Constitutional Disorders of the Skeleton in Dogs and Cats

This chapter [From: Textbook of Small Animal Orthopaedics, C. D. Newton and D. M. Nunamaker (Eds.) Publisher: International Veterinary Information Service (www.ivis.org), Ithaca, New York, USA.] will consider genetically determined disorders of the osseous skeleton. To attempt to make some sense of the disorders that have already been reported and to provide a framework for classification of those disorders that will be reported in the future, I will use a system of classification consistent with that adopted for human disorders at a meeting of the European Society for Pediatric Radiology in November 1969. This meeting resulted in the Paris Nomenclature for Constitutional (Intrinsic) Disorders of Bone (Table 57-1).(52) This nomenclature was revised in May 1977(60) (Table 57-2), and this new terminology will be employed. Other veterinary authors have also adopted this classification to describe skeletal malformations.(45)

McCusick has pointed out the difficulty in attempting to classify and categorize bone dysplasias due to the many types that have been, and continue to be, described in humans and to the relatively rare occurrence of most of these dysplasias.(49) The best characterized of such disorders have tended to be those with a dominant mode of inheritance and those recessively inherited conditions that occur in genetic population isolates. These are characterized best because there are sufficient members of affected persons that the natural history of the disease can be studied and described adequately.

In humans many constitutional disorders of the bones occur as sporadic cases and represent new mutations or the expression of rare recessive traits. The same is true in animal populations, and most affected animals are removed from breeding populations. Interestingly, however, many bone dysplasias that have occurred in dogs and cats and are classifiable as diseases in Paris nomenclature have been selected by breeders and have become considered "normal" for the involved breeds. Most of these "desirable" conformational anomalies are inherited as autosomal dominants, often with variable expressivity. Unfortunately, breeders of animals with such traits have usually ignored their detrimental effects on the animals or have refused to recognize their association with the gene or genes responsible for the bony conformation.

Since such breeding practices are not likely to be drastically altered in the near future, it is important for the veterinarian dealing with these animals to understand the implications of these practices and to provide adequate counseling to the breeders and owners so that the detrimental effects can at least be minimized by judicial selection of animals to be used for breeding.

Many of those traits that are recessively inherited occur in relatively high frequency in certain breeds or within a group of animals within a breed. Breeding practices in purebred animal populations are controlled almost entirely by the owners of the animals; random matings rarely occur in these groups. Human populations, on the other hand, exhibit primarily random mating practices, limited only in certain circumstances, such as by religious restrictions, by which genetic isolates have arisen. Animal breeders commonly use inbreeding, often euphemistically referred to as "line-breeding," to "fix" certain desirable traits in a breed. Such practices fix these traits by increasing the homozygosity of alleles at all genetic loci. Therefore, along with those alleles that produce desirable traits, some that produce undesirable traits may also appear in increased frequency and result in an increase in the number of animals exhibiting that trait. Another common practice in these populations is the widespread breeding of a few males that exhibit desirable traits, usually show champions. If such a dog or cat has a recessive allele for some undesirable trait, it can rapidly become widespread in the population, since 50% of all his offspring will potentially carry this gene. It may not be until several backcrosses or matings of the F. and future generation offspring occur that such a situation becomes apparent. By that time the gene may be widespread in the population. This is known as the "founder effect" and can have extremely deleterious effects on a breed. Therefore, when problems, such as bone dysplasias, are recognized in purebred animals, it becomes important to report them in the literature so that other veterinarians will have a frame of reference for

any new cases seen. Possibly such problems in a breed can thereby be recognized early enough to help prevent widespread dissemination of the mutant gene or genes responsible for these disorders. It is also important to try to educate breeders to the widespread implications of such problems and help to minimize the long-existent practice of "hiding your mistakes." Many breed clubs have established genetic committees to help identify such problems and monitor their populations for their occurrence. Hopefully, this practice will become standard in all breed clubs, since recognition and elimination of such disorders can only be to the benefit of all breeders.

TABLE 57-1 *The Paris Nomenclature for Constitutional Disorders of Bone*

I. Constitutional diseases of bone with unknown pathogenesis: osteochondrodysplasias (abnormalities of cartilage and/or bone growth and development)
- A. Defects of growth of tubular bones and/or spine
  - 1. Manifest at birth
    - a. Achondroplasia
    - b. Achondrogenesis
    - c. Thanatophoric dwarfism
    - d. Chondrodysplasia punctata (formerly stippled epiphyses chondrodystrophia calcificans congenita), several forms
    - e. Metatropic dwarfism
    - f. Diastrophic dwarfism
    - g. Chondroectodermal dysplasia (Ellis–van Creveld syndrome)
    - h. Asphyxiating thoracic dysplasia (Jeune syndrome)
    - i. Spondyloepiphyseal dysplasia congenita
    - j. Mesomelic dwarfism
      - (1) Nievergelt type
      - (2) Langer type
    - k. Cleidocranial dysplasia (formerly chleidocranial dysostosis)
  - 2. Manifest in later life
    - a. Hypochondroplasia
    - b. Dyschondrosteosis
    - c. Metaphyseal chondrodysplasia (formerly metaphyseal dysostosis), Jansen type
    - d. Metaphyseal chondrodysplasia (formerly metaphyseal dysostosis), Schmid type
    - e. Metaphyseal chondrodysplasia, McKusick type (formerly cartilage-hair hypoplasia)
    - f. Metaphyseal chondrodysplasia with malabsorption and neutropenia
    - g. Metaphyseal chondrodysplasia with thymolymphopenia
    - h. Spondylometaphyseal dysplasia (Kozlowski type)
    - i. Multiple epiphyseal dysplasia (several forms)
    - j. Hereditary arthro-ophthalmopathy
    - k. Pseudoachondroplastic dysplasia (formerly pseudoachondroplastic type of spondyloepiphyseal dysplasia)
    - l. Spondyloepiphyseal dysplasia tarda
    - m. Acrodysplasia (formerly peripheral dysostosis)
      - (1) Trichorhinophalangeal syndrome (Giedion syndrome)
      - (2) Epiphyseal type (Thiemann syndrome)
      - (3) Epiphysiometaphyseal type (Brailsford syndrome)
- B. Disorganized development of cartilage and fibrous components of the skeleton
  - 1. Dysplasia epiphysealis hemimelica
  - 2. Multiple cartilaginous exostoses
  - 3. Enchondromatosis (Ollier's disease)
  - 4. Enchondromatosis with hemangioma (Maffucci syndrome)
  - 5. Fibrous dysplasia (Jaffé–Lichtenstein syndrome)
  - 6. Fibrous dysplasia with skin pigmentation and precocious puberty (McCune–Albright syndrome)
  - 7. Cherubism
  - 8. Multiple fibromatosis
- C. Abnormalities of density, of cortical diaphyseal structure, and/or of metaphyseal modeling
  - 1. Osteogenesis imperfecta congenita (Vrolik or Porak–Durante syndrome)
  - 2. Osteogenesis imperfecta tarda (Lobstein syndrome)
  - 3. Juvenile idiopathic osteoporosis
  - 4. Osteopetrosis with precocious manifestations
  - 5. Osteopetrosis with delayed manifestations
  - 6. Pyknodysostosis
  - 7. Osteopoikilosis
  - 8. Melorheostosis
  - 9. Diaphyseal dysplasia (Camurati–Engelmann syndrome)
  - 10. Craniodiaphyseal dysplasia
  - 11. Endosteal hyperostosis (Van Buchem syndrome and other forms)
  - 12. Tubular stenosis (Kenny–Caffey syndrome)
  - 13. Osteodysplasty (Melnick–Needles syndrome)
  - 14. Pachydermoperiostosis
  - 15. Osteoectasia with hyperphosphatasia
  - 16. Metaphyseal dysplasia (Pyle's disease)
  - 17. Craniometaphyseal dysplasia (several forms)
  - 18. Frontometaphyseal dysplasia
  - 19. Oculo-dento-osseous dysplasia (formerly oculo-dento-digital syndrome)

