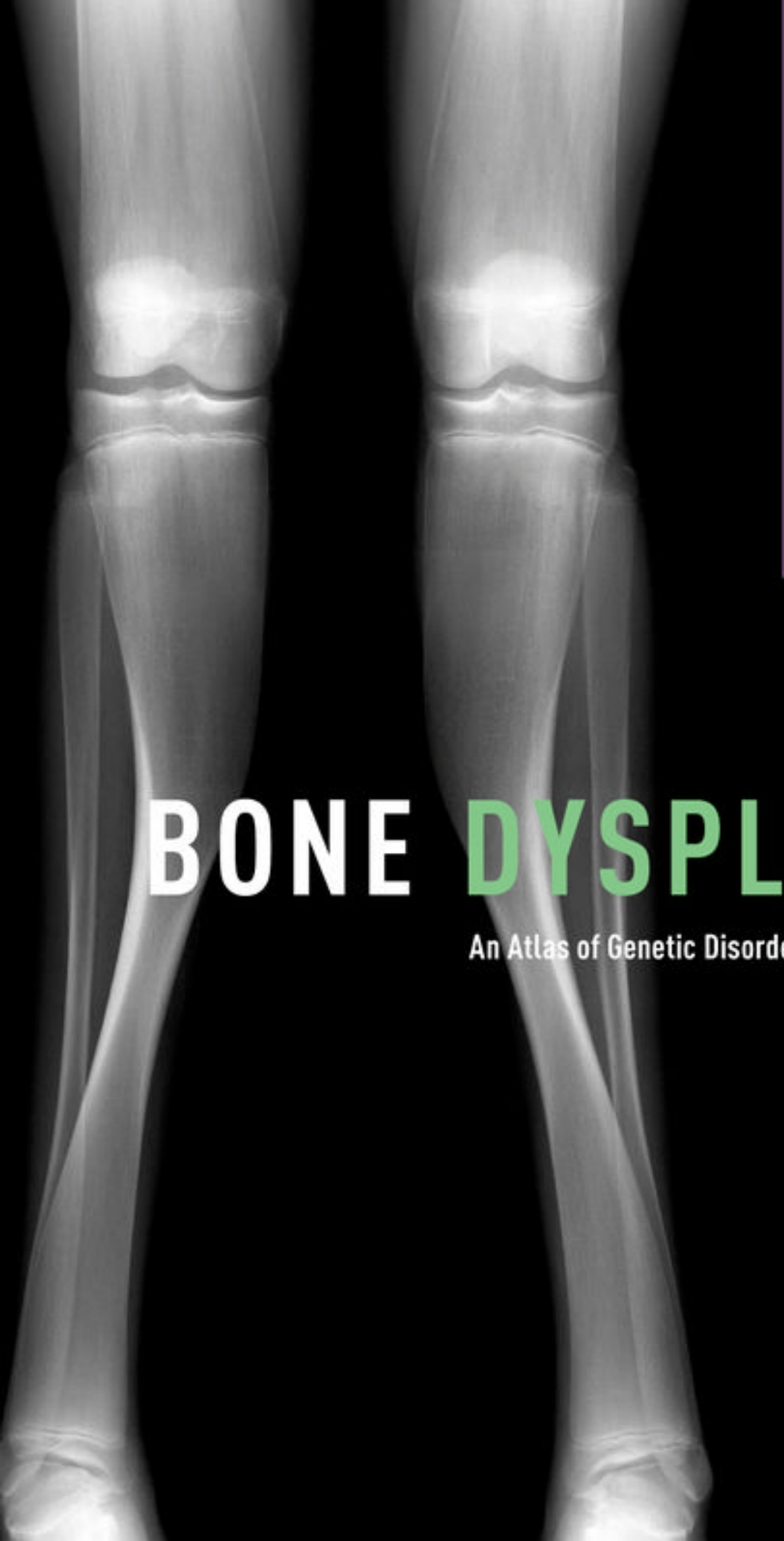

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BONE DYSPLASIAS

An Atlas of Genetic Disorders of Skeletal Development

FOURTH EDITION

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FOREWORD

Ten years ago, Victor A. McKusick, renowned pioneer of North American medical genetics, encyclopedist, cardiologist, and expert at the human disorders of connective tissue (especially the Marfan syndrome) wrote the preface for the second edition of the magisterial Spranger et al. *Atlas on Bone Dysplasias*.

It was McKusick who in 1968 initiated the annual Conferences on the Clinical Delineation of Birth Defects, the first five at John Hopkins Hospital. In 1968, two days were devoted to the skeletal dysplasias with input and discussion by Maurice Lamy, Jürgen W. Spranger, David Rimoin, Judith G. Hall, John Dorst, Leonard O. Langer, and Hans Zellweger, among others. Centers of excellence were flourishing or being established in Los Angeles, Seattle—later Vancouver, Baltimore, Kiel, Paris, and Madison (briefly with Jürgen Spranger, Len Langer, Enid F. Gilbert, and myself "under one roof"). Extremely active working relationships were established between these and other European experts including Maurice Lamy, Pierre Maroteaux (Paris), Andres Giedion (Zürich), K. Kozlowski (Australia), G. Camera (Italy), Jiri Kučera (Prague), and many others. After the thalidomide disaster, Widukind Lenz (Münster) became an outstanding authority on the limb dysostoses.

Sadly, Dr. McKusick did not live to write a revision of his preface for this edition.

Early efforts in this field were primarily nosological with *delineation* of an ever-increasing number of entities, subsequently lumped with or split from others, few remaining as originally set out (achondroplasia!). *Definition* of skeletal dysplasias as *causal* entities was then, and to some extent still is, based on family structure (e.g., the spectacular pedigree of the first family segregating for the Nievergelt syndrome), presence or absence of parental consanguinity, clinical manifestations, and paternal age (Penrose, achondroplasia).

As noted by McKusick, these efforts culminated in several early monographs, for example, by Mørch (1941) and A. Birch-Jensen (1949) on defects of upper limbs in Copenhagen, Hobaek (Norway, 1961), Lamy and Maroteaux (Paris), Rubin (United States, 1964), and Grebe (1964); other earlier contributors were members of the Galton Laboratory, also R.R. Gates in London (1946), and Hanhart in Switzerland. Refinements of radiologic technique, bone histology, and histochemistry and collagen chemistry led to a gradual improvement of nosology and a deeper understanding of pathogenesis.

While some (Müller-Hill, 1984) have expressed concerns about the provenance of some of Grebe's material, others have, unwittingly, profited from collaboration with Grebe (Grebe and Wiedemann 1953). Wiedemann was a pediatrician with a strong interest in skeletal dysplasias and other human constitutional anomalies. Wiedemann's small text on the great constitutional anomalies of the skeleton (1960) appeared while Jürgen Spranger was house officer in Wiedemann's department in Kiel (1961–1974).

