothyroidism but both will inevitably occur eventually. Renal transplantation is effective but does not prevent progression of the disease in other organs. Among the rare renal tubular defects associated with rickets, mutations in the CLCN5 chloride channel gene cause Dent disease (X-linked recessive hypercalciuric nephrolithiasis). In this condition there is also low molecular weight proteinuria, which reflects a failure of endo cytosis of these proteins in the brush border of the proximal renal tubule cells; this is normally mediated by the multiligand proteins megalin and cubilin, which are themselves physically associated with CLCN5 but are absent from the brush border in Dent disease. Other rare causes of renal tubular rickets and osteomalacia with generalized aminoaciduria are inherited, such as Wilson disease and the X-linked oculocerebral renal syndrome, or acquired, such as multiple myeloma, cadmium poisoning, and the toxic effects of ifosfamide used in the treatment of childhood malignant disease. Anticonvulsant osteomalacia In patients treated with anticonvulsants, the incidence of rickets and osteomalacia is higher than normal. This has been attributed to the induction by the anticonvulsants of hepatic enzymes (PXR) that metabolize vitamin D to biologically inactive derivatives. However, epileptic patients in institutions are often vitamin D de ficient because they are also deprived of sunlight; osteomalacia in such patients probably has several causes. Tumour rickets An unusual form of hypophosphataemic rickets or osteomal acia, tumour rickets or oncogenic osteomalacia, occurs in patients who have mesenchymal tumours, often of a particular histological type, namely sclerosing haemangiopericytomas or nonossifying fi bromas. A tumour should be considered in any adult who develops hypophosphataemic osteomalacia, particularly with prominent myopathy. The disorder is improved by oral phosphate and cured by removal of the tumour. Current evidence suggests that it inter feres with the renal 1α-hydroxylation of 25OHD, since the circu lating levels of 1,25(OH)2D are abnormally low but rapidly return to normal when the tumour is removed. In this form of osteomal acia, there is an increase in the circulating level of FGF23, which upregulates expression of a renal tubular sodium phosphate trans porter, thereby promoting renal phosphate excretion. Oncogenic osteomalacia has also been described in cases of prostatic cancer and in small-cell carcinoma of the lung. Hypophosphataemic osteo malacia also sometimes occurs in adults with neurofibromatosis and polyostotic fibrous dysplasia. Vitamin D-dependent rickets (VDDR) Patients with these very rare, recessively inherited forms of rickets show the features of severe rickets without vitamin D deficiency. There are at least two types of VDDR. In type 1 VDDR (MIM 264700), the activity of the renal 1α-hydroxylase is reduced so that the concentration of 1,25(OH)2D is abnormally low. However, it can be increased by large doses of the native vitamin, which shows that the enzyme block is not complete. In type 2 VDDR (MIM 277440), there is end-organ resistance to 1,25(OH)2D, which is present in high concentrations, due to mutations in the vitamin D receptor. In both forms, there is severe rickets and myopathy from infancy; in type 2 VDDR, lifelong total alopecia is a striking feature. Type 1 VDDR responds to very large doses of vitamin D or physio logical doses of 1,25(OH)2D. Type 2 VDDR may also respond to large doses of vitamin D or its metabolites or to prolonged intra venous calcium. Recent work on type 2 VDDR (otherwise known as hereditary 1,25(OH)2D-resistant) shows that the 1,25(OH)2D receptor de fects, which are responsible for the end-organ resistance in this dis ease, are due to a variety of point mutations, either in its steroid- or DNA-binding domains. Phosphate-deficiency rickets If patients ingest large amounts of phosphate-binding drugs, such as aluminium hydroxide, a form of hypophosphataemic osteomalacia may develop. This differs clinically from inherited

hypophosphataemic osteomalacia by the presence of severe muscle weakness. Other biochemical features include increased calcium absorption with hypercalciuria, associated with an increase above normal in the concentration

of 1,25(OH)2D. Paget’s disease of bone Paget’s disease of bone, osteitis deformans, was first described more than a century ago. It is the most common of the so-called metabolic bone diseases after osteoporosis. Its hallmark is excessive and disor ganized resorption and formation of bone (Fig. 20.1.11). Its cause is

multifactorial, but recent studies on pagetic osteoclasts and gen etics studies have provided important insights. The new generation of bisphosphonate drugs now provide highly effective treatment. Rare related disorders include familial expansile osteolysis, expan sile skeletal hyperphosphatasia, and

idiopathic hyperphosphatasia (juvenile Paget’s disease) (see next). Pathophysiology Historically there has been great interest in the observations that Paget’s disease behaved in many respects like a multicentric neo plasm or a slow virus disease that begins in young adult life. Virus- like inclusion bodies have been seen in the

osteoclasts of patients with Paget’s disease. Some studies have suggested that various viruses, including measles, respiratory syncytial virus, or canine distemper virus might be involved, but confirmation has been elu sive. In contrast, there is now overwhelming evidence of a genetic contribution to Paget’s disease, with the

most frequent mutation in the gene coding for the ubiquitin-binding protein, sequestosome1, a scaffold protein in the RANK/nuclear factor kappa B signalling pathway. Several related disorders are also caused by genes acting in this pathway. These include familial expansile osteolysis—the RANK (TNFRSF11A) gene; juvenile

Paget’s disease (MIM 602080)—the osteoprotegerin gene (TNFRSF11B); and inclusion body myopathy with early onset Paget’s disease (MIM 167320)—the clathrin gene (VCP). All result in overactivity of the osteoclast. Histology shows multinucleate osteoclasts that appear to be re sorbing bone and busy osteoblasts

that appear to be replacing it; these activities are closely linked and both cell types are involved. There is also excess fibrosis in the marrow. The bone matrix is laid down in all directions and loses its birefringence and strength. Mineralization may be defective, probably because of the excessive rate at which the organic bone matrix is laid down.

The cement lines and the mosaic appearances of the bone result from the tidemarks of resorption followed by formation. Osteosarcoma, which occurs in Paget’s disease, is presumably the result of the excessive and pro longed activity of the bone cells. Pagetic bone is large, vascular, and deformed. Its physical characteristics

depend on the stage of the disorder and it may be hard or soft. In any event, it fractures more readily than normal. Incidence Paget’s disease occurs in about 3% of subjects over 55 years of age in the United Kingdom, is more common in men than in women, and its frequency increases with age. It is not unknown in younger people. In the

United Kingdom, about 750 000 people may have Paget’s disease, as many as 30% have symptoms related to the dis ease. It appears to be a peculiarly Anglo-Saxon affliction, being very rare in Scandinavian countries and Japan. The high frequency of the P392L mutation in SQSTM1 in familial and sporadic cases of Paget’s disease represents strong

evidence for a genetic founder effect. Within England, early radiological surveys in the 1970s showed that it occurred most often in Lancashire towns and in northern industrial regions (Table 20.1.10). It is also more fre quent in recent British immigrants to Western Australia than in the Genetic (a) (b) Viral Cytokines Fracture Sarcoma

Nerve compression Fracture New fragile bone Increased formation markers Increased resorption markers Excessive resorption Resorption +++

+++ Formation Fig. 20.1.11 Paget’s disease of bone. (a) Histological appearance of bone in Paget’s disease: cellular activity is increased with many large multinucleated osteoclasts and there is, in addition, fibrosis in the marrow and a mosaic pattern in the mineralized bone; and (b) diagram to show the causes and effects of Paget’s disease of bone; the interrupted curves demonstrate the continued ‘coupling’ of resorption and formation even when cellular activity is very much increased. Table 20.1.10 Radiological prevalence of Paget’s disease in the United Kingdom Town Men (%) Women (%) Preston 8.6 6.3 Bolton 7.7 6.4 Blackburn 8.8 3.8 Bradford 7.9 3.6 Hull 7.6 3.1 Southampton 6.6 3.6 Bath 5.3 4.7 Stoke 4.7 4.2 York 5.8 2.5 Modified from Barker DJP, et al. (1977). Paget’s disease of bone in 14 British towns. Br Med J, 1, 1181–3, Copyright © 1977. Adapted by permission from BMJ Publishing Group Limited.

SECTION 20 Disorders of the skeleton 4640 indigenous population, but less frequent than in those relatives who remained in the United Kingdom. Such studies do not distinguish between the effect of environment and heredity. Between 15 to 40% of affected individuals may have an affected first-degree relative but, clearly, for such a common disease this may often be due to chance. Recent data show a significant reduction in the prevalence of Paget’s disease, which emphasizes the importance of (unknown) environ mental factors. These data are based on more than 500 patients in each town. The age-standardized incidence is always higher in men than in women. The high incidence in Lancashire towns is not explained. Recent data suggest a decline in radiological prevalence (see Further reading). Clinical features Many subjects with Paget’s disease have no symptoms. Pain, deformity, fracture In Paget’s disease, the bone itself may be painful or pain may be due to arthritis of a nearby joint, to an associated fracture, or to the development of sarcoma. It has been suggested that there is a specific type of hip joint disorder associated with Paget’s dis ease. Bone pain could be due to stretching of the periosteum, since this part of the bone (and the

vessels within bone) con tains nerves sensitive to pain. Clinically, the affected bones are enlarged, deformed, and warm. The enlargement is clearly seen in bones such as the tibia and the skull; in the former, the bone is typically bowed forwards; the latter shows a characteristic en largement of the vault that is said to look like a soft beret or tam- o'-shanter, which appears to descend over the ears. Other long bones may become bent and a kyphosis may develop. Although any bone can be affected, including the maxilla and the pha langes, the most common sites for Paget's disease are the pelvis and the spine. Fracture may be the first symptom of undiagnosed Paget's disease. Deafness and nerve compression Deafness in Paget's disease is one of its most disabling symptoms and responds little to treatment. It has many causes, of which nerve compression is only one. Most nerves can be compressed by enlarging pagetic bone. The spinal cord is particularly at risk, due to the combined effects of increased bone size, vertebral collapse, and excessive vascularity. Paraplegia or cauda equina lesions may occur. Alterations in the shape of the skull may produce multiple cranial nerve palsies and brainstem lesions, with dysphagia, dysarthria, and ataxia. Basilar invagination with obstruction of cerebrospinal fluid drainage can lead to internal hydrocephalus, raised intracranial pressure, and confusion. Heart failure In severe Paget's disease, cardiac output may be increased by the excessive vascularity of the affected bones, but there is no convin cing evidence of large arteriovenous shunts within the skeleton. The heart failure that results may be of the high-output variety, but this is excessively rare. Since heart failure and Paget's disease of bone are common in older people, their occurrence together is almost always coincidental. Associated disorders Paget's disease is said to be associated with other disorders such as osteoarthritis, gout, vascular calcification, and articular chondrocalcinosis. Since all these occur more often in older people, the associations have little significance. In contrast, Paget's disease in half those >60 years old who develop osteosarcoma, which is nevertheless a rare complication of the disease. Investigations Biochemistry There is a marked increase in the level of plasma alkaline phos phatase, derived from the overactive osteoblasts, which is roughly related to the extent of clinical and radiological involvement with Paget's disease. In contrast, the acid phosphatase (derived partly from osteoclasts) level is only slightly increased. The rapid turn over of bone matrix collagen increases urinary hydroxyproline (and hydroxylysine) in proportion to the increase in alkaline phos phatase and also the urinary excretion of cross-linked collagen- derived peptides. Plasma calcium and phosphate levels are normal; hypercalcaemia suggests coexistent hyperparathyroidism, malig nant disease, or immobility. Radiology The radiological appearances of Paget's disease are legion. The most characteristic is an increase in size of the affected bone. Resorption predominates early in the disease and in the young patient. A re sorbing front may be seen in a long bone (blade of grass sign) or in the skull (osteoporosis circumscripta) (Fig. 20.1.12a). Excessive re sorption is inevitably followed by disordered bone formation and, at this stage, the bone becomes thick and deformed (Fig. 20.1.12b). In older subjects, the affected bone may be very osteoporotic and liable to fracture. Multiple partial fractures (microfractures, fissure frac tures) are common on the deformed convex surface of long bones (see Fig. 20.1.13), particularly the femur and tibia. The use of bone-scintigraphic agents (such as 99m-technetium- labelled disodium etidronate) has been particularly informative in Paget's disease. Affected bones take up the isotope avidly, which demonstrates both the extent of the bone lesions and the effects of treatment. In one study, 180 patients with Paget's disease underwent whole-body scintigraphy and 826 lesions were identified—one- third of the patients had only one lesion and only 10 patients had no symptoms. The increase in plasma alkaline phosphatase and urinary total hydroxyproline was proportional to scintigraphic involve ment and patients with skull involvement had the highest values. Apart from the number of sites involved, any distinction between monostotic and polyostotic disease appeared

to be artificial. Diagnosis The diagnosis of Paget’s disease is usually obvious. Bone biopsy is not recommended unless there is suspicion of another generalized bone diseases, such as osteomalacia. Paget’s disease may initially be confused with osteomalacia because of the high plasma alka line phosphatase level; rarely, an elevated plasma calcium should suggest additional hyperparathyroidism or malignant disease. In prostatic carcinoma with osteoblastic bone secondaries, the dense bones are not enlarged (in contrast to Paget’s disease) and the acid phosphatase level is considerably and disproportionately increased

20.1 Skeletal disorders—general approach and clinical conditions 4641 in relation to that of alkaline phosphatase. Of many other condi tions with similar radiological appearance, fibrous dysplasia (see next), in which the alkaline phosphatase may also be slightly in creased, may be difficult to distinguish; in the generalized form of fibrous dysplasia (polyostotic), the asymmetric bone lesions, skin pigmentation, and sexual precocity (in women) are character istic. Another very rare disorder usually mistaken for Paget’s dis ease is fibrogenesis imperfecta ossium (see next), where the bone trabeculae are thickened without bony enlargement and there are multiple abnormal fractures. Sarcoma The incidence of sarcoma in Paget’s disease has sometimes been overestimated in the past; it probably occurs in 1% or less of those with symptoms. Sarcoma should be considered in a patient known to have Paget’s disease if pain has developed for the first time, or has worsened, or if deformity has altered. Radiologically, the appearance of the pagetic bone alters, with evidence of bone destruction (Fig. 20.1.14); the tumours occur most often in the medulla. A review of 85 bone sarcomas associated with Paget’s dis ease confirmed the humerus as a high-risk site: rapidly worsening pain was the main symptom; lytic lesions were more common than Fig. 20.1.13 Paget’s disease of bone. Fissure fractures are seen in
the proximal tibia, predominantly on the convex border of the area
of grossly abnormal bone. (a) (b) Fig. 20.1.12 Paget’s disease of bone. (a) A resorbing front replacing normal bone in the skull vault, ‘osteoporosis circumscripta’; and (b) Paget’s disease of the pelvis demonstrating enlargement of the bones and disordered trabecular architecture in the left hemipelvis. Fig. 20.1.14 Paget’s disease of bone. Sarcomatous change in the skull is demonstrated on MRI scan. The presenting symptom was proptosis.