II. Constitutional diseases of bone with unknown pathogenesis: dysostoses (malformation of individual bones, singly or in combination)
- A. Dysostoses with cranial and facial involvement
  - 1. Craniosynostosis, several forms
  - 2. Craniofacial dysostosis (Crouzon syndrome)
  - 3. Acrocephalosyndactyly (Apert syndrome)
  - 4. Acrocephalopolysyndactyly (Carpenter syndrome)
  - 5. Mandibulofacial dysostosis (Treacher-Collins–Franceschetti syndrome)
  - 6. Mandibular hypoplasia (includes Pierre Robin syndrome)
  - 7. Oculomandibulofacial syndrome (Hallermann–Streiff–François syndrome)
  - 8. Nevoid basal cell carcinoma syndrome
- B. Dysostoses with predominant axial involvement
  - 1. Vertebral segmentation defects (including Klippel–Feil syndrome)
  - 2. Cervico-oculo-acoustic syndrome (Wildervanck syndrome)
  - 3. Sprengel's deformity
  - 4. Spondylocostal dysostosis (several forms)
  - 5. Oculovertebral syndrome (Weyers syndrome)
  - 6. Osteo-onychodysostosis (formerly nail-patella syndrome)
- C. Dysostoses with predominant involvement of extremities
  - 1. Amelia
  - 2. Hemimelia (several types)
  - 3. Acheiria
  - 4. Apodia
  - 5. Adactyly and oligodactyly
  - 6. Phocomelia
  - 7. Aglossia-adactylia syndrome
  - 8. Congenital bowing of long bones (several types)
  - 9. Familial radioulnar synostosis
  - 10. Brachydactyly (several types)
  - 11. Symphalangism
  - 12. Polydactyly (several types)
  - 13. Syndactyly (several types)
  - 14. Polysyndactyly (several types)
  - 15. Camptodactyly
  - 16. Clinodactyly
  - 17. Biedl–Bardet syndrome
  - 18. Popliteal pterygium syndrome
  - 19. Pectoral aplasia–dysdactyly syndrome (Poland syndrome)
  - 20. Rubinstein–Taybi syndrome
  - 21. Pancytopenia–dysmelia syndrome (Fanconi syndrome)
  - 22. Thrombocytopenia–radial-aplasia syndrome
  - 23. Orofaciodigital (OFD) syndrome (Papillon–Léage syndrome)
  - 24. Cardiomelic syndrome (Holt–Oram syndrome)

III. Constitutional diseases of bone with unknown pathogenesis: idiopathic osteolyses
- A. Acro-osteolysis
  - 1. Phalangeal type
  - 2. Tarsocarpal form, with or without nephropathy
- B. Multicentric osteolysis

IV. Primary disturbances of growth
- A. Primordial dwarfism (without associated malformations)
- B. Cornelia de Lange syndrome
- C. Bird-headed dwarfism (Virchow and Seckel forms)
- D. Leprechaunism
- E. Russell–Silver syndrome
- F. Progeria
- G. Cockayne syndrome
- H. Bloom syndrome
- I. Geroderma osteodysplastica
- J. Spherophakia-brachymorphia syndrome (Weill–Marchesani syndrome)
- K. Marfan syndrome

V. Constitutional diseases of bones with known pathogenesis: chromosomal aberrations

VI. Constitutional diseases of bones with known pathogenesis: primary metabolic abnormalities
- A. Disorders of calcium/phosphorus metabolism
  - 1. Hypophosphatemic familial rickets
  - 2. Pseudodeficiency rickets (Royer or Prader syndrome)
  - 3. Late rickets (McCance syndrome)
  - 4. Idiopathic hypercalciuria
  - 5. Hypophosphatasia (several forms)
  - 6. Idiopathic hypercalcemia
  - 7. Pseudohypoparathyroidism (normo- and hypocalcemic forms)
- B. Mucopolysaccharidoses
- C. Mucolipidoses and lipidoses
  - 1. Mucolipidosis I (Spranger–Wiedemann syndrome; lipomucopolysaccharidosis)
  - 2. Mucolipidosis II (Leroy syndrome; I-cell disease)
  - 3. Mucolipidosis III (pseudo–Hurler polydystrophy)
  - 4. Fucosidosis
  - 5. Mannosidosis
  - 6. Generalized G_{M1} gangliosidosis (two forms)
  - 7. Sulfatidosis with mucopolysaccharidurie (Austin–Thieffry syndrome)
  - 8. Cerebrosidosis, including Gaucher's disease
- D. Other metabolic extraosseous disorders

VII. Bone abnormalities secondary to disturbances of extraskeletal systems
- A. Endocrine disturbances, *e.g.*, hypothyroidism
- B. Hematologic disturbances, *e.g.*, thalassemia
- C. Neurologic disturbances *e.g.*, sensory neuropathy
- D. Renal disturbances, *e.g.*, cystinosis
- E. Gastrointestinal disturbances, *e.g.*, celiac disease
- F. Cardiopulmonary disturbances, *e.g.*, hypertrophic osteoarthropathy

Maroteaux P: Nomenclature internationale des maladies osseuses constitutionnelles. Ann Radiol 13:455, 1970

TABLE 57-1 The Paris Nomenclature for Constitutional Disorders of Bone

TABLE 57-2 *International Nomenclature of Constitutional Diseases of Bone: Revision, May 1977*

OSTEOCHONDRODYSPLASIAS
Abnormalities of cartilage or bone growth and development or both

I. Defects of growth of tubular bones and/or spine
  A. Identifiable at birth
    1. Achondrogenesis type I (Parenti–Fraccaro)
    2. Achondrogenesis type II (Langer–Saldino)
    3. Thanatophoric dysplasia
    4. Thanatophoric dysplasia with cloverleaf skull
    5. Short rib-polydactyly syndrome type I (Saldino-Noonan) (perhaps several forms)
    6. Short rib-polydactyly syndrome type II (Majewski)
    7. Chondrodysplasia punctata
      a. Rhizomelic form
      b. Dominant form
      c. Other forms. Exclude: symptomatic stippling in other disorders (*e.g.*, Zellweger syndrome, warfarin embryopathy)
    8. Campomelic dysplasia
    9. Other dysplasias with congenital bowing of long bones (several forms)
    10. Achondroplasia
    11. Diastrophic dysplasia
    12. Metatropic dysplasia (several forms)
    13. Chondroectodermal dysplasia (Ellis–van Creveld)
    14. Asphyxiating thoracic dysplasia (Jeune)
    15. Spondyloepiphyseal dysplasia congenita
      a. Type Spranger–Wiedemann
      b. Other forms (see B.11 and 12)
    16. Kniest dysplasia
    17. Mesomelic dysplasia
      a. Type Nievergelt
      b. Type Langer (probable homozygous dyschondrosteosis)
      c. Type Robinow
      d. Type Rheinardt
      e. Others
    18. Acromesomelic dysplasia
    19. Cleidocranial dysplasia
    20. Larsen syndrome
    21. Otopalatodigital syndrome
  B. Identifiable in later life
    1. Hypochondroplasia
    2. Dyschondrosteosis
    3. Metaphyseal chondrodysplasia type Jansen
    4. Metaphyseal chondrodysplasia type Schmid
    5. Metaphyseal chondrodysplasia type McKusick
    6. Metaphyseal chondrodysplasia with exocrine pancreatic insufficiency and cyclic neutropenia
    7. Spondylometaphyseal dysplasia
      a. Type Kozlowski
      b. Other forms
    8. Multiple epiphyseal dysplasia
      a. Type Fairbanks
      b. Other forms
    9. Arthro-ophthalmopathy (Stickler)
    10. Pseudoachondroplasia
      a. Dominant
      b. Recessive
    11. Spondyloepiphyseal dysplasia tarda
    12. Spondyloepiphyseal dysplasia, other forms (see A.15 and 16)
    13. Dyggve–Melchior–Clausen dysplasia
    14. Spondyloepimetaphyseal dysplasia (several forms)
    15. Myotonic chondrodysplasia (Catel–Schwartz–Jampel)
    16. Parastremmatic dysplasia
    17. Trichorhinophalangeal dysplasia
    18. Acrodysplasia with retinitis pigmentosa and nephropathy (Saldino–Mainzer)