At a meeting of the European Society of Radiology in Paris in 1968, a group of experts considered nosology in the skeletal dysplasias with Spranger making the fundamental biological distinction between skeletal *dysplasia* and *dysostoses*. The first edition of the Langer, Spranger, and Wiedemann book was a milestone in this field combining clinical, radiologic, genetic, and histologic advances on the eve of a major molecular reshaping of our understanding based, in part, on Spranger's important concept of the *families* of skeletal dysplasias identified on the basis of roentgenological and pathogenetic criteria (think: type II collagenopathies, i.e., *COL2A1* disorders: achondrogenesis type 2, platyspondylic lethal dysplasia [Torrance] in humans and mice, hypochondrogenesis, spondyloepiphyseal dysplasia, spondyloepimetaphyseal dysplasia [SEMD], SEMD Strudwick type, Kniest dysplasia, spondyloperipheral dysplasia, Stickler syndrome type 1, vitreoretinopathy and phalangeal epiphyseal dysplasia, and so on.)

The present group of collaborators on this edition of *Bone Dysplasias: An Atlas of Genetic Disorders of Skeletal Developmen*t, all have decades of experience in this field. Besides Jürgen Spranger (pediatrician, geneticist, and skeletal radiologist), there is Paula W. Brill (New York), whose interest in the field was inspired by Leonard O. Langer and John Dorst, and who collaborated on the second and third editions. Dr. Brill is currently Professor Emerita of Radiology at Weill Cornell Medical College, where she previously served as chief of Pediatric Radiology. Gen Nishimura (Tokyo) claims he was drawn to the field by an earlier version of this book; he is widely regarded as one of the world's finest diagnosticians of skeletal dysplasias; as head of Pediatric Imaging at Tokyo's Metropolitan

Children's Medical Center he contributed substantially to this revision, particularly the dysostoses.

Sheila Unger, who trained with the late David Rimoin, and Andrea Superti-Furga, who learned from Andres Giedion and Jürgen Spranger, are well-known to all readers of the *American Journal of Medical Genetics* as compilers of the *Nomenclature of Skeletal Dysplasias*, now incorporated into this revision, complementing each other as pediatricians and medical geneticists with an emphasis on skeletal development, as well as the organizers of the annual Skeletal Dysplasia Course that has attracted so many young talents to this field.

Palaeontologists working with an organism's best preserved tissues, bone and teeth, are to an ever-increasing measure able to infer age, growth, and function from direct and indirect evidence, even from material that may be as old as the Devonian, some 360 million years ago. Form, growth, and function are more easily inferred in a recently stillborn fetus (e.g., with campomelic "dysplasia") on the basis of prenatal ultrasonography, physical and radiological examination, histological studies of gonads, examination of growth plate and brain, as well as structure of the dominantly inherited *SOX9* gene mutations in fetus and parents. If neither parent has the infant's mutation, is the recurrence risk as low as the mutation rate at the gene? No, because of germinal mosaicism. Thus, dear reader, please note the word "genetic" in the title of this book.

But the greatest challenges are presented to the clinician caring for a child with a previously apparently undescribed skeletal dysplasia (there are still many, but check Spranger et al., 2012 first!), but nowadays perhaps exome sequencing may uncover a phylogenetically ancient gene that must have been present in LUCA (i.e., the ***l***ast ***u***niversal ***c***ommon ***a***ncestor of the archaea, bacteria, and eukaryotes) and may provide a homologous condition ("animal model") in a more or less closely related species. But the greatest clinical skill is required to perform phenotype analysis in such a child so astutely as to infer prognosis and required care. And, toward that end, this revision of the Langer, Spranger, and Wiedemann classic will be enormously useful.

John M. Opitz
University of Utah, Salt Lake City
April 2012

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The Children's Hospital of the University of Freiburg, Germany, now houses the Mainz Bone Dysplasia Registry containing much of the material used in this book. Bernhard Zabel, Ekkehard Lausch, and their staff in Freiburg provided the support and friendship needed to gather the experience and compose a new edition. The authors are part of an international skeletal dysplasia network (ESDN) that assists colleagues in need of a diagnosis. Part of the new material stems from ESDN and is used with permission of the submitting colleagues. Other cases were shown to the authors on a personal basis and are part of extensive electronic databases created by GN in Tokyo and ASF in Lausanne.

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INTRODUCTION

HISTORICAL PERSPECTIVE

SHORT STATURE, DWARFS, LILLIPUTIANS, AND SUPERSTITIOUS BELIEFS

Disorders of bone are part of humankind's genetic burden. Their existence in prehistory is documented by archaeological findings. A large number of paintings, engravings, and sculptures depict short-statured individuals, often in great detail (Enderle et al., 1994). Individuals with constitutional diseases of the skeleton attract attention because of their smaller size, because of deformities, and/or because of the disproportion between body parts. Individuals with achondroplasia, a common skeletal short-stature condition, have short arms and legs, a head that is usually larger than normal, and a typical facial appearance with a prominent forehead and a sunken nasal bridge. They are usually healthy (at least as children and young adults) and are said to be witty. Although there are no scientific data to confirm the latter claim, their personal perspective on life may lead to particular insights. Perhaps for these reasons, individuals with achondroplasia (along with individuals with other deformities) have often played special social roles in human societies, from being members of royal courts to participating in circus shows or other public entertainment. Short-statured individuals have also fueled the fantasy of writers, and indirectly of the public, like in Jonathan Swift's *Gulliver's Travels*. The misconception of a separate race (such that of the Lilliputians) was frequent in the past and still lingers even in the present. Around the turn of the twentieth century, in Paris, there existed an institution called *le jardin d'acclimatation* where short-statured individuals (with diverse diagnoses ranging from achondroplasia to growth hormone deficiency) were offered a place to live; perhaps this was an act of charity but certainly also one of segregation (Bloch, 1909). The halo around individuals with short stature, deformity, or disproportion has thus stood in the way of a scientific or medical approach to the definition of their conditions, so much so that still, in 1886, when the French physician Joseph Marie Jules Parrot described a short-limbed patient and coined the name *achondroplasie*, he believed that achondroplasia was a manifestation of rickets and that rickets itself was a consequence of hereditary syphilis (Parrot, 1886). As late as 1912, the Dutch orthopedist Murk Jansen supported the concept that achondroplasia was caused by "amnion-pressure" (Jansen, 1912). Another popular belief was that achondroplasia was caused by "weak semen" (this latter belief may have been prompted by the observation that achondroplasia individuals are often the youngest siblings, in accordance with the paternal age effect on *de novo FGFR3* mutations). The strong aura surrounding little people, dwarfs, or Lilliputians is surprising and in contrast to the notion that the genetic difference between an individual with achondroplasia (or pseudoachondroplasia, or spondylo-epiphyseal dysplasia congenita) and a normal-stature individual is a single nucleotide at heterozygosity.