SECTION 20 Disorders of the skeleton 4642 sclerotic; periosteal reaction was uncommon; and radionuclide bisphosphonate scintigraphy usually showed areas of decreased uptake (contrasting with the underlying pagetic bone). Treatment Many patients with Paget’s disease require no treatment, but it may be required for symptoms, to suppress the activity of the disease and to prevent its further progress. Indications include bone pain, nerve compression, and the suppression of vascularity before elective orthopaedic surgery. Since medical treatment is now so effective, these indications may be widened especially in young people. Medical treatment Patients with painful Paget’s disease should first be treated with a simple analgesic. Where possible, it should be determined whether the pain is directly due to the bone disease or to associated arthritis. Specific treatment aimed at the pagetic bone should be considered for those who have pain due to bone disease despite analgesia or who have the complications of deformity, nerve compression, deafness, or, very rarely, heart failure. This treatment should also be considered in the young person with Paget’s disease to prevent further progression. There is no evidence that the rapid course of pagetic sarcoma is altered by any treatment. Historically many agents have been tried in Paget’s disease, including aspirin, fluoride, corticosteroids, and mithramycin, and calcitonin. Currently the overwhelming majority of symptomatic patients with Paget’s disease will be treated

with bisphosphonates. The bisphosphonates are a series of compounds with a P–C–P structure resistant to the naturally occurring phosphonates and pyrophosphatases. They are effective both orally and parenterally and reduce excessive bone turnover in Paget's disease. According to their dose, the bisphosphonates may take up to six months to produce their effect on symptoms, histology, and biochemistry. Many new bisphosphonates have now been developed based on side-chain sub stitutions in the basic P–C–P structure. The aminobisphosphonates are particularly effective. These new bisphosphonates are many times more potent than the earliest form of etidronate. They include pamidronate, tiludronate, alendronate, risedronate, ibandronate, and zoledronate. Oral alendronate and intravenous pamidronate are equally effective. They may produce almost complete and per manent suppression of Paget's disease. A single intravenous dose of zoledronate (5 mg) suppresses the overactivity of Paget's disease for up to six years, judged biochemically. The details of bisphosphonate dose regimes and expected responses are dealt with in larger re views. Short-term side effects of such compounds are rare, but there may be long term effects. One randomised trial reported that long- term intensive bisphosphonate therapy conferred no clinical benefit over symptomatic therapy but was associated with a nonsignificant increase in the risk of fractures and other serious adverse events. One important side effect, particularly of the powerful intravenous bisphosphonates, is osteonecrosis of the jaw. This risk is significantly greater in those with poor dental hygiene in whom bisphosphonates should either be avoided or used only with caution. Calcitonins are now rarely used for the treatment of Paget's disease and a potential risk to cancer has led to its withdrawal in Europe. Salmon calcitonin is the most effective commercially avail able form. Various dose regimens can be used, for which 100 IU given three times a week is average. Injected calcitonin may pro duce nausea and vomiting; if side effects are troublesome, it is best given in the evening together with an antiemetic. Indications for the use of bisphosphonates and calcitonins are different. Calcitonin is particularly useful to treat bone pain and osteolytic Paget's dis ease and for preoperative treatment. Some evidence suggests that it may halt the progression of deafness. Spinal cord compression is also alleviated. Thus, treatment of eight patients with paraparesis due to pagetic vertebrae with either calcitonin or bisphosphonate produced marked clinical improvement, at least comparable to the results of surgical decompression. Calcitonin can also be given by the nasal route (200 IU daily), which is more acceptable to the patient but less effective. Surgical treatment Fractures through pagetic bone require the usual surgical treatment, although union may be delayed. Where fracture occurs through a de formed bone, this deformity should be corrected. In addition, elective osteotomy with intramedullary nailing or Ilizarov correction may be considered for a severe long-bone deformity. Spinal cord compres sion not responding to medical treatment requires surgery. In patients with hip or spine pathology, diagnostic infiltration of structures such as the hip joints or lumbar nerve roots with local anaesthetic may be valuable. Rarely, hydrocephalus may require a ventriculojugular shunt. Whatever form of surgery is undertaken, it is important that the period of immobility is as short as possible, to avoid the develop ment of hypercalciuria and hypercalcaemia. Without good evidence, many patients receive zoledronate prior to surgery. Familial expansile osteolysis (MIM 174810) This rare condition has similarities to Paget's disease. Bone pain from early life is associated with progressive focal expansion in the long bones with pathological fractures. The pelvis and skull are not affected. Hearing loss begins from childhood. Inheritance is auto somal dominant, and the activating mutations have been identified in TNFRSF11A, the gene encoding RANK that plays a central role in osteoclast differentiation and activation. Juvenile Paget's disease (MIM 239000) This rare condition, which simulates Paget's disease, has autosomal recessive inheritance and is due to homozygous deletion in the TNFRSF11B gene, which encodes

osteoprotegerin, the decoy re ceptor for RANKL (the cognate ligand for RANK). The phenotype is variable but typically there is severe deformity from childhood asso ciated with high bone turnover and a considerable increase in plasma alkaline phosphatase. Treatment with recombinant osteoprotegerin has been shown to be effective in small studies. Parathyroids and bone disease Knowledge of the biochemistry of parathyroid hormone has in creased so rapidly that it now occupies a large and deserved part of any clinical description of parathyroid disorders (see Chapter 13.4). The close relationship between these endocrine glands and the skel eton has become less obvious with increasing recognition of the many other ways in which parathyroid disease presents. However, primary hyperparathyroidism was first identified because of its ef fects on bone and only later was it realized that it might more often present with renal stones, pancreatitis, and the signs and symptoms

20.1 Skeletal disorders—general approach and clinical conditions 4643 of hypercalcaemia, or that it might be a chance discovery as a result of multichannel biochemical analysis. The subject is discussed fur ther in Chapter 13.4. Molecular advances With the discovery of the calcium-sensing receptor and extensive work on the cause of the multiple endocrine neoplasia syndromes, our understanding of the rarer causes of abnormal plasma calcium levels has considerably increased. Thus, missense mutations of the CASR gene cause both familial benign hypocalciuric hypercalcaemia (MIM 145980) and neonatal hyperparathyroidism (MIM 239200), whereas gain-of-function mutations in this receptor can cause fa milial hypoparathyroidism (MIM 146200). Multiple endocrine neo plasia syndromes have traditionally been divided into two types: type 1 multiple endocrine neoplasia (MIM 131100) presents with hyper parathyroidism, pituitary adenomas, insulin- and gastrin-secreting tumours of the pancreas, and gastric hyperacidity (Zollinger–Ellison syndrome); type 2, also known as Sipple’s syndrome (MIM 171400), presents with hyperparathyroidism, medullary carcinoma of the thy roid, and phaeochromocytoma. The molecular elucidation of these differences has identified subgroups. In type 1 multiple endocrine neoplasia, the principal genetic abnormality involves mutations in the MEN1 gene together with loss of alleles on chromosome 11; in type 2 multiple endocrine neoplasia (both A and B subgroups), there are mutations in the RET proto-oncogene. Hypercalcaemia Of the known causes of hypercalcaemia in hospital inpatients, neoplasm is the most important (Table 20.1.11). It should always be considered and excluded clinically. The relative frequency of the causes of hypercalcaemia varies according to the population studied. In apparently healthy outpatients, primary hyperparathyr oidism is the most frequent cause. In those patients with primary hyperparathyroidism, with hypercalcaemia, hypophosphataemia, hyperphosphatasia, and radiological evidence of osteitis fibrosa, and without clinical evidence of neoplasm, little further investiga tion is needed. Since only a few patients with hyperparathyroidism have clinical bone disease, further differentiation from other causes of hypercalcaemia is usually necessary. In practice, this means the exclusion of neoplasm, sarcoidosis, thyrotoxicosis, vitamin D over dosage, treatment with lithium or thiazide diuretics, or the ‘milk al kali’ syndrome. The subject is addressed further in Chapter 13.4. Secondary (and tertiary) hyperparathyroidism Where hypocalcaemia is prolonged, as in renal glomerular failure or gluten-sensitive enteropathy, the parathyroid glands increase both their size and activity in an attempt to restore the plasma cal cium level to normal. This increases bone resorption and is a par ticular feature of renal glomerular osteodystrophy. Occasionally hypercalcaemia develops and persists in such patients, despite cor rection of the underlying disease. It has been proposed that one of the hyperplastic parathyroid glands becomes autonomous and, thus, the label ‘tertiary hyperparathyroidism’ has been given. Hypercalcaemia

may also occur after renal transplantation (see Chapter 21.7.3). Hypoparathyroidism (see also Chapter 13.4) Parathyroid insufficiency may occur after surgical removal of the parathyroids, in idiopathic hypoparathyroidism, and in a familial form of hypoparathyroidism that is often associated with mani festations of autoimmune disease, including systemic candidiasis, malabsorption, thyroid and adrenal failure, and pernicious an aemia. In such patients, the levels of immunoreactive PTH are undetectably low but the cAMP response to exogenous PTH is maintained. This distinguishes parathyroid insufficiency from pseudohypoparathyroidism, in which the biochemical features of hypoparathyroidism are associated with characteristic skeletal ab normalities, including short fourth and fifth metacarpals (Albright's hereditary osteodystrophy). Pseudohypoparathyroidism is inherited as an autosomal dominant trait. In the most common form, the cAMP response to exogenous PTH is defective and the circulating level of immunoreactive PTH is high. Patients who have the skeletal mani festations of pseudohypoparathyroidism but with normal biochem istry may be found in families with pseudohypoparathyroidism; to them the term 'pseudopseudohypoparathyroidism' is applied. Investigation has shown that the end-organ resistance to parathy roid hormone is due to loss-of-function mutations in GNAS1, which encodes the α-protein subunit of the Gs protein signalling system. So far as the skeleton is concerned, the most striking changes are found in pseudohypoparathyroidism. Clinical features include intel lectual disability, short stature, round face, short neck, and abnormal metacarpals (or metatarsals), of which the most common change is shortness of the third, fourth, and fifth. The bones may be exces sively dense, and widespread ectopic calcification and ossification Table 20.1.11 The causes of hypercalcaemia according to their frequency Cause Disorder Common Primary hyperparathyroidism Malignant disease Less common Drug induction Vitamin D toxicity Lithium Thiazide diuretics Endocrine Thyrotoxicosis Addison disease Granulomatous disease Sarcoidosis Immobilization Rare Drug induction Milk alkali syndrome Endocrine Familial hypocalciuric hypercalcaemia Granulomatous disease Tuberculosis Others Lymphoma Vitamin A overdosage Hypophosphatasia Renal failure Total parenteral nutrition Aluminium intoxication Jansen metaphyseal dysplasia Williams syndrome From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission.

 may also occur, in the basal ganglia and the subcutaneous tissues, respectively. Treatment of the hypocalcaemia is the same as for idio pathic hypoparathyroidism, with 1α-hydroxycholecalciferol. Osteogenesis imperfecta: The brittle bone syndrome This disorder, which has emerged from the status of an obscure oste opathy to a metabolic bone disease, provides remarkable lessons concerning the effects of mutations in the collagen genes. The cor relation between genotype and phenotype is by no means exact and leaves interesting problems. Osteogenesis imperfecta affects about 1 in 20 000 births; since the milder forms may never be diagnosed, this could be an underesti mate. It is a leading cause of lethal short-limbed dwarfism and crip pling skeletal dysplasia. There is no convincing evidence of different racial frequency. Many patients with osteogenesis imperfecta do not fit easily into the Sillence classification (Table 20.1.12) and in some cases hypermobility and features of the Ehlers–Danlos syndrome (see next) are dominant. Pathophysiology Osteogenesis imperfecta involves those tissues that contain the main fibrillar collagen, type 1. These include particularly bone and dentine, but also the sclerae, joints, tendons, heart valves, and skin. The pathology in bone varies with the type and severity of the dis ease and with age, previous fracture, and surgery. The skeletal ef fects of osteogenesis imperfecta are most severe in the lethal forms (type 2) and at

the region of the growth plate. There is faulty conver sion of apparently normal mineralized cartilage to defective bone matrix. The collagen fibres are thin but show the normal striated pattern. The endoplasmic reticulum of the osteoblasts is dilated by retained mutant collagen. The bone structure is completely disorgan ized and structurally useless. In type 3 osteogenesis imperfecta, which is less severe, there are variable amounts of woven immature bone, with disorganized trabeculae and an apparent excess of osteocytes as in other forms of the disorder. At the growth plate, there are multiple islands of cartilage in the epiphyses and metaphyses. Accounts of the bone pathology in type 4 are sparse. Defective mineralization is described in a rare form of osteogenesis imperfecta (type 6). In the so-called mild type 1 osteogenesis imperfecta, there is a re duction in the amount of bone (and hence in measured bone min eral density) and of defective bone formation at the cellular level, such that the osteoblasts each make approximately half as much bone collagen as normal. The result is an osteoporotic bone with an apparent excess of osteoblasts and osteocytes. This appearance of ‘hyperosteocytosis’ suggests (to some) an increase in bone turnover rate. The overall bone structure is otherwise normal, apart from oc casional woven bone. In affected dentine, the odontoblasts produce short, branched dentinal tubules, and fill in the dental pulp. In the ear, the auditory ossicles may be imperfect or fractured. Table 20.1.12 Clinical classification of osteogenesis imperfecta Type Main clinical features Inheritance Main biochemical abnormalitya Approximate relative frequency (% of all patients) 1 Mild bone fragility, blue sclerae, early onset deafness, near-normal height, normal teeth (IA); dentinogenesis imperfecta (IB) AD Nonfunctional allele for COL1A1 60% 2 Severe bone disease; multiple fractures; perinatal lethal; dark sclerae; broad long bones (2A); ribs show some modelling (2B); ribs and long bones thin with many fractures (2C) AD AR Most frequent single base mutations in COL1A1, COL1A2 replacing glycine 10% 3 Progressive deforming disorder; scoliosis; very reduced height; sclerae often white AD, rarely AR Similar to type2; Very rare absence of α2(1) chain, leading to α1(1) trimers 20% 4 Moderate bone disease and deformity; sclerae often white AD Often COL1A2 mutations 10%b 5 OI with hyperplastic callus AD IFITM5 mutation Rare 6 OI with excess osteoid AR SERPINF1 mutation Rare 7 Rhizomelic OI severe and perinatal lethal AR CRTAP mutation Very rare 8 Severe and perinatal lethal AR LEPRE1 mutation Very rare 9 Moderately severe AR PPIB mutation Very rare 10 Severe deforming disease AR SERPINH1 mutation Very rare 11 Mild to severe forms AR FKBP10 mutation Very rare 12 Clinically similar to type 4 AR Osterix (SF7) mutation Extremely rare 13 Generalized deformity AR BMP1 mutation Extremely rare 14 Variable severity Normal teeth, sclerae AR TMEM38B mutation Very rare 15 Moderate to severe, deforming disease AR WNT1 mutation Very rare AD, autosomal dominant; AR, autosomal recessive. a For details of specific mutations, see text. b The frequency of type 4 osteogenesis imperfecta is difficult to establish because of its heterogeneity. From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission.