II. Disorganized development of cartilage and fibrous components of skeleton
  A. Dysplasia epiphyseal hemimelica
  B. Multiple cartilaginous exostoses
  C. Acrodysplasia with exostoses (Giedion–Langer)
  D. Enchondromatosis (Ollier)
  E. Enchondromatosis with hemangioma (Maffucci)
  F. Metachondromatosis
  G. Fibrous dysplasia (Jaffé–Lichtenstein)
  H. Fibrous dysplasia with skin pigmentation and precocious puberty (McCune–Albright)
  I. Cherubism (familial fibrous dysplasia of the jaws)
  J. Neurofibromatosis

III. Abnormalities of density of cortical diaphyseal structure and/or metaphyseal modeling
  A. Osteogenesis imperfecta congenita (several forms)
  B. Osteogenesis imperfecta tarda (several forms)
  C. Juvenile idiopathic osteoporosis
  D. Osteoporosis with pseudoglioma
  E. Osteopetrosis with precocious manifestations
  F. Osteopetrosis with delayed manifestations (several forms)
  G. Pyknodysostosis
  H. Osteopoikilosis
  I. Osteopathia striata
  J. Melorheostosis
  K. Diaphyseal dysplasia (Camurati–Engelmann)
  L. Craniodiaphyseal dysplasia
  M. Endosteal hyperostosis
    1. Autosomal dominant (Worth)
    2. Autosomal recessive (Van Buchem)
  N. Tubular stenosis (Kenny–Caffey)
  O. Pachydermoperiostosis
  P. Osteodysplasty (Melnick–Needles)
  Q. Frontometaphyseal dysplasia
  R. Craniometaphyseal dysplasia (several forms)
  S. Metaphyseal dysplasia (Pyle)
  T. Sclerosteosis
  U. Dysosteosclerosis
  V. Osteoectasia with hyperphosphatasia

DYSOSTOSES
Malformation of individual bones, singly or in combination

I. Dysostoses with cranial and facial involvement
  A. Craniosynostosis (several forms)
  B. Craniofacial dysostosis (Crouzon)
  C. Acrocephalosyndactyly (Apert) and others
  D. Acrocephalopolysyndactyly (Carpenter) and others
  E. Mandibulofacial dysostosis
    1. Type Treacher-Collins–Franceschetti
    2. Other forms
  F. Oculomandibulofacial syndrome (Hallermann–Streiff–François)
  G. Nevoid basal cell carcinoma syndrome

II. Dysostoses with predominant axial involvement
  A. Vertebral segmentation defects (including Klippel–Feil)
  B. Cervico-oculo-acoustic syndrome (Wildervanck)
  C. Sprengel anomaly
  D. Spondylocostal dysostosis
    1. Dominant form
    2. Recessive forms
  E. Oculovertebral syndrome (Weyers)
  F. Osteo-onychodysostosis
  G. Cerebrocostomandibular syndrome

III. Dysostoses with predominant involvement of extremities
  A. Acheiria
  B. Apodia
  C. Ectrodactyly syndrome
  D. Aglossia-adactyly syndrome
  E. Congenital bowing of long bones (several forms) (see also osteochondrodysplasias)
  F. Familial radioulnar synostosis
  G. Brachydactyly (several forms)
  H. Symphalangism
  I. Polydactyly (several forms)
  J. Syndactyly (several forms)
  K. Polysyndactyly (several forms)
  L. Camptodactyly
  M. Poland syndrome
  N. Rubinstein–Taybi syndrome
  O. Pancytopenia–dysmelia syndrome (Fanconi)
  P. Thrombocytopenia–radial-aplasia syndrome
  Q. Orodigitofacial syndrome
    1. Type Papillon–Léage
    2. Type Mohr
  R. Cardiomelic syndrome (Holt–Oram and others)
  S. Femoral facial syndrome
  T. Multiple synostoses (includes some forms of symphalangism)
  U. Scapuloiliac dysostosis (Kosenow–Sinios)
  V. Hand-foot-genital syndrome
  W. Focal dermal hypoplasia (Goltz)

IDIOPATHIC OSTEOLYSES

I. Phalangeal (several forms)

II. Tarsocarpal
  A. Including François form and others
  B. With nephropathy

III. Multicentric
  A. Hajdu–Cheney form
  B. Winchester form
  C. Other forms

CHROMOSOMAL ABERRATIONS
(Specific disorders not listed): primary metabolic abnormalities

I. Calcium and/or phosphorus
  A. Hypophosphatemic rickets
  B. Pseudodeficiency rickets (Prader Royer)
  C. Late rickets (McCance)
  D. Idiopathic hypercalciuria
  E. Hypophosphatasia (several forms)
  F. Pseudohypoparathyroidism (normocalcemic and hypocalcemic forms, includes acrodysostosis)

II. Complex carbohydrates
  A. Mucopolysaccharidosis, type I (α-L-iduronidase deficiency)
    1. Hurler form
    2. Scheie form
    3. Other forms
  B. Mucopolysaccharidosis, type II-Hunter (sulfoiduronate sulfatase deficiency)
  C. Mucopolysaccharidosis type III-San Filippo
    1. Type A (Heparin sulfamidase deficiency)
    2. Type B (*N*-acetyl-alpha-glucosaminidase deficiency)
  D. Mucopolysaccharidosis, type IV-Morquio (N-acetylgalactosamine-6-sulfate-sulfatase deficiency)
  E. Mucopolysaccharidosis, type VI-Maroteaux–Lamy (arylsulfatase B deficiency)
  F. Mucopolysaccharidosis, type VII (β-glucuronidase deficiency)
  G. Aspartylglucosaminuria (aspartyl-glucosaminidase deficiency)
  H. Mannosidosis (α-mannosidase deficiency)
  I. Fucosidosis (α-fucosidase deficiency)
  J. G_{M1}-Gangliosidosis (beta galactosidase deficiency)
  K. Multiple sulfatase deficiency (Austin, Thieffry)
  L. Neuraminidase deficiency (formerly mucolipidosis I)
  M. Mucolipidosis II
  N. Mucolipidosis III

III. Lipids
  A. Niemann–Pick disease
  B. Gaucher disease

IV. Nucleic acids
  A. Adenosine-deaminase deficiency
  B. Others

V. Amino acids
  A. Homocystinuria
  B. Others

VI. Metals
  A. Menkes kinky hair syndrome
  B. Others

TABLE 57-2 International Nomenclature of Constitutional Diseases of Bone: Revision, May 1977

Another reason for identification of animals with genetically determined disorders of the skeleton is that such animals represent an important resource for the biomedical research community. Availability of spontaneous models of human disorders can provide researchers with invaluable information about the pathogenetic mechanisms by which such disorders arise and thereby allow design and testing of new modes of therapy for such disorders. Disorders that may not have a counterpart in human medicine are just as valuable, since they may provide new insights into normal bony development by determination of the defects in development that are responsible for production of the lesion or lesions in affected animals. Obviously, not all the disorders that might be classified by the Paris nomenclature can be covered in a single chapter. Many such disorders are dealt with in detail in other chapters of this text. Only examples of selected disorders will be outlined here to illustrate the general usefulness of using this method of classification. Also, assume that the classification scheme for the human disorders will continue to be revised. The general descriptions of the human disorders in the text to follow are amalgamations from several sources and, where not specifically cited, were obtained primarily from textbooks dealing with these disorders.(9,49,78)

Classification of many of the canine and feline disorders has been difficult owing to the paucity of reports about these rare conditions in companion animals. While I have an aversion to case reports in the veterinary literature that document only a slightly different presentation of some common disease in a single animal, such as canine Cushing's syndrome, I strongly encourage reports of well investigated, unusual bony disorders. It is only through such reports that other veterinarians may recognize and report other causes of such disorders and thereby allow some estimate of their prevalence to be made. Often such reports lead to recognition of a condition as being clustered in a given breed, and its genetic nature is thereby uncovered.