Although medical descriptions of rare cases can be found in the seventeenth and eighteenth centuries, it was only in the nineteenth century that physicians and scientists began to approach affected individuals more systematically and to describe the aberrant growth pattern by observation of anatomy and pathology. In 1878, the French physician Parrot described an individual with short-limb dwarfism and coined the name *achondroplasia*, but in 1886, in his treatise on child diseases, he expressed the belief that achondroplasia was a manifestation of congenital syphilis (Parrot, 1878, 1886). In 1892, the German pathologist Eduard Kaufmann studied the macroscopy and pathology of a series of 13 stillborns with what was then called "fetal rickets" and concluded that there were at least three different patterns of anatomical changes; this was the first recognition of heterogeneity and attempt at classification (Kaufmann, 1892). Regarding achondroplasia, it is interesting to note that even as late as in 1912, the Danish physician Murk Jansen (who also described the metaphyseal dysplasia that still bears his name) supported the view that it was due to intrauterine fetal restriction: reduced growth as a consequence of "external pressure" applied to the fetus (Jansen, 1912).

Around the beginning of the twentieth century, the use of x-rays to investigate medical conditions, particularly those affecting the skeleton, opened the way to the recognition of several "new" conditions as defined by their peculiar, and sometimes specific, radiographic appearance. Among these conditions (the list is not exhaustive by far) are osteopetrosis (Albers-Schönberg, 1904), melorheostosis (Léri & Ioanni, 1922), diaphyseal dysplasia (Camurati, 1922; Engelmann, 1929), dyschondrosteosis (Leri & Weill, 1929), osteopoikilosis (Ledoux-Lebard et al., 1916), Pyle disease (Cohn, 1933; Pyle, 1931), infantile hyperostosis (Caffey, 1946), and many others. In 1917, Hunter described two brothers with a "rare disease" affecting the skeleton (now known as mucopolysaccharidosis type 2), and in 1919 Gertrud Hurler described two unrelated patients with similar features including corneal clouding and mental retardation (later defined as mucopolysaccharidosis type I). In 1929, Luis Morquio reported on a siblingship with a form of

"familial osseous dystrophy" characterized by platyspondyly and short trunk (Morquio, 1929); the report was followed by a large number of related observations, and "Morquio disease" (now mucopolysaccharidosis type IV) became the prototypic form of short-trunk dwarfism. Two distinct forms of "multiple epiphyseal dysplasia" were described in 1937 (Ribbing, 1937) and in 1947 (Fairbanks, 1947); we know today that at least six different genetic forms exist. Identification and delineation of new conditions based on specific radiographic signs, often in combination with specific clinical findings, flourished throughout the twentieth century and still today constitutes the basis for the identification of the pathogenic gene(s).

CHROMOSOMES, LYSOSOMES, AND ENZYMES

The years following World War II saw a rapid advancement of biochemistry and genetics. Following the implementation of rickets prophylaxis with vitamin D, hypophosphatasia was recognized as a "genetic form of rickets" associated with low alkaline phosphatase activity (Rathbun, 1948). In the 1950s, a new cellular organelle was identified, the lysosome, that contained a number of different hydrolytic enzymes (de Duve, 1959; de Duve et al., 1955). This led to the discovery that some of the previously identified clinical syndromes were caused by genetic deficiencies of individual enzymes. In 1952, Brante reported evidence of mucopolysaccharide material in "gargoylism," and by 1957, experimental evidence established that Hurler disease was characterized by impaired degradation of mucopolysaccharides (Brante, 1952; Dorfman & Lorincz, 1957). Biochemistry had joined the field of genetic skeletal diseases for good. In the late 1950s, the correct number of chromosomes in humans was finally determined; this triggered the recognition of the aneuploidies (trisomies 21, 13, and 18, monosomy X, and others) in rapid sequence. With chromosomes and enzymes, laboratory tests could help medical geneticists and pediatricians confirm a diagnosis and explore the phenotypic variability of the individual disorders. Thanks to these advancements, the field of medical genetics gained attention and importance.

THE GOLDEN 1960S

The discovery of chromosomal and biochemical bases for their clinical observations must have reassured pediatricians and geneticists that what they were observing was real, and this freed their minds. It was no longer necessary to be conservative by forcing different observations into one category; whereas the 1950s were still hesitant and saw new entities such as "recessive achondroplasia" and "pseudoachondroplasia," the 1960s saw the full delineation of achondroplasia (Maroteaux & Lamy, 1964; Langer et al., 1967) and flourished with newly recognized entities that were given new names, such as diastrophic dysplasia (Lamy et al., 1960), familial metaphyseal dysostosis (Spahr et al., 1961), cartilage-hair hypoplasia (McKusick et al., 1965), spondylo-epiphyseal dysplasia congenita (Spranger & Wiedemann, 1966), tricho-rhino-phalangeal syndrome (Giedion, 1966), metatropic dysplasia (Maroteaux et al., 1966), spondylometaphyseal dysplasia (Kozlowski, Maroteaux, & Spranger, 1967), and more (the list is arbitrary and not exhaustive). This freedom to recognize genetic disorders in the 1960s culminated in the Birth Defects Conferences, a first series of which was organized between 1969 and 1971 at the Johns Hopkins Hospital; the proceedings, two of which are dedicated to dysostoses and skeletal dysplasias, are still a pleasure to read because of the richness in new observations as well as the freshness of the presentations and discussions.

ATLASES AND CLASSIFICATIONS

In 1951, the British orthopedic surgeon Thomas Fairbank published an *Atlas of Generalized Affections of the Skeleton* (Fairbank, 1951). Sir Fairbank was interested in genetic bone disorders; in 1947, he had described a form of "dysplasia epiphysealis multiplex" (Fairbank, 1947). Although rudimentary by today's standards, this work was a milestone in the development of the field of constitutional disorders of bone. In 1961, Pierre Maroteaux and his mentor Maurice Lamy published a monography on "genotypic chondrodystrophies" (Maroteaux & Lamy, 1961). Unlike the Fairbank atlas, this work did not discuss all genetic skeletal conditions but was focused on the "chondrodysplasias." The Maroteaux and Lamy classification included eight different groups of bone dysplasias. The literature index of the monograph lists an impressive number of case reports from the nineteenth century to the 1950s, demonstrating the abundance of case reports but also the lack of a systematic approach. In 1964, the radiologist Philip Rubin from Rochester University published his *Dynamic Classification of Bone Dysplasias* (Rubin, 1964). Although some of the diagnoses have changed (e.g., rhizomelic chondrodysplasia punctata was called "congenital multiple epiphyseal dysplasia"), the book was remarkable because it classified disorders based on the "dynamic pathogenesis" with speculations on what physiologic process on bone growth and remodeling was affected. Extensive correlations were made to what was known at the time about bone modeling. Rubin modestly wrote that the success of his book would be measured paradoxically by the rapidity in which its content would become outdated. In 1974, Jürgen Spranger, Len Langer, and Hans-Rudolph Wiedemann published their *Bone Dysplasias: Atlas of Constitutional Disorders of Skeletal Development*, an extensive atlas that was based on the correlation of radiographic, clinical, and genetic data to delineate conditions (Spranger et al., 1974); in 1975, the radiologists

Hooshang Taybi and Ralph Lachman published their *Radiology of Syndromes and Skeletal Dysplasias* (Taybi and Lachman, 1975). Both the Spranger and the Taybi-Lachman books have been revised periodically and are in their fourth and fifth editions, respectively.