 The reduction in collagen is repeated in nonskeletal tissues. Thus, the sclerae are thin (leading to their blueness since the pigmented coat of the choroid becomes visible), the tendons are gracile and weak, the thin heart valves may become incompetent, and the aortic root dilated. Clinical features Type 1 osteogenesis imperfecta is the most frequent and least ser ious form and it accounts for 60% of all patients with the disorder. Fractures sometimes occur in the perinatal period but equally may be delayed even until the early menopause. After the menopause, the overall fracture rate has been recorded at seven times more than in the normal population and the vertebral bone mineral content in adults with type 1 osteogenesis imperfecta is about 70% of normal. Childhood fractures in type 1

osteogenesis imperfecta may be numerous but rarely lead to deformity unless treated inappropri ately. Any type of fracture can occur but they become less frequent with age. Overall, fractures are more frequent in the lower limbs. Significant scoliosis is rare. The skull shows interesting changes; in addition to multiple Wormian bones (Fig. 20.1.15) (which can occur in other disorders, such as pycnodysostosis, cleidocranial dysplasia, Menkes syndrome, Prader–Willi syndrome, progeria, and, rarely, in normal subjects), the vault may overhang the base, leading to basilar impression requiring surgical correction. Clinical dentinogenesis imperfecta occurs in only some patients; the appearance varies widely and affects some teeth more than others; the teeth are discoloured and the enamel (which is normal) fractures easily from the dentine, leading to rapid erosion of both the first and second dentition. Blueness of the sclerae is a particularly important physical sign of osteogenesis imperfecta. The cause of the early (juvenile) arcus is unknown: limited investigation excludes hypercholesterolaemia. The cardiac manifestations of osteogenesis imperfecta are also important, not only because of their effects but because tissue fragility makes surgery dangerous. Aortic incom petence, aortic root widening, and mitral valve prolapse all occur. Patients with osteogenesis imperfecta often show hypermobility of joints, with resultant flat feet, hyperextensible large joints, and occa sionally dislocation. Type 2 osteogenesis imperfecta is nearly always lethal, but the severity does differ: some children may be born dismembered, whereas others may (rarely) survive the perinatal period to later merge into the type 3 form. Not all infants with multiple fractures at birth succumb immediately. It is possible to give a prognosis from the extent of ossification of the skull, the shape of the long bones and ribs, and the number of fractures. In the most frequent form of lethal osteogenesis imperfecta (2A), the infant is short with dis proportionately short and deformed limbs, the skull is deformed and soft, and the sclerae are often deep grey blue. Whole-body radiographs, which distinguish osteogenesis imperfecta from other forms of lethal short-limbed dwarfism, show grossly defective min eralization of the skull, short broad limbs with multiple fractures, and broad ribs with innumerable fractures (Fig. 20.1.16). In type 2B, the ribs have some structure; in 2C, the long bones are narrow and beaded at the site of fractures and show some evidence of mod elling. Perinatal death results from the mechanical uselessness of the skeleton, which leads to respiratory failure or intracranial haemorrhage. Type 3 osteogenesis imperfecta causes most clinical difficulty, since the disability is severe and progressive. During the early years of life, progressive deformity affects the skull, the long bones, and the spine, chest, and pelvis; the deformity is associated with frac tures but can probably occur without them. The radiological ap pearance of the bones changes rapidly with age. The face appears triangular, with a large vault, prominent eyes, and small jaw. The sclerae may be blue in infancy but take on a normal colour in child hood. Eventual disability and deformity is considerable. Such pa tients rarely walk, even after multiple operations, and have a very short stature (four to six standard deviations below the mean). The changes in the long bones are often bizarre, with long, thin diaph yses and comparatively wide metaphyses. Cartilaginous islands often develop at the end of the long bones in the epiphyses and the metaphyses, spreading into the diaphysis, giving the appearance of Fig. 20.1.15 Osteogenesis imperfecta. Innumerable centres of ossification are found in the vault of the skull (Wormian bones) in an infant with severe deforming (type 3) osteogenesis imperfecta. Wormian bones are usually most obvious in the occipital region. Fig. 20.1.16 Whole-body perinatal radiograph of lethal (type 2) osteogenesis imperfecta. The vault of the skull is not calcified, and the ribs and long bones show multiple fractures. There was no family history.

 ‘popcorn’ bone. Early death may occur from respiratory infections superimposed on the restrictive reduction in vital capacity associ ated with severe

scoliosis (Fig. 20.1.17). Progressive deformity re quires specialized orthopaedic care. Type 4 osteogenesis imperfecta is clinically intermediate between type 1 and type 3 and is inherited as a dominant trait. The sclerae are of normal colour after infancy. Overall stature is reduced, and disability is variable. The rare complication of hyperplastic callus occurs most often in the type 5 variant of OI which is otherwise similar in severity (Fig. 20.1.18). This begins with a swollen, painful, and vascular swelling, most often over the long bones, an increase in plasma alkaline phosphatase, and, sometimes, a systemic illness. Recent investigations of osteogenesis imperfecta-affected families with hyperplastic callus have failed to find collagen mutations in affected children. Some classify this form as type 5 osteogenesis imperfecta (Table 20.1.12). Numerous other rare forms of brittle bone disease have been recently characterized (Table 20.1.12). These include: type 6 in which there is excess osteoid and indeterminate inheritance; type 7, a recessive rhizomelic form with coxa vara, minimally blue sclerae, congenital fractures, and major ambulatory problems in adulthood; and type 8, a severe/lethal autosomal recessive variant with white sclerae, round face, and barrel chest. Distinguishing mutations have been found for at least 15 types of OI, most of which are in the type 1 collagen structural genes or others involved in the processing of collagen. For example, in type 7 there are mu tations in CRTAP, which encodes cartilage-associated protein that is part of a complex that includes cyclophilin B and P3H1, which encodes prolyl-3-hydroxylase 1 that is required for the prolyl-3- hydroxylation of collagen. Mutations in this gene can also cause the recessive lethal type 2B OI, accounting for 3% of all lethal cases. Finally, type 8 is caused by mutations in P3H1 that leads to ab normal posttranslational modification of collagen. Diagnosis In the perinatal period, the concern is with alternative causes of lethal, short-limbed dwarfism. These include severe hypophosphatasia, achondrogenesis, thanatophoric dwarfism, and the asphyxiating thoracic dystrophies. A perinatal whole-body radiograph is essential. In the first few years of life, nonaccidental injury, ‘battered baby syndrome’, is the main differential diagnosis. This is suggested by multiple fractures at different sites and of different ages, especially if associated with clinical signs of neglect. Some fractures, such as metaphyseal ‘corner’ fractures and posterior rib fractures, are more often seen in nonaccidental injury, but any type of fracture can occur in osteogenesis imperfecta. The distinction between osteogenesis imperfecta and nonaccidental injury is legally important and can be difficult. Idiopathic juvenile osteoporosis needs to be distinguished during late childhood and adolescence. This begins during growth, with fractures of the long bones, reduction in growth rate (due to verte bral collapse), and metaphyseal compression fractures. In adult life, mild osteogenesis imperfecta may go unrecognized. In the recessively inherited osteoporosis pseudoglioma syndrome (MIM 259770), there is severe osteoporosis leading to fracture and near blindness from infancy. This very rare disease used to be clas sified as a form of osteogenesis imperfecta. It is now known to result from mutations in the LRP5 gene (Table 20.1.1). Biochemistry It is impossible to generalize about the clinical effect of a collagen gene mutation, but some patterns are emerging. In type 1 osteogen esis imperfecta, there appears to be a null allele for collagen type 1, so that only 50% of collagen is produced but this is of normal composition. Lethal osteogenesis imperfecta (type 2) results most commonly from single base changes in COL1A1 or COL1A2. Such changes convert a glycine codon to one for another amino acid with a side chain. The effect on the triple helix of incorporating such a mutant chain appears to be most marked when the substitution oc curs near the C-terminal end of the chain (the helix winds up from this end), when the substituting amino acid is large, and when it oc curs in the α-1 rather than the α-2 chain. Such mutations delay helix formation and render collagen mechanically unsound by causing overhydroxylation and overmodification of the lysine residues. Such Fig. 20.1.17 Severe scoliosis in type 3 osteogenesis imperfecta. Fig. 20.1.18 The radiological appearance of

hyperplastic callus in osteogenesis imperfecta (type 5). The densely mineralized mass is recent. The apparently thickened femoral shaft is probably due to incorporation of previous episodes of excess callus formation.

20.1 Skeletal disorders—general approach and clinical conditions 4647 abnormalities are common in type 2 osteogenesis imperfecta and less well defined in type 3, which may rarely result from a failure to synthesize α-2 chains. Type 4 osteogenesis imperfecta is more often due to changes in the α-2 chain. However, this is probably an over simplification of the molecular pathology. In the more severe forms of osteogenesis imperfecta clusters of mutations have been defined in regions of the collagen molecule interacting with other compo nents of the organic bone matrix, such as integrins and proteogly cans. Mutations in COL1A1 or COL1A2 can be found in up to 90% of individuals with osteogenesis imperfecta. In children with brittle bones who do not have a demonstrable mutation in type 1 collagen alternative mutant loci may be demonstrable by DNA sequencing, particularly in those with more severe forms of the disease, thereby allowing more definitive diagnosis to be achieved in many cases. This information can be invaluable for the provision of accurate gen etic advice and family planning. Genetic advice Parents who have already had an infant with osteogenesis imperfecta need accurate advice about further pregnancies. This can be diffi cult, because the facts are not clear. Where the mutant gene is dom inant (type 1 and 4) and where one parent is affected, the likelihood of affected children is 50%. Where appropriate the mutation status of the fetus in such circumstances can be determined by sequence ana lysis of the type 1 collagen genes COL1A1 and COL1A2. Difficulties arise where neither parent is clinically affected and with the lethal or progressively deforming varieties of the brittle bone syndrome. It may be impossible to give a statistically accurate prediction of the likelihood of another affected child, particularly since the strict ap plication of mendelian principles may be inappropriate because of the possibility of germline and somatic cell mosaicism. However, there are some guidelines. Where one offspring of clinically un affected parents has a form of osteogenesis imperfecta that fits into type 1 or type 4, this is likely to be a new dominant mutation (50% of whose offspring will be affected) and the risk of a further affected sibling is little more than in the general population. Fortunately, it is now possible to infer the likely mode of inheritance of the more severe/lethal cases from determining the mutant locus accurately in the affected offspring. Thus, severe osteogenesis imperfecta (type 8 OI) caused by mutations in LEPRE1 is recessively inherited (with a recurrence risk of 1 in 4), while lethal disease (type 2A OI) with a COL1A1 mutation is most likely to be a new dominant (with a cor respondingly low risk of recurrence although germline mosaicism means that this risk cannot be excluded entirely). It is now clear that some (c.3%) lethal forms of the disease (type 2B) are recessively in herited due to CRTAP mutations (see earlier in this chapter). These have some phenotypic differences from the more common type 2A (caused by collagen type 1 mutations), including relatively small head circumference, a degree of proptosis due to shallow orbits and relatively normal coloured sclerae. Such clinical features may help to raise the suspicion of an unusual phenotype and prompt a detailed genotypic analysis. Prenatal diagnosis This may be done by analysis of fetal DNA from a chorionic villus biopsy in the first trimester and by ultrasound examination and appropriate radiographs from the second trimester. The appro priateness of such an investigation depends on the information previously available. In a dominantly inherited form of osteogenesis imperfecta where the mutation is already known from other affected family members, analysis of chorionic villus DNA is the most direct approach. Diagnosis by ultrasound examination is possible only in the more severe forms of osteogenesis imperfecta (e.g. types 2 and 3). Since the severe forms of

osteogenesis imperfecta are typically sporadic and therefore unsuspected, it is important to be able to detect them early and rapidly by routine scanning. Ultrasonographic features suggestive of osteogenesis imperfecta are shortness and deformity of the limbs, an abnormal skull shape with lack of mineralization, which makes the intracranial structures abnormally visible, and de formity of the ribs leading to a ‘champagne cork’ appearance on the anteroposterior projection. Confirmation of the diagnosis may sub sequently be sought by DNA analysis. Prognosis and management The presence of fractures in utero or the perinatal period is a broad but unreliable indicator of the prognosis. The immediate prognosis may already be answered by perinatal death, so that it remains to deal with the prognosis of survivors. Not all born with multiple frac tures succumb immediately and radiographic appearances can give a good guide to outcome. Those with severe disease who survive (typically type 3 OI) re quire lifelong specialist care. Such individuals are of normal intel ligence and prolonged admission to hospital, either for repeated surgery or for investigation, should not necessarily take prece dence over education. Intramedullary rodding and osteoclasis to correct deformity and improve mobility should be very selective since the bones are often so abnormal that there is no advantage from such procedures. An organized programme of rehabilita tion is important. Analysis of life expectancy and cause of death in osteogenesis imperfecta shows that survival is normal in type 1 osteogenesis imperfecta and near normal in type 4. It is those with type 3 who have the shortest lifespan and the most disability, of which basilar impression with neurological complications is a significant problem, particularly in those with multiple Wormian bones. The use of cyclic intravenous pamidronate is a considerable advance to alleviate symptoms, increase bone density, and reduce fracture rate particularly in severe osteogenesis imperfecta. The in dications for the use of pamidronate in osteogenesis imperfecta and the reasons why it is effective in a disorder that is primarily due to osteoblast failure have yet to be agreed. Observational studies of oral bisphosphonates in milder forms of osteogenesis imperfecta also show beneficial effects on bone density. Animal studies targeting lrp5 and sclerostin mediated anabolic bone pathways have shown promise in murine models of osteogenesis imperfecta but these await translation into humans. Marfan syndrome (MIM 154700) (see also Chapter 20.2) For many years, it was thought that the basic defect in Marfan syn drome involved collagen, but this was excluded by the demonstra tion of pathogenic mutations in FBN1, encoding fibrillin 1, one of the major components of the 10 nm microfibrils found in elastic tissues. However, any suggestion that Marfan syndrome merely represents a

 simple structural failure of these tissues due to defective fibrillin has subsequently proved too simplistic. Recent research has implicated deranged TGFβ signalling with resultant abnormal elastic fibre gen esis and, to bring the wheel full circle, excessive rather than reduced collagen in the affected tissues. Pathophysiology Marfan syndrome is most often caused by mutations in the epidermal growth factor-like regions of FBN1. Fibrillin is the major constituent of the microfibrillar system and of the suspensory ligament of the lens, and it is also associated with elastin-containing tissues such as the aorta. This explains the association between dislocation of the lens and dissection of the aorta. The aorta dilates at its proximal part at the sinus of Valsalva and returns to normal diameter below the innominate artery, unless a dissection is present. The cusps of the aortic valve do not close efficiently. Dissection is most often above the aortic valves in the area of greatest dilatation. The dissection may progress forwards or backwards. Retrograde dissection may tear the attachment of the coronary arteries and rupture into the pericardial sac. Histopathology shows a reduction in elastic fibres, which are swollen and fragmented. The valve cusps are usually diaphanous and redundant. In the eye, the suspensory

ligament of the lens is disor ganized. Other aspects of the condition have always been more dif ficult to explain; the tall stature, dysmorphic facial features, reduced muscle mass, and abnormalities of the lung architecture mimicking emphysema are more suggestive of an abnormality of growth and development, not easily attributable to fibrillin at first glance. Most of the FBN1 mutations described in the Marfan syndrome are consistent with qualitative or quantitative defects of fibrillin; many of the observed clinical abnormalities, such as aortic aneurysm and lens dislocation, can also be understood on this basis. However, it is increasingly apparent that interactions between fibrillin and TGFβ also play a key role in several clinical features, such as the growth dis turbance, vascular fragility, and other developmental abnormalities found in the Marfan syndrome and related disorders. TGFβ is com monly sequestered in an inactive form bound to latent TGFβ binding protein in the extracellular matrix of many tissues, including those containing fibrillin. The loss of fibrillin microfibrils in Marfan syn drome causes an increase in the amount of active TGFβ present in these tissues; this can lead to the generation of abnormal matrix in the elastic tissues of the aorta, abnormal septation of the developing lung alveoli, and abnormal muscle mass. In the fbn1 knockout mouse model of Marfan syndrome, these phenotypic effects can be reversed by using neutralizing antibodies to TGFβ. The abnormally increased TGFβ signalling through its TGFβ receptor can also be blocked by angiotensin II type 1 receptor blockers, such as losartan. There are now encouraging results from preliminary clinical trials to suggest that these drugs may be valuable in humans. Clinical features Marfan syndrome is dominantly inherited. Its main effects are on the skeleton, cardiovascular, and ocular systems. There is consider able phenotypic variation. In the typical patient with Marfan syn drome, overall height is increased (relative to unaffected siblings or a matched population) and the limbs are long relative to the trunk (so that the crown to pubis measurement is markedly less than pubis to heel). Long, thin fingers (arachnodactyly) are common. Together with hypermobility, this disproportion forms the basis of clinical signs of variable utility. However, not all patients with Marfan syn drome are long and thin. The skeletal phenotype differs from one family to another and also differs within families. Asymmetric an terior chest deformity is associated with either depression or prom inence of the sternum. Scoliosis is common, may be severe, and worsens during preadolescent growth as in the idiopathic form (Fig. 20.1.19). The hard palate is often narrow and high-arched (gothic), leading to dental crowding. Dislocation of the lens is the main ocular feature of Marfan syn drome (Fig. 20.1.20). Typically, this occurs upwards or sideways Fig. 20.1.19 Some of the characteristic major musculoskeletal criteria for Marfan syndrome. (a) Positive wrist and thumb signs; (b) MRI showing severe pectus excavatum; and (c) severe localized thoracolumbar scoliosis.