OSTEOCHONDRODYSPLASIAS

Abnormalities of cartilage or bone growth and development or both.

I. DEFECTS OF TUBULAR BONES AND/OR SPINE

A. IDENTIFIABLE AT BIRTH

7. CHONDRODYSPLASIA PUNCTA

This category includes several entities in humans. One is a recessive form characterized by rhizomelic dwarfism and often has associated joint contractures, depression of the nasal bridge, cataracts, and dermatitis. Radiographic changes, in addition to stippling of epiphyseal ossification centers, include vertebral abnormalities, short humeri and femora, and metaphyseal abnormalities in the long bones. Patients are usually mentally retarded and die young. In its dominant forms, there may be similar abnormalities, except intelligence is unimpaired and adult stature may be nearly normal.

Stippled epiphyses can occur in a variety of other disorders not classified as primary chondrodysplasia punctata. A multiple epiphyseal dysplasia has been reported in beagles that was characterized by stippled epiphyses.(59) This condition has been referred to as chondrodysplasia punctata, but whether it truly belongs to this category or to the group B.8, multiple epiphyseal dysplasia, is not clear, since the pups were not radiographed until 8 weeks old. Poodles with pseudoachondroplasia also have stippling of the epiphyses radiographically (vide infra).

10. ACHONDROPLASIA

Achondroplasia is the prototypic chondrodystrophy for those human forms of short-limbed dysplasia evident at birth. It is diagnosable in human neonates on the basis of characteristic

radiographic signs, which include excessive cartilaginous separation of ossification centers in the vertebral bodies, caudal narrowing of interpedunculate intervals in the lumbar spine, a narrowed spinal canal, and shortened iliac wings. In the appendicular skeleton, there is a rhizomelic shortening, and the epiphyseal ossification centers are set into the metaphyses, which are flared. The hand is usually trident in appearance. The chondrocranium is also defective, with depression of the nasal bridge, maxillary hypoplasia, and a small foramen magnum.

Achondroplastic infants are hypotonic, which results in breaking of upper lumbar vertebrae that may progress to formation of wedge vertebrae and a marked lumbar gibbus. Loose-jointedness of the knees due to ligamentous laxity contributes to bowing of the legs.

Several breeds of dogs have characteristic features similar to those outlined for human achondroplasts that would place them in this category. These include the bulldogs, the Boston terrier, the pug, the Pekinese, the Japanese spaniel, and the Shih Tzu. The bony abnormalities observed in these include rhizomelic limb shortening and flared metaphyses, a depressed nasal bridge, and a shortened maxilla (resulting in their characteristic relative mandibular prognathism). They also have a small foramen magnum, and, especially in the bulldogs, there are often wedge- or hemivertebrae. These dogs tend to have upper airway problems associated with the facial conformation, including stenotic nares and overlong soft palates. The latter represents a normal soft tissue mass that has been translocated to an abnormal position by the bony anomalies. Elbow luxations and medial patella luxations occur and are probably associated with increased joint laxity, as in humans. Achondroplasia is an autosomal dominant disorder in humans (although exceptions have been reported) and appears to be an incompletely dominant autosomal trait in the dog.(74)

B. IDENTIFIABLE IN LATER LIFE

I. HYPOCHONDROPLASIA

Hypochondroplasia has many similarities to achondroplasia but is generally less severe, especially in regard to abnormalities of the skull and pelvis. Radiographic changes in the long bones are most similar to those in achondroplasia, but less severe. The skull is relatively normal, with a slightly prominent frontal area sometimes noted. McCusick and co-workers reported a case that suggested that the genes for achondroplasia and hypochondroplasia are allelic.(50) Because some patients are also recognized to be dwarfed at birth, McCusick has suggested that this disorder would be better reclassified in group A with achondroplasia.(49,50)

Hypochondroplastic-type changes, characterized by rhizomelic limb shortening and a normal skull, are commonly seen in many breeds of dogs. Among these are dachshunds, Welsh corgis, Dandie Dinmont terriers, Scottish terriers, Skye terriers, basset hounds, and beagles, although McCusick did not consider that the dachshund fit into any of the human categories.(49) Major problems associated with these changes are intervertebral disk disease and elbow dysplasia.

There are considerable variations in the degree of limb shortening in some breeds affected by this condition, suggesting the possibility of more than one allele at the locus producing this condition. This has also been suggested for the condition in humans, among whom there is considerable phenotypic variation in the disorder. This variation may also reflect diversity in the phenotypic expression of other genes that act in concert with the gene at the hypochondroplasia locus. Certainly development of the proximal portion of a limb, for example, requires the expression of many genes before a final conformation is produced. Some breeds, which are known to be otherwise relatively heterogeneous genetically, seem to show a wide variation in expression of what is probably the hypochondroplasia locus. Fox hounds and beagles are good examples of this phenomenon.

A condition reported as achondroplasia in a litter of Scottish terriers may in fact represent a severe manifestation of hypochondroplasia, since the skulls of the affected animals appeared

relatively normal.(53) Alternatively, they might also be an equivalent of thanatophoric dysplasia (A.3), since the femoral shape in the published radiographs is reminiscent of the bowed "telephone receiver" shape seen in that disorder.

Hypochondroplasia apparently occurs frequently as a new mutation in humans. Sporadic cases do not appear to be uncommon in dogs. It has been reported in a cocker spaniel,(8) and I have seen hypochondroplasia in poodles, a German shepherd, and mixed breed dogs.

2. DYSCHONDROSTEOSIS

This disorder is characterized by a mild mesomelic dwarfism and a bilateral malformation of the distal radius and ulna usually referred to as Madelung's deformity. Madelung's deformity is a dyschondroplasia of the distal radial epiphysis.(4) Interestingly, McCusick ascribes it to a hypoplasia of the distal ulna.(49) Some authors have suggested that Madelung's deformity can also occur as a separate genetic trait, as a nongenetic deformity, or in conjunction with other skeletal dysplasias, and that only patients with shortening of the tibia relative to the femur have dyschondrosteosis.(27)

Deformities similar to those of dyschondrosteosis have been reported in dogs. Specifically, the autosomal recessive dwarfism in malamutes associated with spherocytosis and membrane abnormalities has many similarities.(25) The condition of ocular dysplasia and forelimb deformities described in Labrador retrievers also has similarities,(16) as does a syndrome in Samoyeds that involves ocular abnormalities and limb deformities much like those in Labradors.(55) In the Samoyed syndrome, which is inherited as an autosomal recessive trait, the females are often affected more severely than the males. Dyschondrosteosis in humans is thought to be an autosomal dominant trait, or perhaps an X-linked dominant. However, females are often affected more severely than their male relatives, and the suggested X-linked nature may be attributable to a bias of ascertainment. The syndromes in the Labradors and the Samoyeds also have features in common with hereditary arthroophthalmopathy (B.9), especially the retinal detachment and cataracts.(13)

3. - 6. METAPHYSEAL CHONDRODYSPLASIAS

This is a group of conditions in which abnormalities of the metaphyses predominate, with essentially normal epiphyses, skull, and trunk. Immunologic and endocrine dysfunctions are associated with several of these disorders in humans. Severity of the observed abnormalities varies greatly in this group of disorders.