NOMENCLATURE AND NOSOLOGY

Contemporary to the description of well-defined disorders in the late 1950s and 1960s, it became clear that much confusion had been caused by the inhomogeneous denomination of entities. Clinically different disorders had been reported under the same name (e.g., "chondrodystrophy"), and individual disorders had been reported under different names. In 1969, in the wake of the Birth Defects Conference on Skeletal Dysplasias, a group of experts (mainly radiologists) convened in Paris in 1970 to prepare an "International Nomenclature of Constitutional Diseases of Bones," a list of conditions grouped by their main radiographic or clinical features. This "Paris nomenclature," compiled by one of us (JS), was so welcome that it was published, with minor variations and comments, in at least five different journals (e.g., Kozlowski et al., 1969). The 1970 nomenclature underwent revisions in 1977, 1983, 1992, 1997, 2001, 2005, 2010, and 2015 (see Bonafe et al., 2015; Superti-Furga et al., 2007; Warman et al., 2011). Following the foundation of the International Society for Skeletal Dysplasias (ISDS) in 1999, the revisions were prepared by an ad hoc group within the ISDS; the term *nomenclature* has been replaced with *nosology*. The 2015 revision contains over 450 distinct entities. Notably, recent revisions of the *Nosology* have included more dysostoses to reflect the fact that there is often a common genetic basis, that elements of dysostosis and dysplasia may occur in the same condition, and that patients with dysplasias or dysostoses are often seen in the same clinic. The *Nosology* should help in the delineation of new conditions by providing a list of those conditions that have been recognized as distinct entities on clinical, radiographic, and genetic grounds. Notwithstanding the many ties of friendship between the *Nosology* experts and the late Victor A. McKusick and the subsequent curators of the MIM catalogue, there are inconsistencies between the *Nosology* and OMIM due to the fact that while OMIM grows rather appositionally, the *Nosology* committee does more pruning of obsolete entities.

Molecular data and the clinical-radiographic classifications: There have been times when skeletal dysplasia experts suffered from a dubious reputation. For many colleagues, it seemed hard to believe that there was a rationale for preparing long lists of very rare conditions with Greek-derived names. Yet, cell biology, biochemistry, and molecular genetics have confirmed the work of the clinical and radiographic "stamp collectors": there is an extraordinary variety of molecular mechanisms at the basis of skeletal conditions. Morphogenesis, development, growth, and homeostasis of the skeleton and its over 200 distinct elements is a complex mechanism with many levels of integration and control, and because of our ability to recognize morphologic changes in children and adults, as well as in bones on radiographs, the skeleton is a sensitive reporter. Thus, whereas biochemical bases of genetic bone disease (such as the many forms of genetic rickets or the lysosomal storage disorders) were identified in the 1960s, the 1970s and early 1980s saw the first evidence of "molecular pathology" with the collagens (collagen 1 and osteogenesis imperfecta, collagen 3 and the Ehlers-Danlos syndrome type IV, and collagen 2 and chondrodysplasias), and the late 1980s (thanks to the possibility of molecular cloning and then, particularly, the polymerase chain reaction technique) saw the underlying gene mutations unravel. In 1983, a multi-exon deletion in *COL1A1* was identified in lethal osteogenesis imperfecta (Chu et al., 1983); in 1988, a multi-exon deletion in *COL3A1* was identified in Ehlers-Danlos syndrome type IV (Superti-Furga et al., 1988) (not a skeletal condition, but the "collagen field" was united at that time); and in 1989, a single-exon deletion was identified in a family segregating congenital spondylo-epiphyseal dysplasia (Lee et al., 1989). At the time, exon deletions were easier to identify by southern blotting, while single nucleotide variations necessitated extensive cloning and sequencing. In 1986, a heterozygous single nucleotide substitution in *COL1A1* was identified as the cause of lethal osteogenesis imperfecta (Cohn et al., 1986); rapidly, glycine substitutions in the triple helical domain of collagen type 1 were established as the main cause of severe osteogenesis imperfecta. In 1988, a homozygous point mutation in the *TNSALP* gene was identified as the cause of lethal hypophosphatasia (Weiss et al., 1988). The 1990s surprised us with the notion that the genes at the basis of skeletal diseases were not only structural proteins or enzymes but frequently genes involved in signaling pathways and in transcription regulation, such as *FGFR3* or *CBFA1/RUNX2* (Hermanns et al., 2001). A first molecular-pathogenetic classification was drafted (Superti-Furga et al., 2001). Ever since, there has been a constant flow of new gene-phenotype identification; while a small number of genes may account for a large proportion of individuals with genetic skeletal conditions, rarer associations are still being found on a monthly basis. As an example, the majority of cases of osteogenesis imperfecta are determined by mutations in *COL1A1* and *COL1A2* but no less than 20 other genes can produce a brittle bone phenotype, although the number of cases is much smaller. In general, molecular data have determined some degree of "lumping," that is, the regrouping of conditions sharing a similar pathogenesis; but, on the other hand, the data continue to reveal extensive heterogeneity and to identify novel conditions, leading to "splitting" and thus to a steady increase in the number of conditions listed in the Nosology.

Genetic disorders of bone and their contributions to genetics and medicine: In many ways, the skeletal field has had a pioneering role in medical genetics by contributing fundamental concepts. Among these are the observation that a single nucleotide substitution at the heterozygous state may result in a lethal phenotype (lethal osteogenesis imperfecta, lethal collagen 2 dysplasias) (Cohn et al., 1986); the concept of "protein suicide," precursor to the concept of "dominant negative" (Prockop 1984); the concept of functional topology of a molecule (different mutations in *COL1A1* giving different phenotypes because they affect different functional domains); the formulation of the concept of disease families with mild to severe manifestation arising from the same gene (collagen 1, collagen 2, *COMP,* and *FGFR3*) (Spranger, 1988); the observation of gonadal mosaicism as the explanation of affected siblings born to clinically unaffected parents (again *COL1A1* mutations) (Cohn et al., 1990); the discovery of highly recurrent mutations such as the "achondroplasia mutation" G380R in *FGFR3* that occurs at the nucleotide with the highest mutation rate known in the human genome (Rousseau et al., 1994; Shiang et al., 1994); and the demonstration that they occur almost exclusively of paternally derived alleles, highlighting the paternal age effect (Wilkin et al., 1998). These concepts that are firmly accepted today were pioneered by the "bone dysplasia" field.