 (somewhat in contrast to the downward dislocation often seen in homocystinuria) and it may be present at birth or occur later, but it rarely becomes apparent for the first time after 10 years of age. Dislocation causes the unsupported iris to wobble on movement (iridodonesis). Other important ocular features are myopia and ret inal detachment. The axial length of the globe is increased, and the cornea tends to be flattened (keratoconia). The most severe complication of Marfan syndrome is dilatation of the ascending aorta leading to aortic incompetence and dissection. Progressive widening of the aorta can be readily measured by serial echocardiography. Less serious manifestations of Marfan syndrome include cutaneous striae, hernias, spontaneous pneumothorax, and dural ectasia. The mean life expectancy in those with Marfan syn drome is significantly reduced, predominantly due to cardiovascular catastrophe. However, elective cardiac surgery has considerably im proved the outlook for those at greatest risk. It is difficult to estimate the overall reduction in life expectancy

given that milder variants of the condition are now recognized and that previous estimates sug gesting a 50% reduction were based on patients with particularly se vere and largely untreated disease. Diagnosis In those with equivocal clinical features and no family history, the diagnosis of Marfan syndrome can still be difficult. Formal assess ment of the musculoskeletal system (Box 20.1.2) should be under taken to identify systematic features of the disease (sometimes including full length radiographs of the spine to detect less severe forms of scoliosis and pelvic radiographs to identify acetabular pro trusion). Slit lamp examination of the eye is essential to exclude minor degrees of lens subluxation (formal optometry is in practice rarely required); MRI of the lumbar spine and chest is often valu able to detect dural ectasia and to obtain accurate measurements of the aortic root; and two-dimensional echocardiography should be undertaken routinely in those suspected of having Marfan syn drome and forms the basis of routine cardiology follow up (with in creased frequency during pregnancy). The requirements for the diagnosis of Marfan syndrome are indicated in Box 20.1.1 and 20.1.2. Major involvement of at least two organ systems (cardio vascular, eyes or musculoskeletal) is required for diagnosis unless there is an unequivocally affected first-degree relative. The original 1996 Ghent criteria have been extensively revised to place additional emphasis on cardiac and ocular manifestations in the Brussels criteria (Loeys et al. 2010). Homocystinuria (see next), which has a recessive mode of inher itance, should be excluded. Other important alternative diagnoses include congenital contractural arachnodactyly (Beal syndrome MIM 121050), familial tall stature, isolated mitral valve prolapse, familial or isolated annuloaortic ectasia, Shprintzen-Goldberg Fig. 20.1.20 Marfan syndrome showing dislocation of the ocular lens (slit-lamp appearance). The redundant strands of the suspensory ligament are shown (arrows). Box 20.1.2 Scoring of systemic features Wrist and thumb sign 3 Wrist or thumb sign alone 1 Pectus carinatum deformity 2 Pectus excavatum or chest asymmetry 1 Hindfoot deformity 2 Flat thin foot alone 1 Pneumothorax 2 Dural ectasia 2 Protrusio acetabuli 2 Reduced upper segment/lower body segment ratio and increased 1 arm/height ratio (in absence of severe scoliosis) Scoliosis or thoracolumbar kyphosis 1 Reduced elbow extension 1 Facial features (dolichocephaly, enophthalmos, downward slanting 1 palpebral fissures, malar hypoplasia, retrognathia): (3/5) Skin striae 1 Myopia >3 diopters 1 Mitral valve prolapse (all types) 1 Maximum total: 20 points; score ≥7 indicates systemic involvement From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission. Box 20.1.1 Brussels revision of Ghent nosology (2010) In the absence of family history:* (1) Ao (Z≥2) + EL = MFS (2) Ao (Z≥2) + FBN1 = MFS (3) Ao (Z≥2) + Syst (≥7pts) = MFS (4) EL + FBN1 with known Ao = MFS EL ± Syst without Ao ± FBN1 not known with Ao = ELS Ao (Z>1.5 and <2) + Syst without EL = BASS Ao (Z<1.5) and MVP + Syst without EL = MVPS In the presence of family history:* (5) EL + FH of MFS (as defined above) = MFS (6) Syst (≥7pts) + FH of MFS (as defined above) = MFS (7) Ao (Z≥2) + FH of MFS (as defined above) = MFS Ao, aortic diameter at sinuses of Valsalva above indicated Z-score or aortic dissestion; BASS, borderline aortc systemic syndrome; EL, ectopia lentis; ELS, ectopic lentis syndrome; FBN1, fibrillin-1mutation; FBN1 not known with Ao; FBN1 mutation identified in an individual with aortic aneurysm; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; Syst, systemic score; Z, Z-score.

- Caveat: without discriminating features of Shprintzen-Goldberg syndrome, Loeys–Dietz syndrome, or vascular (type 4) Ehlers–Danlos syndrome. From Smith R, Wordsworth P (2016). Oxford Textbook of Clinical and Biochemical Disorders of the Skeleton, 2nd edn. Oxford: Oxford University Press, with permission.

SECTION 20 Disorders of the skeleton 4650 syndrome (MIM 182212), Weill-Marchesani syndrome (MIM 608328), and kyphoscoliotic form of Ehlers–Danlos syndrome (type 6 – MIM 225400). Contractures can occur in Marfan syndrome but are of a late onset. In congenital contractural arachnodactyly, which is inherited as an autosomal dominant trait, contractures involving the hands, feet, and larger joints are present from birth and tend to improve. Abnormal ears are described and developmental abnormalities, such as duodenal atresia or structural cardiac defects, are more common than in Marfan syndrome. This disorder results from mutations in another fibrillin gene, FBN2. Of particular importance is a group of disorders related to Marfan syndrome in which there may also be demonstrable FBN1 muta tions, but which do not necessarily carry the same adverse cardiac prognosis. These include the following in which there is major in volvement of one organ system but not others—isolated ectopia lentis, isolated Marfan-like body habitus, and benign ‘so-called’ fa milial thoracic aneurysm. In contrast, some individuals exhibit an array of minor signs often associated with Marfan syndrome but have the MASS phenotype (mitral valve prolapse, aorta in the upper end of the normal range, limited skeletal signs, and striae). It is im portant to recognize individuals with the MASS phenotype since they probably have an altogether milder condition that can usually be distinguished from Marfan syndrome and does not carry the same adverse consequences for health or insurance. Finally, it has recently been recognized that certain individuals, previously thought to have atypical forms of Marfan syndrome, have a quite separate condition now known as Loeys–Dietz syndrome (MIM 609192). This is characterized clinically by aortic aneur ysms, generalized arterial tortuosity, hypertelorism, cleft palate, and bifid uvula; it is caused by mutations in the TGFβ receptor genes (TGFBR1 or TGFBR2), which alter TGFβ signalling, with implica tions for extracellular matrix biology, including disarray of elastic fibres and excessive collagen. Treatment There is no specific treatment yet for the underlying defect, but many of the clinical manifestations require attention. Scoliosis may be progressive and severe, particularly in adolescence. Bracing is largely ineffective and operative stabilization may be necessary. Excessive height in girls may be prevented by giving oestrogen to gether with progestogen in the prepubertal years. Marked sternal deformity may need correction for cosmetic or cardiopulmonary reasons, but opinions on the value of surgery vary widely. The po tential conflict between anterior chest wall surgery undertaken for largely cosmetic reasons and the subsequent need for cardiac sur gery for aortic disease is one clear example. In the eyes, it is rarely necessary to remove dislocated lenses unless they prolapse into the anterior chamber, but myopia should be corrected. The main decisions concern the management of the cardiovascular prob lems: when and if to operate on the dilated ascending aorta or to replace incompetent valves, and whether aortic dilatation can be prevented by reducing the intermittent force on its walls due to left ventricular systole. β-blockers, such as atenolol, reduce the rate of aortic dilatation to some extent although the results in individual cases are highly variable. Angiotensin receptor blockers, such as losartan, appear to have similar efficacy but there are no head-to- head trials or studies to evaluate whether these drugs might have additive effects. As regards surgery on the aorta, it is clear that progressive aortic widening (measured regularly by echocardi ography), together with progressive aortic incompetence and left ventricular strain, provides strong indications for surgery of the proximal aorta. There is substantial debate about the timing and nature of the surgery that should be undertaken and whether the aortic valve can be preserved in those undergoing surgery to pro tect the aortic arch. However, it is evident that the risk of dissection or rupture increases dramatically when the maximum proximal aortic root diameter rises to 5.0 cm or more; in these circumstances, prophylactic surgery is usually justified. Mitral valve replacement may also be necessary, and it is more commonly required in chil dren then aortic surgery. Genetic advice

Genetic advice is based on clinical observations and the know ledge that inheritance is of the autosomal dominant pattern. Up to 90% of those with classic Marfan syndrome have demonstrable FBN1 mutations. Numerous mutations in the fibrillin genes have now been described but the correlations between genotype and phenotype are not clear cut. Cysteine mutations in the epidermal growth factor-like domains correlate with ocular lens involvement and only some FBN1 mutations are associated with progressive aortic dilatation (which is of some prognostic value). Mutations occurring between exons 20 and 28 of FBN1 tend to be associ ated with more severe disease. However, 30% of cases arise from new dominant mutations and the possibility of parental mosai cism should be remembered. Where there is a suspicion of Loeys– Dietz syndrome or an overlapping phenotype, sequential analysis of FBN1, TGFBR2, and TGFBR1 and other genes associated with thoracic aorta aneurysms (COL3A1, ACTA2, MYH11, SMAD3, SMAD4, TGFB2) is justified. Ehlers–Danlos syndrome (see also Chapter 20.2) Ehlers–Danlos syndrome (EDS) includes those conditions with the common clinical features of abnormal velvety hyperelastic skin that heal poorly, hyperextensible joints, and lax ligaments. In some types there are additional specific features, including vascular rup ture in type 4 (vascular) EDS, associated with various mutations in collagen type 3 (MIM 130050). This variant carries the most ad verse prognosis with premature death from rupture of hollow vis cera, including blood vessels commonly occurring before midlife. Pregnancy is particularly dangerous for these individuals. It is im portant to establish the precise type of EDS affecting the patient be cause the prognosis for many individuals with the condition is good; patients with the vascular form of the disease are uncommon and can be distinguished relatively easily from others on clinical grounds or, where necessary, by DNA analysis. In the current (Villefranche) EDS classification, the skeleton is particularly affected in types 6 and 7 EDS (Table 20.1.13). In type 6 EDS (oculo-scoliotic type), the first disorder in which an inborn error of collagen metabolism was identified, the clinical fea tures are due to lysyl hydroxylase deficiency (MIM 225400). Since hy droxylation of peptide-bound lysine is an essential posttranslational step in collagen synthesis and a necessary precursor to crosslink

 formation, this defect weakens collagen structure. The main clinical features are severe scoliosis, microcornea, and ocular fragility. In type 7 EDS (arthrochalasia), there is excessive mobility, peri natal joint dislocations (especially of the hips), and short stature (MIM 130060). There is persistence in the tissues of collagen type 1 molecules with a retained amino-terminal propeptide that leads to defective fibrillogenesis. Classic EDS (types 1 and 2) is associated with cigarette paper scars, pronounced joint hypermobility, redundant skin folds, and pronounced hyperelasticity of the skin (MIM 130000). Most cases result from dominant mutations in the collagen type 5 genes, COL5A1 and COL5A2, although a small minority reflect mutations at collagen type 1 loci. Collagen type 5 is a quantitatively minor component of collagen fibrils in skin compared to collagen type 1 and it has a particular influence on regulating collagen fibre size. Up to one-quarter of patients with the classic and hypermobility forms of the disease have some evidence of dilatation of the prox imal aorta although dissection or aortic valve dysfunction is uncommon, in contrast to Marfan syndrome. Where there is evi dence of dilatation, periodic monitoring by echocardiography is appropriate. Type 3 EDS (benign joint hypermobility type—MIM 130020) is the most commonly seen EDS variant but to what extent it truly reflects a disease state or is merely a normal variant is not al ways clear. Some patients with this condition report chronic joint pains, widespread musculoskeletal symptoms, and other somatic symptoms of the sort often described in fibromyalgia. However, whether these symptoms are truly caused by joint laxity is not entirely