Lang and Biery classified the medial patellar luxation syndrome, seen primarily in small breed dogs, in this category, associating it with hypoplasia of the medial femoral condyle.(45) The condition is discussed in detail elsewhere in this text and will not be considered further here.

A diet-related disorder seen in large dogs and associated with metaphyseal dysplasia is the syndrome of retained endochondral cartilage.(75) The radiographic appearance is that of a triangular metaphyseal radiolucency, usually most obvious in the distal ulna. This condition is discussed in Chapter 41 and is thought to be related to abnormally rapid ossification of the cortical portion of the metaphysis associated with abnormal calcium:phosphorus ratios in the diet.

I have observed a Vizsla who at maturity has the outward conformation of a hypochondroplastic animal but who had large cystic lesions of the metaphyses during development. These extended into the adjacent diaphyseal region and were reminiscent of retained endochondral cartilages (Fig. 57-1), but they occurred to a similar degree in all of the long-bone metaphyses. The radiographic lesions almost certainly represent zones of abnormal classification subsequent to a chondrodysplasia. The affected dog is otherwise normal and has had no evidence of pain associated with these abnormalities, unlike the situation often observed with retained endochondral cartilages.

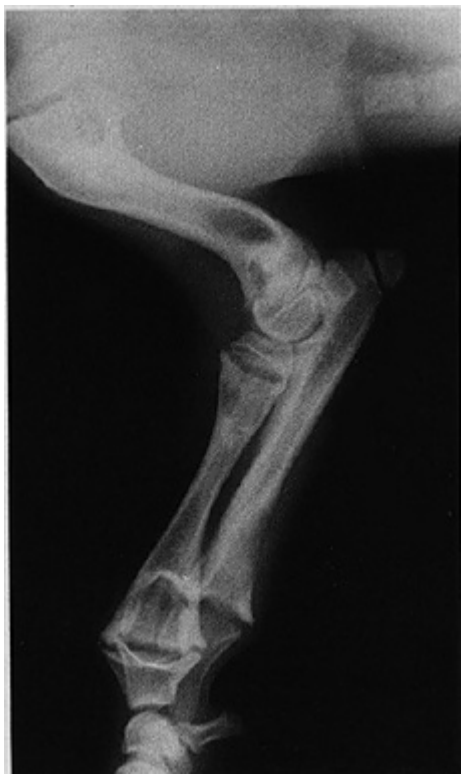

FIG. 57-1 Lateral radio raph of forelimb of a young Viszla dog. Large, undermineralized areas are visible in the metaphyses of the long bones. Clinically, the dog has a rhizomelic dwarfism but is otherwise healthy.

8. MULTIPLE EPIPHYSEAL DYSPLASIA

The major features of multiple epiphyseal dysplasia (MED) in humans are irregular epiphyseal growth with little or no vertebral involvement and, usually, a mild dwarfism. There is certainly more than one type. The more usual form is an autosomal dominant trait, while there is probably also at least one autosomal recessive form. In humans, differentiation from the spondyloepiphyseal dysplasias is aided by a regular appearance of the acetabulum early in life, although it may later remodel to conform to the shape of the femoral head. Stippling of the epiphyses can be seen radiographically in infants, while irregularity and underdevelopment of ossification centers are more apparent with increasing age. Spinal involvement is mild, with only irregular surfaces of vertebral bodies and slight cranial wedging seen. Early changes in the hips resemble Perthes disease, and the differentiation from that condition requires recognition of the generalized nature of the disorder. This should be taken into account when making a diagnosis of LeggCalve-Perthes disease in dogs in whom lesions are present bilaterally.(57) There is also an autosomal dominant form of MED confined to the hip joint, sometimes called "familial Perthes disease," which has similarities to canine hip dysplasia.(72)

9. ARTHRO-OPTHALMOPATHY

As originally described in humans, this disorder is an autosomal dominant condition characterized by progressive myopia, with retinal detachment and blindness, and a premature degenerative arthropathy of the joints.(73) Radiographically, there is an epiphyseal dysplasia. Other conditions with similar features have been grouped in this category but are probably distinct entities. As noted earlier, syndromes described in Labrador retrievers (16) and Samoyeds (56) have some of the features of this condition. It is therefore clear that single gene mutations can seriously affect both ocular and bony development.

10. PSEUDOACHONDROPLASIA

This is a relatively common condition in humans. The body proportions are similar to those of achondroplasia, hence the name, but the head and face are normal, and a trident conformation of the hand is not present. There is severe dysplasia of the epiphyses, with hypertrophy and marked flaring of the metaphyses resulting in a mushroomlike appearance. Marked clinical heterogeneity occurs in this grouping, with both autosomal dominant and recessive forms recognized.

An autosomal recessive form of this disorder has been reported in miniature poodles.(2,13,20,31,34,48,62) It is characterized by dwarfism and difficulties in locomotion due to limb abnormalities, which grossly consist of enlarged, stiff joints. Radiographically, the skull appears normal, but changes are present in the axial and appendicular skeleton. The changes seen are similar to those described in humans, with stippling and patchy densities of the epiphyses observed in young animals. In older animals, the bones are fully ossified but short and severely malformed. Histologically, there is abnormal hyaline cartilage with an associated delay of ossification.

11. SPONDYLOEPIPHYSEAL DYSPLASIA TARDA

In humans, manifestations of this disorder appear in midchildhood, with a shortening of the trunk relative to the limbs. A dorsal kyphoscoliosis usually develops, and the hamstrings tighten. Progressive degenerative osteoarthropathy occurs by midlife. Radiographically, the spine is virtually normal until about age five. Then generalized platyspondyly develops, with kyphoscoliosis and thoracic cage deformities following. There are characteristic malformations of the vertebral bodies involving heaping up of the central and caudal portions and eburnation of the end-plates. A small pelvis with deep acetabulae is present. Epiphyses of the appendicular skeleton are also dysplastic, primarily in the proximal portions. Inheritance is as an X-linked recessive, although similar abnormalities with autosomal dominant and autosomal recessive inheritances have been described.

A "short-spine" deformity in dogs has been reported, both historically in drawings and in the Japanese literature, which appears similar, if not identical, to this condition in humans.(35) The reported lesions differ little from the above description. Similar lesions have also been reported in other species, including cows, goats, and pigs (22,26,56)

II. DISORGANIZED DEVELOPMENT OF CARTILAGE AND FIBROUS COMPONENTS OF SKELETON

B. MULTIPLE CARTILAGINOUS EXOSTOSES

This condition is discussed separately as a type of benign bone tumors in the dog.

Osteochondroma is a cartilage-capped bony projection that may arise in any bone that develops from Cartilages The tumor may be either solitary, a monostotic osteochondroma, or multiple, polyostotic osteochondromas, also referred to as osteochondromatosis or multiple cartilaginous exostosis. Polyostotic osteochondromas are a heritable entity in dogs.

Osteochondromas are found in young immature dogs during the period of active bone growth. They respond to the same trophic influence as the growth plate and cease growth at skeletal maturity.(84) No sex predilection has been noted. Great Danes, Saint Bernards, and Hounds may be affected more commonly than other breeds.