The changing diagnostic scenario: The approach to diagnosis does in part reflect the history of the delineation of disorders. Thus the diagnosis of constitutional skeletal disorders still relies mainly on the meticulous analysis of skeletal radiographs. Correlation with the clinical data (growth curve, clinical findings, history of fractures or pain, other specific features) is essential. Biochemical evidence may be diagnostic (e.g., calcium or phosphate imbalance, or reduced activity of a specific enzyme). Molecular genetic confirmation has long been the last step in the process. The power of massive parallel sequencing and its increasing affordability has changed this scenario drastically. The analysis of gene panels (e.g., a "dysplasia panel," "bone fragility panel," or "chondrodysplasia punctata panel") has already replaced single-gene analysis in most instances. Even broader approaches, such as that of exome sequencing, are already being used as first-line tests. With further reduction in sequencing costs, a "genotype first, phenotype later" approach may be implemented soon. Is the time of careful analysis of clinical features and radiographs lost forever? Probably not, but the approach will be changed. The so-called reverse phenotyping (i.e., to verify whether the patient's features [clinical, radiographic, or biochemical] do fit with a genotype identified by unbiased sequencing) needs as strong an expertise as the a priori generation of a diagnostic hypothesis. The findings from massive sequencing will confront the genetic physician with "common" genetic disorders but also with rare, ultra-rare, or even private conditions; no literature will be available (at least not for some time) for guidance. Sensitive and accurate sequencing, large databases, and precise bioinformatics prediction tools will be needed as much as clinical observation skills and acumen.

Old and novel therapeutic approaches: Whereas the exploration of the pathogenetic bases of skeletal dysplasias has been fascinating, the therapeutic fallout has followed at a much slower pace. Well-structured observational studies, providing much needed information on the natural history of each disorder and its complications, are available only for the more common conditions. Because surgery is so difficult to standardize, there is no high-level evidence on the risk and benefit of most surgical interventions in individuals with skeletal dysplasias. For some conditions, knowledge of the molecular pathogenesis has resulted in the development of specific medical interventions. Several of the lysosomal storage diseases are now amenable to enzyme replacement, substrate reduction, or both (although the skeletal system is less likely to benefit from these treatments than other organs). Enzyme replacement therapy in hypophosphatasia is highly effective and beneficial (Scott, 2016). Several distinct approaches are being studied to counteract increased *FGFR3* signaling in achondroplasia and related conditions (e.g., guanyl cyclase activation by a long-lived C-Natriuretic Peptide analog [Lorget, 2012, #63]), modulation of *FGF* signaling with a soluble "decoy" *FGFR3* receptor (Garcia et al., 2013), and specific inhibitors to inhibit the tyrosine kinase activity of *FGFR3* (Komla-Ebri et al., 2016)). In osteogenesis imperfecta and other conditions with fragile bones, the use of bisphosphonates, which is moderately effective, should soon be accompanied, or replaced, by approaches that target the overall bone architecture (such as sclerostin antibodies; Simsek Kiper et al., 2016; Jacobsen, 2017).

Our evolution in understanding the pathogenesis of the skeletal dysplasias has undergone rapid changes in the past few decades. These studies have unearthed key concepts in genetics. They have also demonstrated the importance of properly naming a condition in order for it to be recognized by scientists, doctors, and patient advocacy groups. We are cautiously optimistic that these steps along a long and winding road will lead to therapeutic advances for our patients.

UNDERSTANDING DYSPLASIAS AND DYSOSTOSES THROUGH THE COMBINATION OF CLINICAL, PATHOGENETIC, AND MOLECULAR CRITERIA

The conditions included in the *Nosology* (many of which are described in this book) are clinically and molecularly heterogeneous. They include dysplasias, dysostoses, osteolyses, and a few disruptions. Their distinction is essential, both from a biological and a practical viewpoint. The

original version of the *Paris Nomenclature for Constitutional Disorders of Bone* published in 1970 defined dysostoses as "malformations of individual bone, singly or in combination" and osteochondrodysplasias as "abnormalities of cartilage and/or bone growth and development." This essentially clinical definition predated the more general distinction, drawn by an international working group on concepts and terms of errors of morphogenesis, between malformations and dysplasias (Spranger et al., 1982). Here, a malformation was defined as a "morphologic defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process." Thus, the terms *dysostosis* and *skeletal malformation* name the same aberrant developmental category. It was also noted that a malformation could result from the *extrinsic* disturbance of normal development. Such a "secondary" malformation resulting from "the extrinsic breakdown of, or an interference with, an originally normal developmental process" was called a *disruption*. A dysplasia was defined as the "abnormal organization of cells into tissue(s) and its morphologic result(s)." Applying these broader concepts to the skeletal system, the constitutional errors of bone development can be defined as follows:

- *Dysostoses* are malformations of single skeletal elements, alone or in combination.
- *Disruptions* are malformations of bones secondary to nonskeletal causes.
- *Skeletal dysplasias* are developmental disorders of chondroosseous tissue.
- *Osteolyses* are regressive disorders which permanently reabsorb and dissolve preexisting bone.

Advances in developmental genetics now provide the biologic bases for this distinction.

FORMATION OF SKELETAL ELEMENTS

Bone formation starts with the patterning of cells. Transcription factors are produced that regulate the expression of genes. Families of genes cooperate to provide programs that govern the patterning process. Signaling proteins and other substances, such as retinoic acid, are produced that diffuse from cell to cell and form gradients that convey positional information through receptors. Thus embryonic cells are instructed about their relative position and influenced to differentiate with regard to that position. Together, these orchestrated signal loops involving transcription factors and signaling molecules regulate the proliferation, migration (including mesenchymal condensation), differentiation, in some cases the apoptosis, and, finally, the function of individual cells. During organogenesis—that is, during the first eight weeks of human gestation when cells segregate into cell groups and tissues into primordia that will form future organs—transcription factors and signaling pathways are instrumental in the formation of single organs and specific tissues. Examples are *WNT7a* and *TBX15*, deficiency of which leads to severe dysostosis of the extremities or of the shoulder and pelvis, respectively. These genes are responsible for the "blueprint" of the skeleton: proper formation, size, and position of one or more skeletal elements. Other signaling factors, like the fibroblast growth factor receptors, are activated at subsequent stages of embryogenesis and continue to be expressed in postnatal life. A third group of signaling factors is active from the period of organogenesis to adult life. To this group of factors belong the runt transcription factor, *RUNX2*, and the cartilage-derived morphogenic protein I, *CDMP1* (also called *GDF5*). Finally, many genes are not essential for the patterning and development of the blueprint of skeletal elements but are crucial to the differentiation and function of cartilage cells or bone cells, or to the growth and development of cartilage and bone as tissues. From these differences in the time and duration of expression, several axioms can be deduced and applied to skeletal development.