clear. Combinations of cognitive therapy and physical treatments particularly aimed at improving proprioception and aerobic fitness may be helpful. One recently described variant of Ehlers–Danlos syndrome de serves mention. Recessively inherited deficiency of tenascin-X, an essential regulator of the deposition of collagen in the extra cellular matrix, causes a syndrome of joint hypermobility and hyperelasticity of the skin but without the tendency to form atro phic scars (MIM 606408). It can be detected by the absence of tenascin-X from the serum. Given the proximity of the TNXB locus to CYP21A2, the steroid 21-hydroxylase locus in the major histo compatibility complex, it is unsurprising that 10% of the deletions underlying 21-hydroxylase deficiency are associated additionally with tenascin-X deficiency. Homocystinuria (see also Chapter 12.2) Homocystinuria (MIM 236200) is phenotypically similar to Marfan syndrome but with a different cause and additional important com plications. It is autosomal recessively inherited due to a deficiency of cystathionine β-synthase. The amount of residual cystathionine synthase activity varies from 0% to 10% in patients and, in obli gate heterozygotes, it is less than 50% of normal. It is generally rare (<1:350 000) but has a higher prevalence in Ireland (1:65 000) and can be screened at birth by measuring blood methionine levels. Pathophysiology Homocysteine lies at the crossroads of two metabolic pathways and is converted to cystathionine by the addition of serine. This reaction is controlled by cystathionine β-synthase. The alternative fate of homocysteine is methylation to methionine. Cystathionine β-synthase activity is controlled by pyridoxine, but not all pa tients with cystathionine-deficient homocystinuria are pyridoxine Table 20.1.13 Classification and main features of the different Ehlers–Danlos syndromes (note that only types 6 and 7 have significant effects on the skeleton) Villefranche classification (1997) Main features Inheritance Collagen or other gene affected Biochemistry Former classifications Classic Hyperextensible skin; hypermobile joints; wide atrophic scars AD 5 Haploinsufficiency of collagen type V usually Types 1 & 2, gravis and mitis Hypermobility Marked hypermobility of joints Variable Usually known. Sometimes 1 Not known Type 3, joint hypermobility Vascular type Rupture of middle-sized arteries, also bowel and uterus; premature ageing in some AD 3 Abnormal collagen type 3 synthesis, secretion, or structure Type 4, arterial (Sack Barabas) Oculoscoliotic type Scoliosis; fragile eyes with keratoconus AR Lysyl hydroxylase deficiency Type 6, oculoscoliotic Arthrochalasis Congenital dislocation of the hips; short stature AD 1 Exon 6 deletion; removes cleavage site for N-terminal peptide from collagen type I Type 7A and B Dermatosparaxis Severe fragility; osteoporosis AR 1 Procollagen type 1 N-protease deficiency Type 7C Occipital horn syndromea Soft skin; bladder diverticula; occipital horns XLR ATP7A Defective Cu2+ transporting ATPase; secondary defect of Cu-dependent lysyl oxidase Type 9, EDS with occipital horns Fibronectin defecta Similar to type 2 EDS AR Fibronectin defect Type 10 Tenascin-X deficiencya Similar to EDS 2 but without atrophic scars AR TNXB Absence of tenascin-X AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome; XLR, X-linked recessive. a These types are not formally included in the 1997 classification.

SECTION 20 Disorders of the skeleton 4652 sensitive. In homocystinuria, there is an increase in both homocyst eine and homocystine, which accumulate proximal to the metabolic block. Cystathionine, normally present in the brain, is undetectable and cysteine (normally made from methionine) becomes an essen tial amino acid. The pathological findings include fraying and disruption of the zonular fibres of the ocular lens, defective bone formation, and multiple central nervous system infarcts. It is not known how the biochemical changes lead to the clinical features. The increased thrombotic tendency is not fully explained by changes in platelet function, cellular endothelium, or soluble factors, although abnor malities have been described in all of them. The neurological abnor malities and intellectual disabilities have not been proven to be due to the

biochemical consequences of cystathionine β-synthase defi ciency or to repeated vascular thromboses. Homocyst(e)ine may increase the solubility of collagen and interfere with its synthesis; for some, this explains the dislocation of the lens due to failure of the ciliary zonule. Since it is now known that this structure is com posed largely of fibrillin, a further explanation is required. There is current interest in the possibility that young adults with premature vascular disease may be heterozygotes for a mutant cystathionine synthase gene. Elevated plasma homocysteine levels are a risk factor for coronary heart disease. Clinical features The clinical features of cystathionine β-synthase deficiency de velop some time after birth and involve four systems; ocular, skel etal, central nervous, and vascular. The main ocular manifestation is downward dislocation of the lens. Myopia, glaucoma, retinal de generation, and detachment also occur, and cataracts, optic atrophy, and corneal abnormalities are described. Some skeletal features also suggest Marfan syndrome. They include a long, thin habitus, pectus excavatum, scoliosis, and genu valgum. There is often radio logical osteoporosis and abnormal modelling of the long bones with epimetaphyseal widening. Many subjects with homocystinuria have learning difficulties (average IQ c.80) and may also have seizures and strokes. It is unknown how closely these follow the increased ten dency to thrombosis or the biochemical changes, especially a lack of cystathionine. Thromboembolism may occur in any vessel and at any age and has been documented in as many as 25% of affected individuals after surgery. Any patient who has the phenotypic features of Marfan syndrome associated with thrombosis, intellectual disability, and affected sib lings should have amino acid analysis of the urine and plasma to confirm the diagnosis. The outlook for patients whose biochemical abnormalities are corrected by large amounts of pyridoxine (i.e. those with pyridoxine- sensitive homocystinuria) is usually better than those who are pyri doxine resistant. The main cause of death is thromboembolism. The management of patients with homocystinuria differs ac cording to the time of diagnosis and whether or not the patient re sponds to pyridoxine. In pyridoxine-responsive patients diagnosed after the newborn period, giving pyridoxine in doses that vary from 250 to 1,200 mg a day appears to prevent thromboembolism. When homocystinuria is detected in the newborn infant (most are discovered by screening and are pyridoxine nonresponsive), a diet low in methionine appears to reduce the incidence of low intel ligence. After the newborn period, in those who are unresponsive to pyridoxine, methionine restriction and the administration of betaine (as a methyl donor) are beneficial. Alkaptonuria (see also Chapter 12.2) This condition (MIM 203500) has a special place in the history of medicine as one of the first recognized inborn errors in which men delian recessive inheritance was proposed, by Garrod more than 100 years ago. In this rare autosomal recessive disorder, decreased activity of homogentisate 1,2-dioxigenase (HGD) leads to accumu lation of homogentisic acid in the urine and increased pigmenta tion (ochronosis) in cartilage and connective tissues. Alkaptonuria, the classic sign of darkening of the urine (which is not always pre sent) is due to the presence of 2,5-dehydroxyphenylacetic acid de rived from the oxidation and polymerization of homogentisic acid. Polymerization increases in alkaline urine and is slowed down by antioxidants such as vitamin C. It is associated with a reduction in lysyl hydroxylase in the tissue concerned and an impairment of the cross-linking of collagen. Alkaptonuria has a general prevalence of around 1:250 000 but is more frequent in Slovakia and the Dominican Republic than else where. It is recessively inherited by mutations in the HGD gene. Abnormal pigmentation is found in the cartilage of the ear (which may be calcified), the nasal cartilage, and the sclerae. The most im portant effects of this disease are on the skeleton and cardiovascular system; initially the spine (Fig. 20.1.21) and subsequently the larger joints are affected. The intervertebral discs lose height and later cal cify; they may also herniate acutely. The spine becomes rigid and kyphotic.

Severe destructive arthritis often affects the large joints, such as the knees, shoulders, and hips. The symphysis pubis may be affected but not the sacroiliac joints. Calcification of the aorta may occur, and cardiac valve surgery may be necessary. In addition, around one-third of patients develop renal stones. The diagnosis of alkaptonuria—often made late—should be sus pected where there is a premature disc degeneration, even if there is Fig. 20.1.21 The appearance of the spine in a man with alkaptonuria. There is universal calcification of the intervertebral discs.

20.1 Skeletal disorders—general approach and clinical conditions 4653 no excessive darkening of the urine. Early degenerative arthritis sug gests the disease, confirmed by finding deeply pigmented articular cartilage at the time of operation. In those patients with lifelong dis coloured urine, the differential diagnosis is from other rare causes of urinary pigmentation. An increase in homogentisic acid in the urine and plasma confirms the diagnosis. The arthritis associated with alkaptonuria typically accelerates after the age of 30 and is more pro nounced in women. It is characterized by excessive calcium pyrophos phate deposition that, in addition to causing chronic joint changes, may be punctuated by episodes of acute inflammation (pseudogout). The herbicide nitisinone, licensed by the Food and Drug Administration for the treatment of tyrosinaemia, dramatically re duces the excretion of homogentisic acid and its place in the treat ment of alkaptonuria appears promising. Hypophosphatasia This rare disorder has similarities with rickets and osteomalacia with considerable phenotypic variation. It is due to a reduction in the tissue nonspecific alkalinephosphatase (TNAP), which leads to defective mineralization and a triad of biochemical disturbances: in creased urinary phosphoethanolamine, plasma pyrophosphate, and plasma pyridoxal phosphate. Although TNAP is widely distributed, its absence leads to lesions only in the bone and teeth. Pathophysiology The characteristic biochemical changes result directly from the al kaline phosphatase deficiency. Increased urinary pyrophosphate excretion is more reliable than urinary phosphoethanolamine as a marker for carriers of the hypophosphatasia gene. Occasionally there is hypercalcaemia and hypercalciuria in childhood and up to half of affected children and adults have increased plasma phos phate levels. Hyperphosphataemia is also described in some carriers of the hypophosphatasia gene. The recorded plasma alkaline phos phatase level must be compared with age-matched control values (which are higher physiologically in children and adolescents). Histological examination of bone shows an excess of osteoid with abnormal tetracycline labelling without evidence of secondary hyperparathyroidism. Matrix vesicles do not contain alkaline phos phatase or hydroxyapatite crystals. The primary dental defect is in the cementum; additionally, the predentine is widened, and the den tinal tubules are enlarged and few. Clinical features Hypophosphatasia occurs in all races. Since it is inherited as an autosomal recessive trait, it is more frequent where there is consan guinity. It has been estimated that hypophosphatasia occurs in 1 in 100 000 live births in Toronto. The four clinical types provide a con tinuous spectrum, from a lethal perinatal disorder to an asymptom atic syndrome in some adults. The first (MIM 241500) is an important cause of lethal, short- limbed dwarfism (see earlier). Some newborn infants survive for a few days, but fever, failure to thrive, anaemia, seizures, and intra cranial haemorrhages occur. Radiographs show grossly defective mineralization, especially in the skull, where only the base may be mineralized, and in diaphyses of the long bones which, rarely, may have bony spurs. In the infantile form (within the first six months), hypotonia, failure to thrive, hypercalcaemia, and hypercalciuria occur. Clinical rickets is noticed and the fontanelle appears wide, but there is a functional synostosis. Craniostenosis can produce optic atrophy, exophthalmos, and raised intracranial pressure requiring surgery. The most variable expression occurs in childhood (MIM 241510). Early loss of deciduous teeth, due to defective cementum, may

be the only feature (ondontohypophosphatasia). The pulp chambers are enlarged and the root canals are short (‘shell’ teeth). If bone dis ease is present, walking is delayed, and deformities occur (e.g. bow legs, knock knees, short stature, and enlargement of the epiphyses at the wrist, knees, and ankles). Features similar to chronic multifocal osteomyelitis have been described. In adults (MIM 146300), progressive stiffness, pain in the bones, and apparent ‘stress’ fractures can occur (Fig. 20.1.22). Approximately 50% of such patients have a childhood history of bone disease resembling rickets or premature loss of deciduous teeth or both. There may also be premature shedding of adult teeth, short stature, and abnormal skull shape. Recurrent poorly healing metatarsal fractures occur. Partial fractures of the long bones characteristically occur on the convex outer surface (in con trast to the concave inner position of the Looser zones in osteo malacia), most often in the upper one-third of the femoral shaft and are often bilateral; other sites include the ribs, tibia, and ulna. They may be unaltered for years or they may increase in size and eventually fracture. Secondary hyperparathyroidism is not seen. Chondrocalcinosis is common and, in a proportion, is associated with clinical pyrophosphate gout (pseudogout). Management In the management of hypophosphatasia, premature synostosis leading to raised intracranial pressure requires surgical relief. Hypercalcaemia may be dealt with by reducing dietary calcium and by giving prednisolone. Intramedullary rods may prevent and treat fractures of the long bones. Dental abnormalities, which can occur in biochemically normal members of hypophosphatasia families, may require treatment. Fig. 20.1.22 Hypophosphatasia in the adult. A pathological ununited fracture in the bones of the foot (arrowed). The woman had lost her teeth in early childhood.

SECTION 20 Disorders of the skeleton 4654 Prenatal diagnosis of a severely affected child can be made by ultrasound examination, and mutations in TNAP may be detected. There is also reduced alkaline phosphatase activity in the amniotic fluid cells. Recombinant bone targeted human TNAP (asfotase-α) has been approved for the treatment of the paediatric form of this disease. Lysosomal storage diseases (see also Chapter 12.8) This large group of diseases is due to various inborn errors that affect the function of specific lysosomal enzymes normally re sponsible for the breakdown of a variety of complex molecules. As a result, these molecules, or their partially degraded derivatives, accumulate in the lysosomes and the tissues that contain them. The effect of this accumulation varies from one tissue to another according to the particular disorder and the skeleton is signifi cantly involved in only a proportion of them. They include some mucopolysaccharidoses and Gaucher disease. Mucopolysaccharidoses Failure of the normal lysosomal breakdown of complex carbohy drates (glycosaminoglycans) leads to their accumulation in the tis sues and produces many clinical abnormalities. The disorders may be divided into two main groups according to the chemistry of the accumulated substance, namely the mucopolysaccharidoses (MPS), and the mucolipidoses. Specific biochemical defects are described elsewhere in this book (see section 11). Since some of these dis orders have a prominent effect on the skeleton, some of them are briefly mentioned here: they are Hurler syndrome (MPS type 1H), Hunter syndrome (MPS type 2), and Morquio syndrome (MPS type 4). With certain exceptions, the bone changes themselves do not permit precise diagnosis of the type of dysplasia or distinction from the mucolipidoses. Hurler syndrome (MPS type 1H)—(MIM 607014) This is the most severe type of mucopolysaccharidosis and causes death at an early age. The enzyme defect is recessively inherited, and all patients have the same appearance, to which the term ‘gargoylism’ was previously applied. Affected infants appear to develop normally in the first few months of life, but then deteriorate mentally and physically. Death often occurs in late childhood, commonly due to pneumonia or to coronary artery disease associated with mucopoly saccharide deposits. The

physical features include proportionate short stature (Table 20.1.4), a typical facial appearance, a short neck with a lumbar gibbus and chest deformity, and a protuberant abdomen. The fa cial features are coarse, with flattening of the nasal bridge, with large open mouth and tongue, and, often, with hypertrophied gums over enlarged alveolar ridges. The eyes are prominent with corneal clouding. There is noisy breathing and variable deafness. The vault of the skull may show scaphocephaly or acrocephaly. Other striking features include the stiff, broad, trident hands and the large ab domen with hepatosplenomegaly. Radiographs show the abnormal shape of the skull, the slipper-shaped sella turcica, the beaking of the vertebrae with the thoracolumbar kyphosis, and the bullet- shaped phalanges. Haematopoietic stem cell transplantation is the treatment of choice for this condition. Recombinant iduronidase is effective in reducing urinary glycosaminoglycan excretion and can be used suc cessfully in the pre- and peri-transplant phase. Hunter syndrome (MPS type 2)—(MIM 309900) This has similar but less severe features to Hurler syndrome but is inherited as an X-linked recessive trait. Two forms of the disease are described: the more severe form, associated with intellectual disability and progressive physical disability, typically causes death by the age of 15; the less severe form is compatible with survival into adult life with slowly progressive cardiac valve disease. Both forms are associated with mutations in the enzyme iduronate-2- sulphatase. There appears to be some benefit from enzyme replace ment with idursulfase but further studies are needed to assess its long-term efficacy. Morquio syndrome (MPS type 4)—(MIM 253010) In this disorder, the orthopaedic manifestations are striking but in telligence is normal. In the first years of life, the child becomes pro gressively more deformed and dwarfed. Characteristically the neck is short, the sternum is protuberant, and there may be a flexed stance with knock knees. There is a striking loss of muscle tone in com parison to the stiffness of MPS type 1H; hypermobility and a loose skin are features. Radiographs in infancy show a spine similar to that seen in those with Hurler syndrome, but later flattening of the ver tebrae with anterior beaking lead to relative shortening of the trunk. The small bones of the hands are different from those of MPS type IH and the metacarpals show diaphyseal constriction (Fig. 20.1.23). Fig. 20.1.23 The appearance of the hand in mucopolysaccharidoses (MPS) type 4 (Morquio syndrome). The bases of the metacarpals are conical, the tubular bones are short, and the growth plates of the radius and ulna are inclined towards each other.