The osteochondromas arise from the metaphyseal portions of long bones in the dog, particularly the femur and tibia (Fig. 75-7).(79,80,81,82,83) Vertebral involvement of cervical and thoracic vertebrae has also been found.(81,85) Tracheal involvement has been noted.

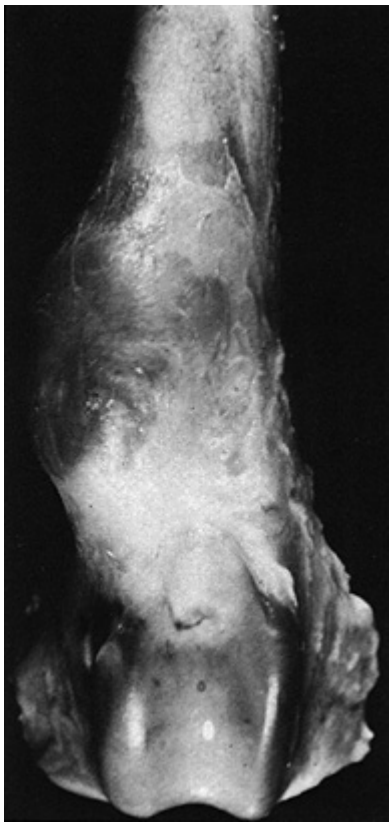

FIG. 75-7 Distal femur of a dog with multiple cartilaginous exostoses. There is asymmetric enlargement of the metaphysis immediately proximal to the articular surface.

Clinical signs associated with osteochondroma are due to compression and distortion of adjacent structures. Lesions on the limbs produce lameness and pain. Those tumors arising in the vertebrae show progressive limb weakness or paraparesis. Tracheal osteochondromas present with respiratory distress localized to the upper airway.

On gross examination the tumor appears as a nodular projection from the surface of the bone that blends with the parent bone at the base of the tumor. A cap of hyaline cartilage covers the surface. On cut section the trabecular bone and marrow spaces of the tumor are continuous with those of the underlying bone (Fig. 75-8).

Histologic examination shows the cartilage cells of the cap to be in rows similar to the orientation of cells in a normal epiphysis (Fig. 75-9). The cartilage cap is thickest in young animals and decreases in thickness with maturity. At the base of the cartilage a zone of chondro-osseous transformation is present. The base of the lesion is trabecular bone with marrow spaces that are continuous with those of the underlying bone.

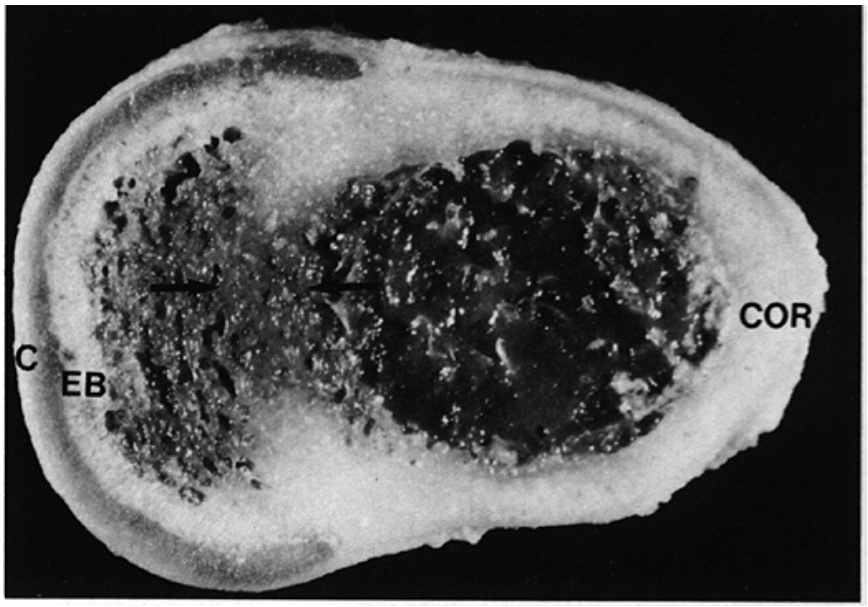

FIG. 75-8 Cross section through the exostosis described in Figure 75-7. There is remodeling of the original cortex (opposing arrows) covered by the exostosis. Enchondral Cancerous bone (EB) is present beneath the cartilage cap (C). (COR, unaffected cortex)

Following complete surgical excision of the mass, the prognosis may be good. When incompletely excised, osteochondromas may recur. Occasionally osteochondromas may undergo malignant transformation to chondrosarcomas and osteosarcomas.

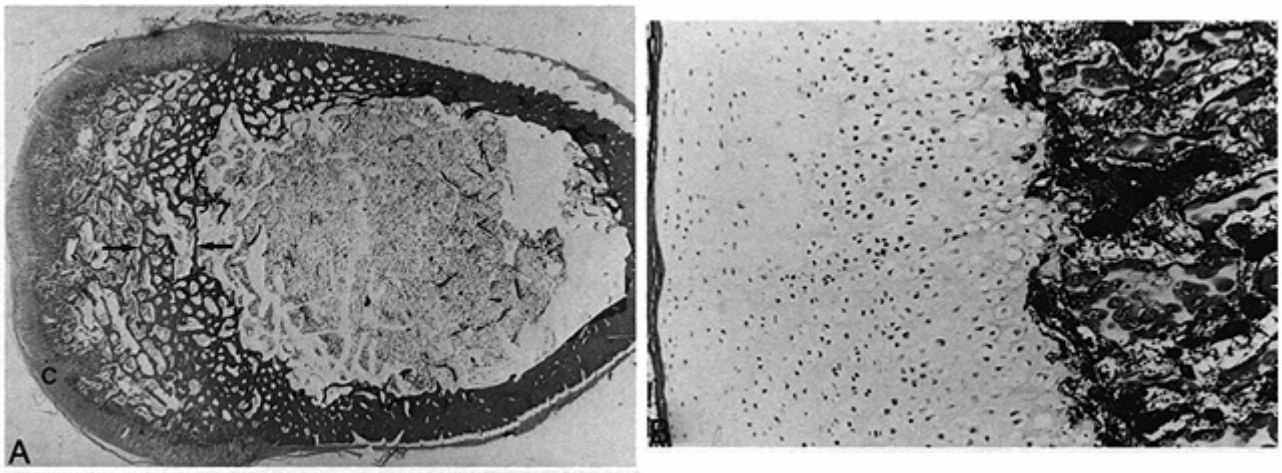

FIG. 75-9 (A,B) Histologic section of a cartilaginous exostosis Note the cartilage cap (C) and remodeling of the cortex underlying the exostosis (opposing arrows).

III. ABNORMALITIES OF DENSITY OF CORTICAL DIAPHYSEAL STRUCTURE AND/OR METAPHYSEAL MODELING

A. OSTEOGENESIS IMPERFECTA COGENITA

In humans osteogenesis imperfecta is one of the most common inherited disorders of the skeleton. Many classification schemes have been proposed based on age at onset, clinical features, and severity. For the sake of conformity, the Paris nomenclature classification will be used here. Bone fragility is the cardinal feature of this condition. In osteogenesis imperfecta congenita, the disease is so severe that fractures occur in utero, with limb shortening and deformities already present at birth. The cranium is usually poorly ossified and stillbirths are common, often resulting from intracranial bleeding. Long bones may be short and wide or thin and gracile. Numerous wormian bones are seen in radiographs of the skull and are

characteristic of these syndromes. Osteoporosis is a prominent radiographic feature later in life. Hernias are common. Blue sclerae, due to the thinness of the sclerae, are usually, although not always, seen when severe bone disease is present. The skin is also characteristically thin and translucent, and the teeth often have an abnormal amber, yellowish brown, or translucent blue coloration. Deafness is an inconsistent feature. The condition is usually inherited as an autosomal dominant. New mutations appear to be common, although autosomal recessive inheritance has been strongly implicated in some cases.