DYSOSTOSES

Many transcription factors are expressed only for a limited period of time during embryogenesis. Genes are turned on and off. In limb development, for instance, *3'* HOX genes are expressed early in development controlling anterior regions of the limb. *5' HOX* genes are expressed later and control more posterior regions. A series of genes are responsible for embryonic segmentation and for the development of vertebrae and ribs. Defects of transcription factors or of signaling factors, which are only transiently expressed during early embryogenesis, result in finite organ defects (i.e., in malformations). Dysostoses are malformations or, in other words, manifestations of defective skeletal organogenesis (Figure 1.1). They are finite, because of the transient nature of the defective process. They may occur singly, in combination, or as part of pleiotropic disorders if the controlling gene is expressed in many organ systems. Examples of known signaling defects leading to dysostoses are summarized in Table 1.1. Clinically, dysostotic lesions may be asymmetrically distributed, notably in the disruptive forms (see later discussion). The chondroosseous histology is normal. Dwarfism is not a primary manifestation unless bones of the vertical body axis or bones of the limbs are defective or missing.

DISRUPTIONS

Similarly to transiently expressed transcription factors or signaling genes, toxic substances or infectious agents may act on the embryo for limited periods of time. They produce secondary malformations, not dysplasias. Thalidomide and rubella embryopathies are prime examples. Mechanical factors may also result in disruptions, the most prominent

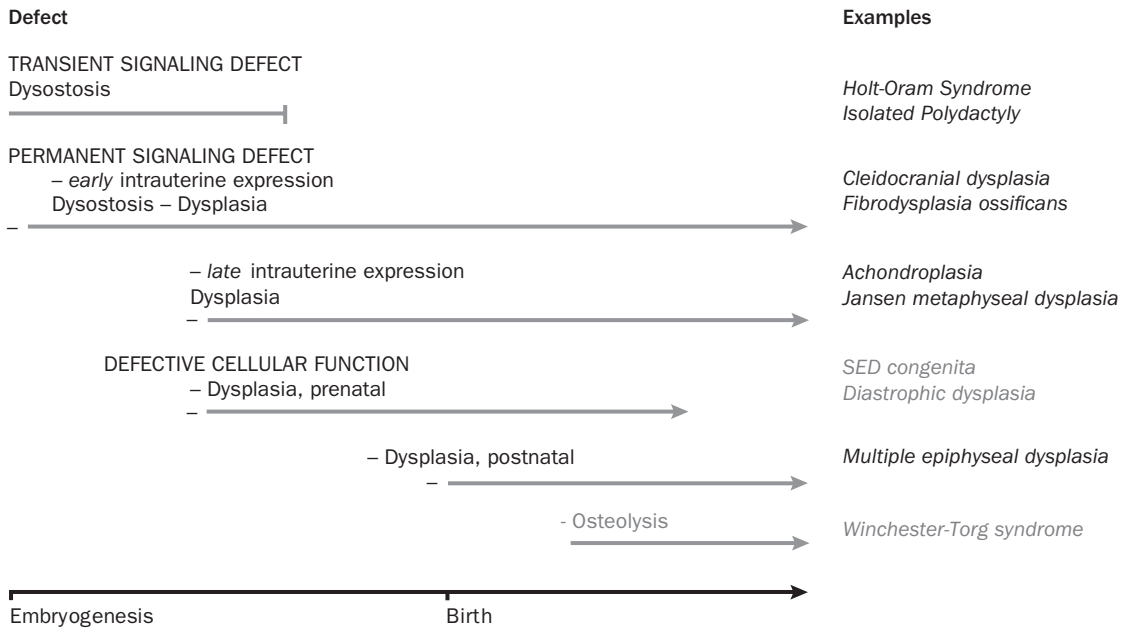

Figure 1.1 Scheme illustrating the concept of time-dependent gene expression and resulting defects.

example being the amniotic band disruption sequence. In cases with symmetric involvement of the fingers, differentiation between amniotic band disruption and a genetically determined primary dysostosis (e.g., brachydactyly type B) can be difficult. In some cases, a genetic defect may be regarded as producing a disruption. In X-linked chondrodysplasia punctata, calcifications originate during embryogenesis and disappear after birth, leaving scar-like areas of defective bone formation. Histology shows no signs of an ongoing dysplasia. The embryopathy caused by warfarin consumption during pregnancy is very similar to chondrodysplasia punctata. It is possible that the accumulation of abnormal sterol products caused by the defective activity of 3-beta-hydroxysteroid dehydrogenase (emopamil binding protein) transiently disrupts normal skeletal development and that warfarin acts by a similar mechanism. At any rate, the skeletal lesions in both appear to be disruptions (i.e., secondary dysostoses rather than dysplasias).

DYSPLASIAS

Defects of genes that are expressed continuously, from intrauterine to extrauterine life, lead to dysplasias (Figure 1.1).

TABLE 1.1 EXAMPLES OF DYSOSTOSES CAUSED BY DEFECTS IN TRANSCRIPTION FACTORS OR SIGNAL TRANSDUCTION PROTEINS

Name	Inheritance	Gene	Protein
Al-Awadi/Raas-Rothschild syndrome	AR	*WNT7a*	Wingless-type MMTV integration site family, member 7A (transcription factor)
Ulnar-mammary syndrome	AD	*TBX3*	T-box 3 transcription factor
Holt-Oram syndrome	AD	*TBX5*	T-box 5 transcription factor
Cousin syndrome	AR	*TBX15*	T-box 15 transcription factor
Hand-foot-genital syndrome	AD	*HOXA13*	Homeobox-containing A13 transcription factor
Greig polysyndactyly, Pallister-Hall syndrome, Postaxial polydactyly A	AD	*Gli3*	GLI-Kruppel family member 3 transcription factor
Brachydactyly A	AD	*IHH*	Indian hedgehog (diffusible signal protein)
Brachydactyly B	AD	*ROR2*	Receptor tyrosine kinase-like orphan receptor 2
Brachydactyly C	AD	*GDF5 (CDMP1)*	Growth and differentiation factor 5 (Cartilage-derived morphogenic protein 1)
Cenani-Lenz syndactyly	AR	*LRP4*	Low density lipoprotein-receptor related protein 4

Note. AD = autosomal dominant; AR = autosomal recessive; MMTV = mouse mammary tumor virus.