 Importantly, the odontoid may be hypoplastic, leading to atlantoaxial instability, compression of the long spinal tracts, and paraplegia. At present no specific therapy is available but mouse studies suggest that there may be a role for enzyme replacement therapy. Gaucher disease (MIM 230800) (see also Chapter 12.8) This is a rare lysosomal storage disorder in which glucocerebroside- containing macrophages accumulate within the bone marrow, spleen, liver, and other organs. This accumulation is the result of deficiency of the enzyme β-glucocerebroside. Gaucher disease is re cessively inherited and overrepresented in Ashkenazi Jews, where the incidence of the adult form (type 2) is about 1 in 2500 births. The skeletal manifestations are often severe and disabling. They vary from a characteristic but clinically insignificant failure of remodel ling in the lower femora (Erlenmeyer-flask appearance) to a diffuse and localized bone loss and osteosclerotic and osteonecrotic lesions, which cause pain and pathological fracture and often require preco cious joint replacement surgery. Enzyme replacement is an estab lished but expensive form of treatment. Skeletal dysplasias The term ‘skeletal dysplasia’ has traditionally been used to cover a variety of generalized disorders of the skeleton, often of unknown cause, affecting both cartilage and bone. One can now distinguish the chondrodysplasias, which are primarily due to mutations affecting

cartilage, from conditions such as diaphyseal dysplasia and assorted dense bone diseases, where the causes are less well known. Since osteopetrosis is caused by well-defined deficiencies of osteoclast function, it is dealt with separately. The mutations in many of the skeletal dysplasias have been described (Table 20.1.1) and the skeletal dysplasias can now be classified into biochemical families according to their causes (Table 20.1.14). Many are due to mutations in specific collagens (types 1, 9, 10, and 11). Achondroplasia is a striking example of a skeletal dysplasia caused by a noncollagen mutation, that is, a mu tation in FGF-receptor 3 (FGFR3). Mutations in FGFR2 can cause craniosynostoses (e.g. Apert and Pfeiffer syndromes). Further de tails can be found in reviews (see Further reading). Clinical features The physician confronted by a patient with a skeletal dysplasia is unlikely to make the correct diagnosis without additional help un less it is clearly one of the more distinctive forms, such as achon droplasia. Accurate classification of the dysplasias is important and has contributed to the rapid advances in clinical and biochemical understanding of these conditions. The most convenient simple classification is a clinical one. Most patients with skeletal dysplasias have restricted growth and most are short-limbed. The bodily pro portions of people with skeletal dysplasias usually provide a clue about whether mainly the limbs or the spine, or both, are affected. In the short-limbed group, achondroplasia and achondroplasia-like dwarfs are the most typical. Other disorders, often with less con spicuous dwarfing, include various inherited epiphyseal dysplasias, diaphyseal dysplasias, and some, but not all, metaphyseal dysplasias. An alternative classification, not based on height, groups the dysplasias according to whether they are predominantly epiphyseal Table 20.1.14 Mutations in the skeletal dysplasias Mutant gene Disease family Collagen mutations COL1A1 and COL1A2 Osteogenesis imperfecta and EDS type 7 COL2A1 Achondrogenesis type 2 SED Kniest dysplasia Stickler syndrome (with ocular manifestations: type 1) COL3A1 Vascular EDS (type 4) COL5A1 Classic EDS (types 1 and 2) COL9A1, 2, 3 Multiple epiphyseal dysplasia (types 2, 3, and 6) COL10A1 Metaphyseal chondrodysplasia (type Schmid) COL11A2 Stickler syndrome (without ocular manifestations; type 2) Noncollagen mutations COMP Pseudoachondroplasia Multiple epiphyseal dysplasia (type 1) SLC26A2 (DTDST) Diastrophic dysplasia Atelosteogenesis type 2 Achondrogenesis type 1B Multiple epiphyseal dysplasia (type 4) PTH–PTHrP receptor Jansen metaphyseal chondrodysplasia Blomstrand chondrodysplasia SOX9 Campomelic dysplasia Arylsulphatase E Chondrodysplasia punctate CDMP1 Acromesomelic chondrodysplasia FGFR3 Achondroplasia Thanatophoric dysplasia Hypochondroplasia Crouzon syndrome with acanthosis nigricans FGFR2 Crouzon syndrome Apert syndrome Jackson–Weiss syndrome Pfeiffer syndrome FGFR1 Pfeiffer syndrome RUNX2 (CBFA1) Cleidocranial dysplasia Cathepsin K Pyknodysostosis Tumour suppressor genes
(EXT1, EXT2) Multiple hereditary exostoses TRAPPC2 Spondyloepiphyseal dysplasia tarda (X-linked) RMRP Cartilage hair hypoplasia (Metaphyseal chondrodysplasia, McKusick type) EVC (on chromosome 4) Chondroectodermal dysplasia (Ellis–van Creveld syndrome) WISP3 SED tarda with progressive arthropathy Matrilin 3 Multiple epiphyseal dysplasia (type 5) EDS, Ehlers–Danlos syndrome; PTHrP, parathyroid-hormone-related protein; PTH, parathyroid hormone; SED, spondyloepiphyseal dysplasia congenita.

 or metaphyseal, whether the spine is predominantly involved, and whether single limbs or segments are involved. Radiographs, taken as early in life as possible and, where possible, consecutively, are es sential to determine whether the metaphyses or the epiphyses of the long bones are primarily affected. For the purpose of this section, osteopetrosis (marble bone dis ease) is dealt with separately as a disorder of bone-cell biology.

Other sclerosing disorders of bone, in which biochemical abnormalities have been described (e.g. Camurati–Engelmann and van Buchem diseases), receive brief mention. Achondroplasia (MIM 100800) This is the prototype form of short limb dwarfism. It is domin antly inherited and due to a highly specific recurrent mutation in the FGFR3 gene encoding the FGF-receptor 3. Activation of this receptor exerts an inhibitory effect on the proliferating columns of chondrocytes in the growth plate. The characteristic glycine for arginine substitution at amino acid 380 in the transmembrane re gion of the receptor facilitates its dimerization and activation after engaging its FGF ligand, thereby causing overactivity and inhib ition of chondrocyte proliferation in the growth plate and reduced longitudinal growth. The FGFR3 mutation is exclusively paternally derived and that it reflects processes specific to spermatogenesis but not oogenesis. As the clinical definition of achondroplasia has not always been exact, its true incidence and natural history are not well defined. There is a high frequency of sporadic cases and a birth in cidence of between 2 to 10 per 100 000. There is a failure of the epi physeal growth of cartilage and bulbous masses of cartilage appear at the ends of the long bones. In contrast, periosteal and membrane bone formation and bone repair are normal. This selective effect on growth cartilage accounts for the skeletal deformity. Achondroplasia can be diagnosed at birth or within the first year of life, when the disparity between the large skull and short limbs becomes obvious. There is a striking disproportion between the normal length trunk and the short arms and legs. Thus, the finger tips may only come down to the iliac crest. The shortness of the limbs particularly affects the proximal segment (rhizomelia). The limbs themselves look very broad, with abnormally deep creases, and the hands are trident-like. In contrast to the short limbs is the enlarged bulging vault of the skull, the small face, and flat nasal bridge or ‘scooped out’ glabella. There is a marked lumbar lordosis. Radiological features include metaphyseal irregularity and flaring in the long bones, irregular and late-appearing epiphyses, a narrow pelvis in its anteroposterior diameter, with short iliac wings and deep sacroiliac notches, and a spine that shows progressive nar rowing of the interpedicular distance from above downwards, which is the reverse of normal. This may cause spinal stenosis par ticularly in later life as degenerative disc and facet joint arthritis are superimposed. A highly characteristic radiographic observation in young children is the presence of anterior wedging of the first lumbar vertebra associated clinically with a thoracolumbar gibbus. Any temptation to correct this surgically should be resisted since it invariably corrects itself as the child starts walking by the age of five years. Children with achondroplasia are of normal intelligence and the complications of this disease arise particularly from the skeletal disproportion. This may lead to early osteoarthritis, obstetric dif ficulties, and the need for caesarean section, hydrocephalus, and paraplegia. Eventual height typically varies between about 120 and 150 cm. Recent reviews emphasize how often spinal stenosis may re quire surgical decompression, sometimes at multiple levels. Growth hormone is ineffective but surgical limb lengthening may be appro priate in carefully selected cases. In infancy hydrocephalus is an important potential complication. As many as 10% of cases require a ventricular shunt and decompres sion of the cranio-cervical junction is undertaken in about 7% of cases before the age of four years. Nocturnal apnoea is an important clinical sign which can be detected by oximetry. Ultrasonography and MRI are useful in the detection of hydrocephalus. Homozygous achondroplasia (the occasional offspring of two affected parents) is severe and lethal. In the condition of hypo chondroplasia, which is included in the same FGFR3 molecular family, the skeletal disproportion and the spinal abnormalities are less severe than in achondroplasia and the skull is unaffected. It may be difficult to distinguish from constitutional short stature without formal DNA analysis. Achondroplasia-like dwarfism For details of these and other causes of short-limbed dwarfism, the reader should consult more specialized texts. Those that most closely resemble

achondroplasia at birth are thanatophoric dwarfism (also caused by FGFR3 mutations), achondrogenesis (caused by COL2A1 mutations), severe hypophosphatasia, and type 2 osteogenesis imperfecta. All can be distinguished radiologically from neonatal radiographs. Spondyloepiphyseal dysplasias This is a heterogeneous group of disorders in which there is prom inent spinal involvement, with the short stature partly due to short ness of the trunk. The most severe type is spondyloepiphyseal dysplasia congenita; milder forms are often collectively referred to as spondyloepiphyseal dysplasia tarda. There are various forms of inheritance. Some forms are due to mutations in type 2 collagen. Spondyloepiphyseal dysplasia tarda (MIM 313400) often has an X-linked recessive mode of inheritance, so that only men are af fected and women are carriers. Causal mutations in TRAPPC2 (encoding a protein involved in vesicle trafficking to the Golgi) have been identified. In affected men, the disproportionately short trunk becomes obvious at adolescence. Failure of ossification in the an terior part of the so-called ring epiphyses leads to central and pos terior humps on the upper and lower parts of the flattened vertebral bodies (platyspondyly). The condition should be distinguished from multiple epiphyseal dysplasia, which involves other major joints more than the spine. Spondyloepiphyseal dysplasia congenita (MIM 183900) can be diagnosed at birth because of the short stature associated with a short trunk. It is due to mutations in COL2A1. There may be resem blance to Morquio disease (MPS type 4, see earlier). The severe form may be distinguished from the age of about four years. The appear ance of the capital femoral epiphyses is delayed (in some patients it may never be seen except by arthrography). Marked lumbar lor dosis, waddling gait, back pain, and progressive disproportion may occur. The odontoid is hypoplastic, kyphoscoliosis may develop, and the interpedicular distances of the lumbar vertebrae is narrow. Paraplegia may occur as a result of all these changes. In this disorder there is often myopia and retinal detachment.

 There is a form of spondyloepiphyseal dysplasia, pseudoa chondroplasia (MIM 177170), which resembles achondroplasia because of the short limbs, but here the face is normal. The short stature only becomes obvious from about two years of age. Lumbar lordosis and scoliosis may develop. The tubular bones are short with irregular metaphyses and small, deformed epiphyses. Joint hypermobility is very marked with additional striking hyperelasti city of the skin; early osteoarthritis, particularly of the hips, is common. Characteristic mutations in the COMP gene, interfering with calcium-binding domains in cartilage oligomeric matrix pro tein, disrupt its secondary structure. Proportionate dwarfism Although it is clinically important to classify short stature into proportionate and disproportionate, there are many conditions in which this distinction is difficult to make. Hypophosphataemic rickets, mucopolysaccharidoses, vitamin D-dependent rickets, and osteogenesis imperfecta may come into both categories. Bone dysplasias without conspicuous short stature The height of patients with multiple epiphyseal dysplasia may be only slightly reduced. Although many epiphyses are affected, the spine is virtually normal. There are also variable forms of inher itance. A variety of clinical types are recognized caused variously by mutations in type 9 collagen, COMP, matrilin 3, and SLC26A2 (encoding a sulphate transporter, deficiency of which causes undersulphation of proteoglycans). In patients with multiple hereditary exostoses, often referred to as diaphyseal aclasis (MIM 133700), stature is typically normal; there is a juxta-epiphyseal disorder of bone growth limited to bones de veloped in cartilage, which gives rise to cartilage-capped exostoses that point away from the joint. Inheritance is autosomal dominant caused by mutations in the genes EXT1 or EXT2, which are tumour suppressor genes involved in cartilage growth. Malignant change may lead to chondrosarcoma in 0.5–2% of cases but

this is rare be fore the age of 10 or after the age of 50. The metaphyseal disorders are rare; some, such as Jansen meta physeal dysplasia (associated with a mutation in the gene for the PTH/PRrP receptor) do cause severe dwarfing (and hypercalcaemia). In others with less severe growth disturbance, such as metaphyseal chondrodysplasia type Schmid (due to a mutation in the collagen type 10 gene, COL10A1), rickets is simulated, and confusion with inherited hypophosphataemia is possible. Cleidocranial dysplasia (MIM 119600) In this rare condition, the clavicles are hypoplastic or absent, the fontanelles remain open, there are supernumerary teeth, and there may be Wormian bones in the skull. Heterozygous mutations in RUNX2, encoding the osteoblast transcription factor CBFA1, are responsible (see earlier). In the mouse cbfa1 knockout, there is failure of the skeleton to mineralize, which is consistent with the key role of this transcription factor in triggering osteoblast activity. Disorders of increased bone density There are two main causes for the inherited dense bone diseases, namely excessive bone formation and reduced bone resorption. Apart from marble bone disease, most physicians' experiences of these conditions are limited by their extreme rarity. Increased bone formation Camurati–Engelmann disease (progressive diaphyseal dysplasia; MIM131300) This rare autosomal dominant condition is inherited through mu tations in the TGFβ1 gene, but penetrance is variable. Mutations are clustered at the C-terminal end of the latency associated pep tide domain of TGFβ1, probably affecting its activation (cf. Marfan syndrome earlier). The condition affects the muscles as well as the skeleton, where the main feature is a variable but progressive endosteal and periosteal thickening of the diaphyses of the long bones (Fig. 20.1.24). In severely affected subjects, the spine, skull, and axial skeleton are all affected. In addition, there is a waddling broad-based gait, muscle wasting, and weakness, loss of sub cutaneous tissues, and pain in the legs during childhood, so that distinction from muscular dystrophy may be necessary. The ap pearance is characteristic; the head is large with a prominent fore head and proptosis, the muscle mass is reduced, and the bones are palpably thickened with fusiform swelling of the bones below the knees. Cranial nerve palsies, deafness, and blindness with raised intracranial pressure can occur. Puberty is delayed. Bone pain re sistant to analgesia is often a presenting and troublesome feature. Anaemia, leukopenia, hepatosplenomegaly, and elevation of the erythrocyte sedimentation rate are described. Radiographic appearances vary, from limited thickening of the diaphyses (often in the lower extremities) to widespread new bone formation that affects all bones including the skull, demonstrated by scintigraphy. The increased bone turnover causes a moderate increase in plasma alkaline phosphatase and urinary hydroxyproline levels. There may be a markedly positive calcium balance, associated with hypocal caemia and hypocalciuria. Hyperphosphataemia has been recorded. Pathological examination confirms gross thickening of the bone with disorganization of internal structure and external shape. The peripheral subperiosteal new bone is woven. The muscles show nonspecific, type 2 fibre atrophy. In the differential diagnosis, the proximal myopathy and abnormal gait simulate muscular dystrophy. The radiographic appearances are diagnostic, although idiopathic hyperphosphatasia may present some difficulties. Fig. 20.1.24 Radiographic appearances of the long bones in Camurati–Englemann disease with pronounced thickening of the femoral diaphyses.