The disorder does not appear to be as common in animals as in humans, although stillborn fetuses or those that die early in life are rarely radiographed. Numerous cases have been described in the older literature, but many of these may be related to nutritional imbalances or represent other conditions (e.g., 15). However, Dammrich described in detail a condition that appeared to be a mild form of osteogenesis imperfecta congenita.(24) I have seen a case of classic osteogeneis imperfecta congenita in a male mixed breed dog.8 He had malformed limbs that the breeders noticed early in life and multiple healing fractures were seen in radiographs taken at 7 weeks. He had eaten well as a pup and was fed the same commercial puppy food diet as his littermates, who were unaffected. He suffered additional fractures early in life not associated with any apparent trauma and continued to do so until he was put to sleep at 5 months. He suffered from severe dyspnea at that time, caused by the disproportionately greater growth of the soft tissues in the thorax, resulting in compression and compromised function of the lungs due to the small rib cage. A radiograph of one forelimb is shown, illustrating the characteristic osteoporosis and multiple fractures (Fig. 57-2). The dog also had blue sclerae and translucent teeth, and multiple wormian bones were seen in skull radiographs. Recent evidence indicates that this group of diseases results from deranged metabolism of collagen, since defects in collagen synthesis have been demonstrated in several patients. (14,30)

B. OSTEOGENESIS IMPERFECTA TARDA

This is a form of osteogenesis imperfecta in which the manifestations are less severe and in which fractures may occur only late in life, or not at all. Dogs with this form of the disease have also been seen, two of whom were littermates. The condition has also been reported to occur in cats, although it has not been well characterized histologically.(32)

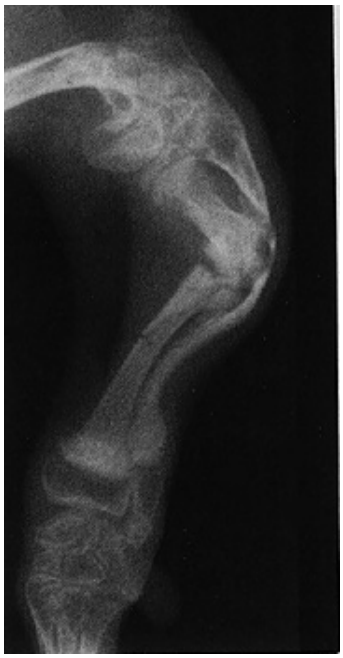

FIG. 57-2 Lateral radiograph of the forelimb of a young, mixedbreed dog with osteogenesis imperfecta congenita. Multiple fractures, with subsequent deformities of the bones, are seen. Bones in the distal portion of the limb are osteoporotic as a result of disuse due to the deformities. Abundant callus formation is seen at the older fracture sites.

C. JUVENILE IDIOPATHIC OSTEOPOROSIS

This is a rare disease of uncertain etiology in humans. Diagnosis is made primarily by exclusion of other causes of decreased skeletal density. Onset is early and the disorder is self-limiting, although there may be residual stunting and skeletal deformities. Radiographic changes include demineralization, bowing of tubular bones, and concavities of the vertebral bodies. No wormian bones are seen in the skull, which aids in differentiating this disorder from osteogenesis imperfecta.

(77) I have seen a case of a young, large, mixed breed dog fed an adequate diet and with no other discernible disorders who presented for difficulty in walking and pain when touched in the pelvic area. Radiographically, there was a compression fracture of the seventh lumbar vertebra, with other changes similar to those outlined above (Fig. 57-3). The dog healed well, and bone density became normal later in life. While the diagnosis is no easier to prove than in humans, the case certainly would seem to fit into this category. The cases reported by Calkins and co-workers as osteogenesis imperfecta in a series of dogs would also seem to fit better into this category.(15)

N. TUBULAR STENOSIS

This form of endosteal hyperostosis is designated as tubular stenosis (infantile cortical hyperostosis), or Caffey disease. The disorder is most common in children under 6 months of age who present with pain, swelling, and inflammation of a localized area. The mandible, shoulder girdle, or a limb is affected most often. Acute episodes are associated with fever, leukocytosis, and an increased red cell sedimentation rate. These episodes resolve spontaneously within a few weeks, but relapses often occur. Radiographically, the cortices of affected bones are widened, sclerotic, and irregular. These abnormalities resolve with remission of the illness. The disorder occurs in familial aggregates, but the mode of inheritance is not well established. The similarity of this disorder to panosteitis,(11) which is discussed in detail in Chapter 49, seems reasonable to me, although it has often been claimed that no analogue of panosteitis exists in other species.

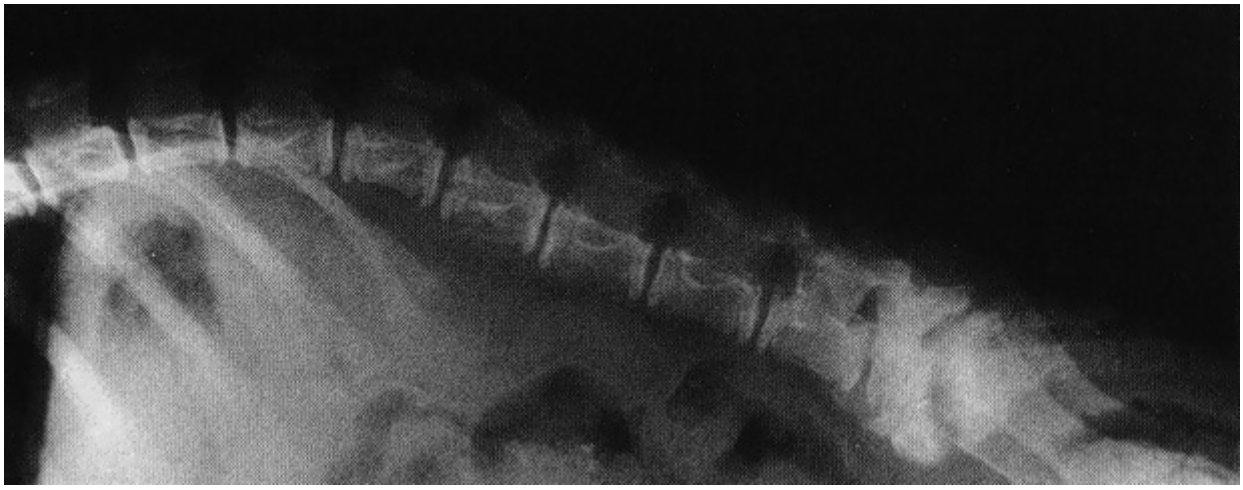

FIG. 57-3 Lateral radiograph of the lumbar spine of a young, large, mixed-breed dog. There is a compression fracture of the seventh lumbar vertebra. Osteoporosis is also present, with undermineralization of the vertebrae and pelvic bones.

S. METAPHYSEAL DYSPLASIA

In this condition in humans, there is a marked disturbance in bone modeling. Clinical features are mild, with valgus deformity of the knees sometimes being the only obvious abnormality, although muscular weakness, scoliosis, and osseous fragility are sometimes present. Radiographic changes are striking, with gross flaring of the metaphyses of the long bones in

the legs, undermodeling of bones in the arms, and thin cortices.