TABLE 1.2 EXAMPLES OF DYSPLASIAS ASSOCIATED WITH MUTATIONS IN TRANSCRIPTION FACTORS OR SIGNAL TRANSDUCING MOLECULES

Name	Inheritance	Gene	Protein
Campomelic dysplasia	AD	*SOX9*	SOX9 transcription factor
Tricho-rhino-phalangeal syndrome	AD	*TRPS1*	TRPS1 transcription factor
Dyschondrosteosis	XD	*SHOX*	SHOX transcription factor
Achondroplasia family (thanatophoric dysplasia, achondroplasia, hypochondroplasia, others)	AD	*FGFR3*	Fibroblast growth factor receptor 3
Craniosynostosis (various types)	AD	*FGFR1,2,3*	Various fibroblast growth factor receptors
Metaphyseal dysplasia type Jansen, Blomstrand dysplasia	AD	*PTHR*	PTH/PTHrP receptor
Robinow syndrome (COVESDEM)	AR	*ROR2*	Receptor tyrosine kinase-like orphan receptor 2

Note. AD = autosomal dominant; AR = autosomal recessive.

In contrast to dysostoses, dysplasias do not result from a disturbance of the skeletal blueprint but from perturbation of growth and homeostasis of cartilage and bone as tissues. *"Primary" skeletal dysplasias* result from mutated genes that are expressed in chondroosseous tissue (e.g., collagen 1 in bone and collagen 2 in cartilage). *"Secondary" dysplasias* are caused by abnormalities of extraosseous factors with secondary effects on the skeletal system. Examples are skeletal abnormalities caused by metabolic errors, such as hypophosphatemic rickets, or endocrine disease, such as hypothyroidism. Since skeletal dysplasias are disorders of cartilage and bone as tissues, mutations of dysplasia genes affect those tissues at all anatomic sites. Homologous sites are affected, and the resulting disorders are mostly symmetric. Short stature is common. The expression may be restricted to, or vary quantitatively in, body segments leading to disproportionate forms of short stature, for example, spinal, rhizomelic, mesomelic, and acromelic dysplasias. Asymmetric lesions, such as in enchondromatosis, multiple cartilaginous exostoses, or fibrous dysplasia, develop under the influence of local mechanical factors or somatic mutations. Primary dysplasias may result from mutated signaling genes or from genes affecting cell structure and/or function.

Dysplasias due to mutated transcription factors and signal-transducing genes: In contrast to the genes responsible for dysostoses, dysplasia-causing signaling genes are expressed after early embryogenesis and remain active after birth. Accordingly, mutations lead to postnatally ongoing errors of cell proliferation, differentiation, and degeneration and thus to defective skeletal growth and development. Examples are achondroplasia, the Jansen type of metaphyseal dysplasia, and others (Table 1.2). Both achondroplasia and Jansen metaphyseal dysplasia are disorders of the growth plate: in achondroplasia, chondrocyte proliferation is reduced because of a mutated fibroblast growth factor receptor, *FGFR3*. In Jansen metaphyseal dysplasia the mutant *PTH/PTHrP* receptor suppresses the differentiation of proliferating chondrocytes into hypertrophic cells and inhibits mineralization wherever the *PTH/PTHrP* receptor is expressed. Some transcription factors also play a pivotal role in signal transduction; hence, their mutations are responsible for dysplasias.

Dysplasias due to mutations of genes that regulate cell structure and/or function: A second group of bone dysplasias is caused by mutations in genes regulating cellular structure and function. With differentiation, cells assume special functions—notably the production or removal of matrix components. Thus a skeletal dysplasia might originate from a mutated gene that encodes a faulty cell product such as collagens. Other skeletal dysplasias result from defective intracellular transport or degradation systems. In diastrophic dysplasia, for instance, the transport of sulfate, crucial for the synthesis of sulfated proteoglycans, is impaired, and in pycnodysostosis, the extracellular matrix cannot be properly degraded because of cathepsin K deficiency. A defective vacuolar proton pump interferes with bone resorption, leading to an infantile form of osteopetrosis. Cellular function may also be more generally impaired as in cartilage-hair hypoplasia, where RNA processing is impaired, or in Schimke immunoosseous dysplasia, in which DNA repair mechanisms are defective. Mutations of the genes controlling these functions may be expressed during fetal life, as in severe cases of osteogenesis imperfecta or diastrophic dysplasia. Other mutations of the same gene become apparent only during later life, as exemplified by mild cases of osteogenesis imperfecta or diastrophic dysplasia. However, as in late-manifesting signaling defects, most genes disrupting cellular structure and/or function are not involved in early embryogenesis. Examples are listed in Table 1.3.

OSTEOLYSES

Osteolyses are disorders in which the primary development of skeletal elements and the first phases of growth are normal but are followed by a phase of gradual bone resorption

TABLE 1.3 EXAMPLES OF DYSPLASIAS AND OSTEOLYSES CAUSED BY DEFECTS IN CELLULAR FUNCTION AND/OR STRUCTURE

Name	Inheritance	Gene	Protein
Osteogenesis imperfecta, dominant forms	AD	*COL1A1, COL1A2*	Collagen 1 protein
Osteogenesis imperfecta, recessive forms	AR	Various	Various
SED congenita family (achondrogenesis type 2, hypochondrogenesis, Kniest dysplasia, SEDC, Stickler arthroophthalmopathy, premature arthrosis, etc.)	AD	*COL2A1*	Collagen 2
Metaphyseal dysplasia, Schmid type	AD	*COL10A1*	Collagen 10
Pseudoachondroplasia and Dominant multiple epiphyseal dysplasia (one form)	AD	*COMP*	Cartilage oligomeric matrix protein
SED tarda, X-linked	XLR	*TRAPPC2*	Sedlin
Achondrogenesis 1B, Diastrophic dysplasia, Recessive multiple epiphyseal dysplasia	AR	*SLC26A2*	Cell membrane sulfate transporter DTDST
Dyssegmental dysplasia, Schwartz-Jampel syndrome	AR	*HSPG2*	Perlecan
Hypophosphatasia	AR	*TNSALP*	Tissue nonspecific alkaline phosphatase
Mucopolysaccharidoses, Oligosaccharidoses (multiple types)	AR, XLR	*Various*	Several lysosomal hydrolases
Osteopetrosis, infantile	AR	*TCIRG1*	Proton pump subunit
Osteopetrosis and renal tubular acidosis	AR	*CA2*	Carboanhydrase2
Pycnodysostosis	AR	*CTSK*	Cathepsin K
Multicentric osteolysis Winchester-Torg	AR	*MMP2*	Matrix metalloproteinase 2
Metaphyseal anadysplasia	AD, AR	*MMP9, MMP13*	Matrix Metalloproteinases 9 and 13

Note. AD = autosomal dominant; AR = autosomal recessive; SED = spondyloepiphyseal dysplasia; SEDC = spondyloepiphyseal dysplasia congenital type; XLR = X-linked recessive; DTDST = diastrophic dysplasia sulfate transporter.

that may eventually lead to the disappearance of skeletal elements. Some forms of osteolysis are generalized, while some are more or less restricted to a group of bones (e.g., the carpal-tarsal osteolyses). The pathogenesis must reside in a defect of homeostasis; bone is formed and can grow, but a defect in its "trophism" leads to gradual reabsorption and lysis. In one of the most dramatic osteolyses, the Winchester-Torg syndrome, the genetic defect in the metalloproteinase 2 (*MMP2*) is believed to result in defective activation of *TGFβ*, but the pathogenesis is not yet entirely understood.