 The course of this disorder is unpredictable, and remission of symptoms may occur during adolescence or adult life, so it is dif ficult to assess treatment. Symptom onset is usually before the age of 30 and, often, before the age of 10. Bone pain may respond to corticosteroids in small, alternate-day doses and there is also evi dence that the bone changes may be reduced. Bisphosphonates are of dubious benefit and may even be

harmful. Occasional case re ports suggest that angiotensin receptor blockers may be of benefit, presumably through their effects on blocking TGFβ signalling (see Marfan syndrome, earlier in this chapter). Limb pain may be re lieved by surgical removal of a cortical window in the diaphysis. Sclerosteosis (MIM 269500) This condition is an autosomal recessive trait caused by mutations in sclerostin, a BMP antagonist. It has a particularly high preva lence in the Afrikaner population of South Africa due to a founder effect. There is progressive overgrowth and sclerosis of the skeleton, including the skull and the mandible. There are similarities to van Buchem disease (endosteal hyperostosis) but the skeletal problems are more severe, and there is often also syndactyly. Prophylactic craniotomy may be necessary to reduce the increased intracranial pressure. van Buchem disease (MIM 239100) In this rare hyperostosis, endosteal thickening of the shafts of the long bones is associated with generalized hyperostosis, including the base of the skull, mandible, clavicle, and ribs. Bilateral facial nerve weakness, deafness, and optic atrophy may ensue. Deletions in the regulatory elements of the SOST gene have been described. A milder variant of endosteal hyperostosis (Worth type; MIM 144750) is often associated with activating mutations in the LRP5 gene. In this con dition the bones are universally dense, there is frontal bossing of the skull and obvious hyperostosis of the base of the skull which may cause cranial nerve dysfunction (particularly facial palsy). Otherwise it is generally asymptomatic. LRP5 is associated with both the syn drome of familial high bone mass and osteoporosis pseudoglioma (see earlier) and has also been linked to the determination of bone mass in the general population. Decreased bone resorption There are several genetic causes of reduced bone resorption that typically result in generalized increase in bone density but also in creased fracture risk. Osteopetrosis (marble bone disease) Among those disorders with increased bone density, marble bone disease, or osteopetrosis (also known as Albers–Schönberg disease), is the best known. It is a heterogeneous disorder with a widespread increase in bone density. The classic bone-within-bone appearance (endobone) is not always apparent (Fig. 20.1.25). In most cases, the basic defect lies in the osteoclasts, which, for various reasons, are unable to resorb mineralized bone. Two main forms are distinguished: recessively inherited se vere osteopetrosis, causing death in childhood; and a dominantly inherited mild form, in which the diagnosis is often made on radiological grounds alone. This distinction is not absolute—two distinct dominantly inherited forms are recognized as well as inter mediate forms. Deficiency of carbonic anhydrase 2 can also cause osteopetrosis associated with cerebral calcification, mild systemic acidosis, growth failure, and learning difficulties. Pycnodysostosis (see next) is another form of osteopetrosis also caused by deficiency of the enzyme cathepsin K. The mutations that cause different types of osteopetrosis have now been identified (Table 20.1.15). They occur in the acidification pathways of the osteoclast. Mild domin antly inherited type 2 osteopetrosis results from mutations in the chloride channel gene CLCN7 and severe recessive osteopetrosis from mutations in the gene TCIRG1, encoding a component of the osteoclast-specific vacuolar H+ATPase involved in acidification. Severe osteopetrosis In severe recessively inherited osteopetrosis (MIM 259700), there is widespread increased density of the bones without modelling or remodelling. This produces the Erlenmeyer-flask deformity of the metaphyses. The increase in bone density is often inter mittent, producing alternating bands of sclerosis. The failure of resorption leads to a reduction in bone marrow space with a leukoerythroblastic anaemia and hepatosplenomegaly. It can also produce nerve compression, blindness, and deafness. Other clinical features in this severe form can include hydrocephalus, delayed tooth eruption, and osteomyelitis. Fracture of the dense bones is common but best managed conservatively except for fem oral neck fracture, which should be treated surgically. The affected infant is short with an apparently large head with frontal bossing and with knock knees.

The plasma calcium level appears to alter with the dietary intake and may be sufficiently low to contribute to rickets. The acid phosphatase concentration (derived from the defective osteoclasts) is increased. Secondary hyperparathyr oidism leads to an increase in calcitriol levels. Blood transfusions may be required to correct anaemia, and antibiotics for frequent infections. Haematopoietic stem cell transplantation should be considered for those with the severe life-threatening recessive forms of osteopetrosis, but its success is highly dependent on the underlying mutation. Those with reduced or absent osteoclasts on bone biopsy may have underlying RANKL mutations and should not be transplanted. In contrast, those with RANK muta tions may be rescued despite being osteoclast poor. Neuropathic osteopetrosis caused by OSTM1 or CLCN7 mutations is also a Fig. 20.1.25 Osteopetrosis. The classic bone-within-bone (endobone) appearance of the bones in a woman with type 2 dominantly inherited osteopetrosis (ADDO2).

20.1 Skeletal disorders—general approach and clinical conditions 4659 contraindication. Those with osteoclast-rich TGIRG1 mutations should do well with transplantation. Mild osteopetrosis The mild forms vary from subjects with an increased number of fractures affecting both the long bones and the small bones of the hands and feet to those in which the disorder is so mild that the diagnosis is made by radiology alone (accounting for apparently un affected generations with the dominant form of the disease). There are more severe forms of dominantly inherited osteopetrosis with nerve compression, deafness and blindness, and anaemia at times of increased physiological requirement, such as pregnancy. Other es tablished features include osteomyelitis and facial nerve palsy. Recent studies of Danish families define two dominantly in herited forms (Table 20.1.15). In the first (MIM 607634), mutations have been described in LRP5; it has uniformly dense bones with sclerosis of the cranial vault and the spine and no increase in the plasma acid phosphatase level. The second (MIM 166600) is caused by mutations in CLCN7; it has variable bone density (giving rise to an endobone appearance, Fig. 20.1.25) and lack of modelling, with a significant increase in the plasma acid phosphatase level. Sometimes CLCN7 mutations can also give rise to the severe infantile form of the disease. Carbonic anhydrase 2 deficiency (MIM 259730) The association of carbonic anhydrase 2 deficiency with osteopetrosis, renal tubular acidosis, cerebral calcification, some degree of intel lectual disability, growth failure, and dental malocclusion is of con siderable interest because of the clues about the normal function of carbonic anhydrase 2 in bone resorption. Carbonic anhydrase 2 is part of the carbonic anhydrase gene family and is widely distributed. It is found in the kidney, brain, red cells, and elsewhere. Deficiency of carbonic anhydrase 2 is autosomal recessively inherited and ap parently normal parents of affected offspring have 50% of normal carbonic anhydrase 2 levels within their red cells. The bone disease is not distinguishable from other forms of osteopetrosis and frac tures occur until adulthood. There is always growth retardation, and height may be more than four standard deviations below the mean. The bone age is also delayed. Radiographic appearances improve in adult life. The renal tubular acidosis is mixed, both proximal and distal. Cerebral calcification affects the basal ganglia within the first decade. It increases during childhood to include the cor tical grey matter and is similar to that occurring in idiopathic or pseudohypoparathyroidism. Bone histology shows unresorbed calcified cartilage and osteoclasts without a ruffled border. The diagnosis of carbonic anhydrase 2 deficiency should be con sidered in any neonate with renal tubular acidosis. Genetic coun selling is possible since adult heterozygotes have reduced levels of the enzyme in their red cells. However, the concentration of carbonic anhydrase 2 is normally very low at birth and cannot be used as a reliable neonatal test for the affected homozygote. DNA based methods have largely superseded the older biochemical tech niques. The condition is more

prevalent in populations around the Mediterranean where it was spread by a founder effect in the dias pora from the Arabian peninsular in the 11th century. The treatment of carbonic anhydrase 2 deficiency is symptom atic. It is possible that correction of the renal tubular acidosis tem porarily increases the rate of growth. In the differential diagnosis of osteopetrosis, there are many disorders with an excessive amount of bone in various parts of the skeleton. These include other skeletal dysplasias, Caffey dis ease (infantile cortical hyperostosis), which causes a temporary increase in bone density from birth and myelofibrosis, renal glomerular osteodystrophy, inherited hypophosphataemia, and fluorosis in adult life. Pcknodysostosis (MIM 265800) Pycnodysostosisis an autosomal recessive disorder, with parental consanguinity in some 30% of subjects. It is caused by mutations in cathepsin K, an enzyme necessary for the osteoclastic resorption of bone matrix. Marked reduction in stature with short limbs is a par ticular clinical feature. The vault of the skull is large, the face and chin small, the palate high-arched, and the teeth crowded, with retained deciduous teeth. The anterior fontanelle (and other cranial sutures) remain unfused. Table 20.1.15 Different types and clinical features of the osteopetroses Type Clinical features Radiology Plasma biochemistry Gene MIM Mild dominantly inherited type 1 (ADO10) Fractures; cranial nerve compression; variable anaemia; osteomyelitis of the jaw Bones uniformly dense; sclerosis of the skull; enlarged thick cranial vault Normal LRP5 mutations in some 607634 Mild dominantly inherited type 2 (ADO2) As above Variable bone density; endobones; sandwich vertebrae; lack of modelling Acid phosphatase increased; calcium and PTH may be increased CLCN7 mutations most frequent 166600 Severe infantile recessively inherited (ARO1) Short stature; severe anaemia; cranial nerve palsies; fractures; deformity; hepatosplenomegaly Other features depend on mutation Uniform increased bone density; lack of modelling Increased acid phosphatase; calcium may be low TCIRG1 CLCN7 RANKL RANK OSTM1 259700 611490 259710 612301 259720 Carbonic anhydrase 2 deficiency, recessive Cerebral calcification; growth retardation As in other forms Systemic acidosis CA2 259730 Pyknodysostosis; cathepsin K deficiency, recessive Disproportionate short stature; blue sclerae; open anterior fontanelle; kyphoscoliosis Responds to growth hormone Uniform osteosclerosis; Wormian bones; acro-osteolysis Normal CTSK 265800

 The painter Toulouse-Lautrec is regarded as a typical example of this disease. The fingers may appear to be clubbed because of hypoplasia of the distal phlanges. The chest may be deformed with kyphoscoliosis and pectus excavatum. Recurrent fractures of long bones and, occasionally, rickets occur. Radiologically, there are simi larities to osteopetrosis with generalized osteosclerosis and fractures but there are no defects of modelling and no endobones. In addition to delayed closure of the cranial sutures, there are Wormian bones; the bony fragility, Wormian bones, and blue sclerae simulate osteo genesis imperfecta. The condition is responsive to growth hormone. Fibrous dysplasia Fibrous dysplasia of bone is a condition in which areas of immature fibrous tissue, either single or multiple, are found within the skel eton (Fig. 20.1.26). The underlying genetic cause is a postzygotic activating mutation in GNAS1, the gene for the α-subunit of the G-protein signalling system. The extent to which this activating mutation affects the bone and other tissues depends on the degree of mosaicism. The condition is not inherited. Monostotic fibrous dysplasia This disorder is relatively common in orthopaedic practice. Although the lesions may occur in any bone, the most frequent presenting symptom at any age is a fracture, often of the upper end of the femur. The biochemistry is usually normal (although the al kaline phosphatase and other bone turnover markers may be ele vated in active disease). The diagnosis is usually made from the radiographic and pathological appearances. There is a smooth- walled translucent area within the bone, often with thinning of the

cortex, sometimes with associated deformity. Pathologically, areas of disorganized fibrous tissue are found, associated with woven bone and wide osteoid seams. This represents mosaic tissue with some normal mesenchymal cells and some carrying the mutation. The differential diagnosis is from other causes of bone cysts, from Paget's disease, and from hyperparathyroidism with osteitis fibrosa cystica. In the monostotic form, treatment is largely orthopaedic. However, the large size of some of the defects in the shafts of the long bones may make conventional stabilization of fractures very difficult. Prophylactic intramedullary nailing is sometimes justified. Treatment with pamidronate or other bisphosphonates may im prove pain and reduce osteoclast overactivity. Polyostotic fibrous dysplasia Interest in this condition (MIM 174800), in which the bone lesions are multiple, arises particularly from its association with pigmenta tion and sexual precocity, especially in women (McCune–Albright syndrome). The bone lesions and the brown pigmentation are typically associated in position (but not in extent) and may be re stricted to one side of the body. Sexual precocity is present in about 50% of women with polyostotic disease and is then the presenting complaint. It may occur at a very early age, with menstruation, and with the appearance of secondary sexual characteristics from in fancy. Where sexual precocity is not a feature, deformity and frac ture are often the first symptoms. Gross deformity of the upper femur and femoral neck produces the 'shepherd's crook' appear ance. Asymmetry of the long bones and of the skull are also seen and, in about half of the cases, the base of the skull is thickened. The macular pigmentation tends to have smooth borders (in contrast to those of neurofibromatosis) and often does not cross the mid line. The bone lesions tend to increase in size and number, but less rapidly after growth has ceased. Skin lesions are generally bilateral and do not correlate with the site of the bone lesions. There are sev eral other features that, like the sexual precocity, are explained by the activating mutation. These include thyrotoxicosis, acromegaly, and Cushing's syndrome. The skeletal lesions may cause complica tions such as spinal cord compression and may be associated with hypophosphataemic osteomalacia. Sarcoma is a rare complication. In the polyostotic disease, both the plasma alkaline phosphatase and other bone turnover markers may be increased and plasma phosphate slightly reduced. Microscopically, there is an abundance of woven bone and an increase in osteoblasts and osteoclasts. The cortex and marrow may be virtually replaced by fibrous tissue, so that the bones are fragile. Healing is rapid with abundant callus for mation. Radiologically, the bones are deformed, the cortex may be difficult to detect, and the medullary bone takes on a 'ground glass' appearance. In polyostotic fibrous dysplasia, the main differential diagnosis is from osseous neurofibromatosis; in the former, there is also bone deformity, and, sometimes, hypophosphataemic osteomalacia. Pigmented naevi occur in both but there are other cutaneous fea tures of neurofibromatosis; the bone deformity in neurofibromatosis can be quite bizarre, with overgrowth or undergrowth of isolated bones; the characteristic spinal change is a very sharp upper thoracic kyphoscoliosis; and, finally, neurofibromatosis often shows clear evi dence of dominant inheritance pattern. The medical treatment of the McCune–Albright syndrome is complex. As for the monostotic form, polyostotic fibrous dysplasia may be improved by bisphosphonates. Fig. 20.1.26 Polyostotic fibrous dysplasia in a 23-year-old woman. A large cyst in the upper femur led to a spontaneous fracture that subsequently united with conservative treatment. Two ribs on the same side of the body show similar abnormalities. Puberty was precocious but pigmentation absent.