MIXED DISORDERS

Mutations of genes that are expressed during early embryogenesis and remain active during later prenatal and postnatal life result in disorders combining single bone defects, or dysostoses, and ongoing tissue defects, or dysplasias (Figure 1.1). An example of such "dysosto-dysplasia" is cleidocranial dysostosis. It is caused by mutations of the *RUNX2* gene encoding the transcription factor *CBFal. CBFa1* acts as an activator of osteoblast differentiation during embryogenesis and its mutation has early "dysostotic" effects, for example on the development of the clavicles. However, the gene is also active postnatally, regulating the expression of osteoblast-specific genes encoding osteocalcin, osteopontin, and type I collagen. In heterozygous mice, the *CBFal* defect leads to osteoporosis, and in humans it is probably responsible for the postnatal changes seen in cleidocranial dysostosis, such as metaphyseal changes and stunted growth. In the related condition, spondylo-megaepiphyseal-metaphyseal dysplasia, there is a severe dysostosis affecting clavicles, pubis, and vertebrae but the continuing action of the gene in childhood is reflected by the appearance of numerous pseudoepiphyses and metaphyseal dysplasia. Other "dysosto-dysplasias" reflecting the disruption of both early patterning and of later cell structure and/or function are listed in Table 1.4.[1]

RECOGNITION AND PRACTICAL IMPLICATIONS OF DEVELOPMENTAL CATEGORIES

Differential criteria of dysostoses, disruptions, and dysplasias are summarized in Table 1.5. Although

[1] The original names of *cleidocranial dysostosis and metaphyseal dysostosis* (Jansen, 1934) have been replaced by the names of cleidocranial dysplasia and metaphyseal dysplasia in the 1970 *Nomenclature*. On the other hand, the old term *dysostosis multiplex*, used to defi ne the pattern of bone changes in the mucopolysaccharidoses, has remained in use although the bone disease is clearly a *dysplasia*.

TABLE 1.4 EXAMPLES OF DEFECTS LEADING TO COMBINED DISORDERS (DYSOSTO-DYSPLASIAS)

Name	Inheritance	Gene	Protein
Cleidocranial dysostosis	AD	*RUNX2*	Runt transcription factor
Campomelic dysplasia	*AD*	*SOX9*	SOX9 transcription factor
Spondylo-megaepiphyseal-metaphyseal dysplasia	AR	*NKX3–2*	NKX3–2 homeobox transcription factor
Grebe/Hunter-Thompson dysplasia	AR	*GDF5 (CDMP1)*	Growth and differentiation factor 5 (Cartilage-derived morphogenic protein 1)
Nail-patella syndrome	AD	*LMX1B*	Lmx1b homeodomain protein

Note. AD = autosomal dominant; AR = autosomal recessive.

occasionally it may be difficult to classify a given disorder, closer analysis of its development may help in the assignment to one of the different etiopathogenetic groups. If the disorder dates back to early embryogenesis and affects the skeletal patterning blueprint, it has the elements of a skeletal malformation (i.e., a dysostosis). When a disorder manifests after organogenesis and when it impairs cellular development, structure, or function and tissue homeostasis, it is a dysplasia. Crouzon syndrome appears to be a dysplasia, although it has been named craniofacial "dysostosis." Allelic mutations may have generalized or localized effects. The *G380R* mutation of the *FGFR3* gene leads to achondroplasia and the *P250R* mutation to coronal craniosynostosis. Knowing that the *FGFR3* gene is postnatally expressed, one has to conclude that both are dysplasias, one generalized and the other localized, even though one is tempted to call the isolated skull defect a "dysostosis." Analysis of a given condition may help predict the stages and principal function of an unknown gene. Thus it can be predicted (a) that the gene causing chondroectodermal dysplasia is a signaling gene expressed in the acral skeleton, heart, teeth, and other organs and (b) that it is expressed during organogenesis and remains expressed throughout postnatal life. Dosage may influence the time of gene expression. Heterozygous *CDMP1* (*GDF5*) mutations result in brachydactyly C—an embryogenetic defect. Brachydactyly C is a dysostosis. Homozygosity for *CDMP1* mutations leads to Grebe dysplasia. From this we must conclude that a full dose of the *CDMP1* effect is needed to ensure normal early limb development but that half the dose suffices to allow for normal skeletal development after the eighth week of embryogenesis.

The distinction of dysostoses, disruptions, and dysplasias has practical implications. For example, the search for detrimental environmental influences should focus on dysostoses rather than on skeletal dysplasias. On the other hand, metabolic studies should focus on dysplasias, as inborn errors of metabolism produce dysplasias, not dysostoses. A third practical consideration concerns malignant degeneration. Since dysostoses are finite disorders caused by a past, closed process, there is no danger of malignant degeneration. An extra finger will not become malignant. This is not always true for dysplasias. Dysplasias, by definition, are caused by mutations of postnatally expressed genes. Some mutated genes involved in cell proliferation or apoptosis may predispose to malignant degeneration. Examples for this are multiple exostoses, enchondromata, notably in combination with hemangiomata (i.e., the Maffucci syndrome), and fibrous dysplasia. Thus examining a child with a dysostosis and dysplasia, looking at radiographs, using morphology to pinpoint a specific diagnosis, and asking for a diagnostic test is challenging and rewarding. Trying to address the pathogenesis—by asking when this disorder originated and whether it affects cartilage, bone, or the growth plate, or the body biochemistry—adds another fascinating dimension to the diagnostic process and brings us much closer to understanding the patient and his or her disorder.

TABLE 1.5 DIFFERENTIAL CRITERIA OF DYSOSTOSES AND DYSPLASIAS

	Dysostoses		Skeletal Dysplasias	
	Primary	Secondary	Primary	Secondary
Affected structure	Skeletal element as organ		Bone and/or cartilage as tissues	
Distribution	Mostly symmetric, often mildly asymmetric, in some cases even unilateral		Mostly symmetric	
Determination period	Organogenesis	Growth period	Growth period	

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