 Ectopic mineralization Deposition of calcium in the soft tissues (ectopic calcification) and on ectopic bone matrix (ossification) has many causes (Table 20.1.16). These are nearly always pathological, but often the

cause is unknown. In older people, calcification in the tissues such as the arteries is so common that it may be regarded as a feature of ageing, in the same way as age-related bone loss. There are some disorders in which calcification and/or ossification are associated with biochemical abnormalities. Table 20.1.16 Causes of ectopic mineralization Type Cause Disorder Tissue distribution Ectopic calcification Dystrophic (damaged tissue, biochemistry normal) Unknown nucleators and inhibitors Inflammation In damaged tissues Haemorrhage In damaged tissues Injury In damaged tissues Age Blood vessels, costal cartilages Systemic sclerosis Particularly around phalanges Dermatomyositis Sometimes in sheets associated with muscles Metabolic (undamaged tissue, biochemistry abnormal) High calcium Hyperparathyroidism Blood vessels, soft tissues Excessive vitamin D Cornea, conjunctivae Excessive vitamin A Tendons and ligaments Sarcoidosis Nephrocalcinosis Low calcium Hypoparathyroidism Basal ganglia Pseudohypoparathyroidism Subcutaneous (ossification) High phosphate Renal glomerular failure Blood vessels, soft tissues Inherited hyperphosphataemia Periarticular soft tissues Low phosphate Inherited hypophosphataemia Tendons, ligaments (also ossification) Chondrocalcinosis Multiple (includes nucleators, deranged pyrophosphate transport, enzyme disorders) Age Joint cartilages Damaged cartilage Hyperparathyroidism Hypophosphatasia Haemochromatosis Familial chondrocalcinosis (ANKH) Gout Familial pyrophosphate arthropathy (MIM 118600) Haemochromatosis (MIM 235200) Wilson disease (MIM 277900) Hypomagnesaemia Ectopic ossification Acquired Local injury Hip replacement Traumatic paraplegia Tumours Others Diffuse idiopathic skeletal hyperostosis Ossification of the posterior spinal ligament (OPLL – MIM 602475)) Ankylosing spondylitis Etretinate therapy Some metabolic enthesopathies (e.g. X-linked hypophosphataemia, Dent disease) Inherited Albright hereditary osteodystrophy Fibrodysplasia (myositis) ossificans progressiva (MIM 135100) Progressive osseous heteroplasia (MIM 166350)

 Ectopic calcification without bone formation Calcification can result from previous damage in soft tissues (dys trophic calcification) or from an increase in the circulating con centration of calcium or phosphate (metastatic calcification, e.g. in advanced renal osteodystrophy). Chondrocalcinosis is a particular example of ectopic mineralization. Dystrophic calcification This occurs in inherited and acquired disorders of connective tissue, such as alkaptonuria (intervertebral discs), pseudoxanthoma elasticum (blood vessels), systemic sclerosis, and dermatomyositis (particularly in childhood), and also after infection, tumours, and trauma. In scleroderma, subcutaneous calcification, often around the phalanges, may be part of the CREST syndrome (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, tel angiectasia) (see also Chapter 19.11.3). The calcific deposits some times ulcerate through the skin, discharging as toothpaste-like material. In dermatomyositis, sheets of subcutaneous calcification can be deposited some time after the initial inflammatory episode, characterized by a systemic illness and painful weak muscles; the calcification can be very extensive but can also disappear rapidly, sometimes in adolescence. Metastatic calcification The distribution of the calcification varies inexplicably with its cause (e.g. in hypoparathyroidism there is subcutaneous and basal ganglia calcification; and in hyperparathyroidism there is vascular calcification), suggesting that metastatic calcification is not simply related to the Ca:P product. Calcification and hypocalcaemia This occurs in idiopathic and postsurgical hypoparathyroidism, as well as in pseudohypoparathyroidism. There may be extensive ec topic calcification, involvement of the basal ganglia (and outside it) and cataract formation. Pseudohypoparathyroidism type 1A is inherited as an autosomal dominant disorder but it is only fully expressed with maternal inheritance of the mutant GNSA1 allele (encoding the Gsα subunit of the G-protein signalling

system); additional clinical features include learning difficulties, round face, short stature, and short third and fourth metacarpals (Albright hereditary osteodystrophy). An important feature is subcutaneous endochondral ossification. There may also be end-organ resistance to other hormones, including thyroid-stimulating hormone and gonadotrophins. Paternal inheritance of the same mutation is char acterized by Albright hereditary osteodystrophy, but without the hormone resistance. This is often referred to as pseudopseudohyp oparathyroidism. Calcification in hyperphosphataemia Familial idiopathic hyperphosphataemia (MIM 211900) is a rare autosomal recessive disorder, with an increase in the maximal tubular resorption of phosphate and an inappropriate increase in the plasma 1,25(OH)2D concentration usually due to loss-of- function mutations in either FGF23 or GALNT3 (which is in volved in regulating the proteolytic breakdown of FGF23 by PHEX). Masses of ectopic mineral, which form around the joints from childhood (tumoural calcinosis), may discharge through the skin. Treatment with large oral doses of aluminium hydroxide or other phosphate-binding agents combined with a low phosphate diet can reduce the plasma phosphate level and the size of the deposits. Calcification in inherited hypophosphataemia A particular feature of X-linked inherited hypophosphataemia is the widespread calcification and ossification of ligaments and tendons at their insertions (enthesopathy) into the periosteum (so-called Sharpey's fibres). Calcification and new bone formation in the ligamenta flava may produce spinal cord compression, some times requiring surgical decompression in relatively early adult life. Chondrocalcinosis In chondrocalcinosis, crystals of calcium pyrophosphate dihydrate are deposited in the fibrocartilage of the knees, the triangular car tilage of the wrists, the symphysis pubis, and elsewhere. Calcium pyrophosphate dihydrate may also form as linear deposits in the hya line cartilage parallel to the subchondral bone. It is most commonly an age-related phenomenon but may also reflect an underlying metabolic disturbance, such as haemochromatosis (MIM 235200), hypophosphatasia, or hyperparathyroidism. Familial forms of chondrocalcinosis also exist; one florid polyarticular form presents with early onset destructive arthritis (MIM 118600) resulting from excessive accumulation of calcium pyrophosphate dihydrate in the extracellular tissues due to activating mutations in the ANKH gene, encoding a transmembrane transporter of inorganic pyro phosphate. Similar activating mutations have also been described in sporadic cases of pyrophosphate arthritis. Ectopic ossification Acquired ectopic ossification may occur at the site of injury, such as after hip replacement, or at a distance from it (e.g. following paraplegia), or in tumours and in a variety of other disorders. Fibrodysplasia (myositis) ossificans progressiva (MIM 135100) is a very rare autosomal dominant disorder caused by activating mutations in activin, a receptor for bone morphogenetic proteins (see next). Acquired ectopic ossification Post-traumatic ossification Local ossification can occur after total hip replacement. The quoted incidence varies widely, depending on the method used to detect it. It is more common in men than women and in certain individ uals (e.g. where ossification follows hip replacement on one side, it is likely to recur if the contralateral hip is replaced). The reason for this is unknown. The bone mainly forms in the hip abductors. Nonsteroidal anti-inflammatory drugs reduce the risk of heterotopic ossification following hip surgery and a small dose of radiotherapy may also delay ectopic ossification after total hip replacement without significantly increasing the subsequent risk of malignancy. Ossification after neurological injury Extensive myositis ossificans can also occur from one to four months after injuries to the head or spinal cord in muscles distant from the injury such as the major muscles of the thigh. Affected muscles be come swollen, red, and warm and, unless the cord lesion is complete, pain and tenderness also occur. At this time the differential diagnosis

20.1 Skeletal disorders—general approach and clinical conditions 4663 may include cellulitis, arthritis, and thrombophlebitis. Radiological calcification is initially absent (appearing at about 6 weeks or more after the injury), but an isotope bone scan will show increased up take before that. Later there is progressive mineralization, with the eventual appearance of organized bone. Because the bone affects the major periarticular muscles, it leads to joint fixation, particularly of the hips. The plasma alkaline phosphatase level may be increased in the early stages. Attempted surgical removal of ectopic bone is technically difficult and produces little increase in movement. The ectopic bone recurs, especially if it is removed too early. Oral disodium etidronate at full dose (20 mg/kg body weight per day) may delay the onset of min eralization but only while it is being given. Likewise, the prevention of further ectopic bone formation after its removal may be delayed by nonsteroidal anti-inflammatory drugs or radiotherapy, which should be commenced as soon as possible. Myositis ossificans can also occur after other neurological dis eases, such as poliomyelitis and meningitis, and also after prolonged coma. The reason why ectopic ossification occurs after head injury is unknown; interestingly, head injury is associated with an in creased rate of fracture healing and excessive callus formation. In such patients, the serum contains increased mitogenic activity for osteoblast-like cells; the source of this activity is unknown, but there could be an increase in bone morphogenetic proteins. Ossification can coexist with calcification and extensive ossifi cation of the spinal ligaments in hypoparathyroidism can lead to progressive stiffness. The enthesopathy in inherited hypophos phataemia (vitamin D-resistant rickets) is a form of ectopic ossi fication. Ossification of the posterior longitudinal spinal ligament and sternoclavicular hyperostosis is particularly described in Japan. Ligamentous ossification has been noted in patients treated with vitamin A analogues, such as etretinate, for dermatological dis orders. Finally, ectopic bone may complicate varicose veins, chronic venous insufficiency, and surgical incisions. Inherited ectopic ossification The inherited causes of ectopic ossification (Table 20.1.16) are rare. In two disorders, fibrodysplasia ossificans progressiva and pro gressive osseous heteroplasia, ossification is a major and disabling feature. Fibrodysplasia ossificans progressiva Fibrodysplasia ossificans progressiva (MIM 135100) is rare, with an incidence of between one and two per million. Since patients rarely reproduce, most cases represent new mutations; activating muta tions in the activin receptor gene, ACVR1, encoding a BMP type 1 receptor are responsible. This discovery is clearly consistent with the known abnormality of ossification in the condition, but it is not clear why this should occur in discrete episodes. Diagnosis depends on the combination of progressive myositis, leading to ossifica tion in the major skeletal muscles and characteristic bony skeletal abnormalities. Pathophysiology Initially there is oedema and cellular infiltration throughout the muscle, with myofibrillar breakdown. Later endochondral ossifica tion leads to mature bone, within which is haemopoietic marrow. Information on the earliest histological appearances is scanty because biopsies are often taken after the acute phase of myositis; for this reason, there is still doubt about the primary lesion. Ectopic ossification occurs when mesenchymal or stromal cells take on the behaviour of osteoblasts. This form of cell differentiation could re sult from an increase in bone-inducing substances or (for unknown reasons) a change in stromal-cell expression. Although the timing of myositis differs widely from one affected patient to another, there is a specific order in which they are affected, from the upper paraspinal to the lower, and from the centre to the periphery. Clinical features Episodes of myositis are the nonskeletal hallmark of this disease. Typically, the affected muscle becomes swollen and hard, some times following injury; after a week or two these features subside, but the apparent improvement is followed in a month or so by os sification within the muscle and progressive joint fixation. Myositis usually begins in the upper paraspinal muscles. By late childhood or adolescence, ossification will have occurred within the

muscles around the shoulders, hips, and knees to fix these joints and to complete the disability (Fig. 20.1.27). The large, striated muscles are affected; ossification does not involve the small muscles of the hands and feet, the diaphragm, or the cardiac or smooth muscles. Ossification in the muscles around the jaw may fix it almost com pletely. Although the overall sequence of ossification is character istic from large upper paraspinal to lower limb muscles, it varies considerably in its rate. The diagnostic skeletal abnormalities affect the big toes (Fig. 20.1.28), the cervical spine (Fig. 20.1.29), and, to a lesser ex tent, the thumbs. The big toes are always abnormal; in the infant, bony changes produce bilateral hallux valgus, and, in the adult, fu sion produces a short fixed monophalangic big toe. In the cervical spine, the vertebral bodies are small and the laminae large. Both are variably fused; this fusion is independent of nearby ossifica tion of the cervical muscles. The appearance of the cervical spine represents a failure of development of the zygapophyseal joints (cf. the monophalangeal great toe) rather than fusion resulting from new bone deposition. Reduced movements of the cervical Fig. 20.1.27 Fibrodysplasia ossificans progressiva. Widespread ectopic ossification of the muscles around the thorax. The chest is completely fixed but the diaphragm is unaffected.

SECTION 20 Disorders of the skeleton 4664 spine may be striking in infants in the absence of any ectopic ossi fication. Finally, the femoral necks are short and wide and there are exostoses from the metaphyses. Differential diagnosis Bilateral hallux valgus in the neonate strongly suggests the possi bility of fibrodysplasia ossificans progressiva. In childhood, myositis may be mistaken for soft-tissue sarcoma and a biopsy showing oe dema and increased cellularity may support this or suggest an ag gressive fibromatosis. Painful swelling of the masticatory muscles simulates mumps, while progressive stiffness with a fixed abnormal neck suggests the Klippel–Feil syndrome or childhood rheumatoid arthritis. Management Since the onset of myositis is quite unpredictable, it is almost im possible to assess the effect of any form of therapy. Corticosteroids 2 7 8 9 18 (a) (b) 4 3 3 2 1 2 8 1 Fig. 20.1.28 Fibrodysplasia ossificans progressiva. (a) Abnormal first toes and (b) appearances in nine patients of different ages, traced from X-rays. The abnormal phalanges of the first toes, present at birth, later fuse into one unusual phalanx. Age in years are shown beneath each tracing. Fig. 20.1.29 Fibrodysplasia ossificans progressiva. Complete fusion of the posterior elements of the cervical spine. The vertebral bodies appear relatively small.

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