A dysplasia of the medial aspect of the distal tibial metaphysis causing an inward curvature of the distal tibia and an associated curvature of the fibula has been reported in dachshunds.(54) This results in a severe varus deformity at the tarsus. In some cases there is an associated exostosis from the craniomedial aspect of the metaphysis. Only one leg is usually affected, although both may be. Data from the published report and from the cases we have seen in miniature dachshunds are consistent with an autosomal recessive mode of inheritance of this disorder.

DYSOSTOSES

Malformation of individual bones, singly or in combination

I. DYSOSTOSES WITH CRANIAL AND FACIAL INVOLVEMENT

E. MANDIBULOFACIAL DYSOSTOSIS

In humans, mandibular hypoplasia occurs as an isolated anomaly or as a component of other syndromes. When associated with a cleft palate and glossoptosis, it is known as the Pierre Robin anomalad. The only major clinical problem associated with mandibular hypoplasia is possible airway obstruction in the neonatal period; otherwise it is primarily a cosmetic problem. The isolated condition in humans is sporadic and assumed to be nongenetic.

This is not an uncommon defect in dogs. Heritable forms have been reported in cocker spaniels (58) and longhaired dachshunds.(33) I have seen several cases, predominantly in poodles and dachshunds. Affected animals do not appear to have any problems eating or drinking. Their major problems are dental ones, associated with the malocclusion. The defect is also seen as part of the syndrome of otocephaly.(29)

II. DYSOSTOSES WITH PREDOMINANT AXIAL INVOLVEMENT

A. VERTEBRAL SEGMENTATION DEFECTS

The predominant feature of these disorders is involvement of the vertebral column, although the shoulder girdle and ribs are sometimes involved, and there may also be soft tissue anomalies. In animals this grouping is represented predominantly by hemivertebrae and block vertebrae.

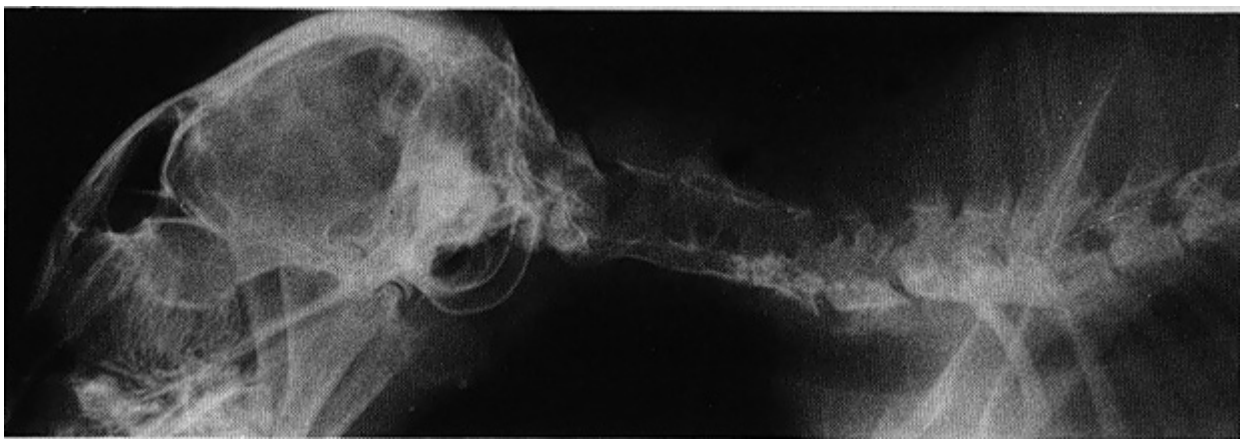

FIG. 57-4 Lateral radiograph of the skull and cervical vertebrae of a 10-month-old Siamese cat. Malformation and fusion of the fourth through sixth cervical vertebrae are seen. This malformation is similar to that of the Klippel-Feil anomaly in humans.

The Klippel-Feil anomalad in humans shows fusion of the cervical vertebrae as the primary defect, with fusion of other vertebrae as inconsistent findings. Other variable findings include deafness, scoliosis, mental retardation, renal abnormalities, cardiac malformation, and spinal defects. We have seen a 10-month-old Siamese cat with this syndrome. The cat exhibited diffuse neurologic manifestations that prompted radiographic examination of the cervical spine. Malformation and fusion of the cervical vertebrae were seen (Fig. 57-4). The major differential diagnosis for this disorder in a young Siamese cat is mucopolysaccharidosis VI (vide infra). This cat, however, lacked the other skeletal malformations seen in the latter disorder, and presence of the enzymatic defect associated with it was ruled out by electrophoresis of urinary glycosaminoglycans and assay of leukocyte arylsulfatase B.

III. DYSOSTOSES WITH PREDOMINANT INVOLVEMENT OF EXTREMITIES

A. ACHERIA

B. APODIA

Congenital absence of the forearm or hand is a relatively common abnormality in humans. Most defects are transverse (amelia) and unilateral. Lower limb deformities are less common and also usually unilateral. There are no familial tendencies to these deformities, and intrauterine amputation by amniotic bands is thought to be a common cause of amelia.

Few reports of this condition have appeared in the veterinary literature. A report of two kittens with complete absence of the hindlimbs has appeared.(64) It is likely that this condition occurs more frequently, but affected animals probably either die, are put to sleep by the breeders without being brought to a veterinarian, or are just not reported in the literature.

Longitudinal limb deficiency, or hemimelia, probably results from defective development of the embryonic limb bud. In humans, hypoplasia or aplasia of the radius, usually with associated anomalies of the hand, is the most common of this type of abnormality. Tibial aplasia (meromelia) has been reported to occur as an autosomal dominant trait in one kindred. (19)

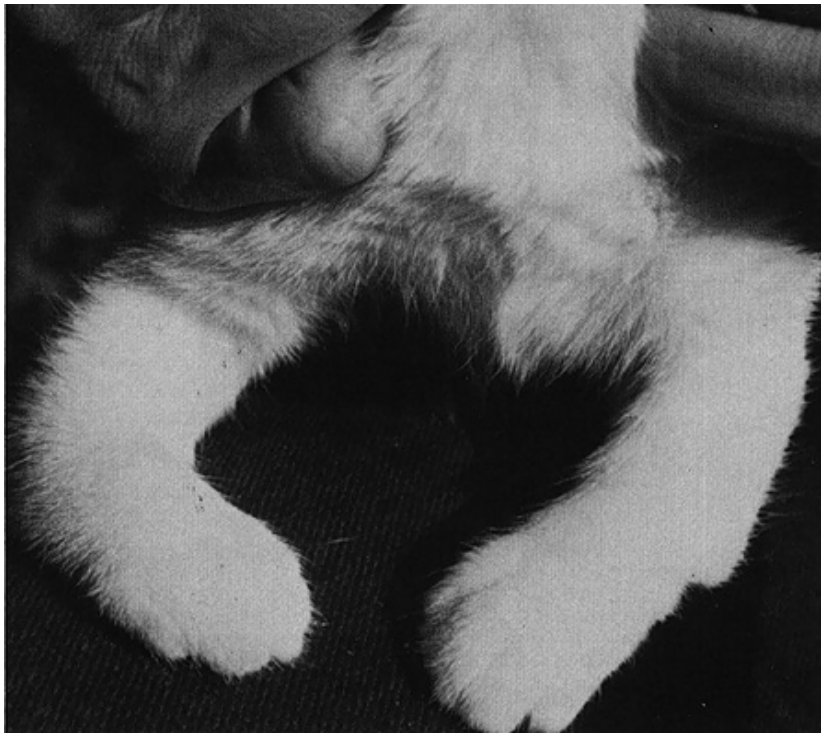

FIG. 57-5 Photograph of the forelimbs of a kitten with radial aplasia shows the characteristic medially directed, angular deformities associated with this defect.

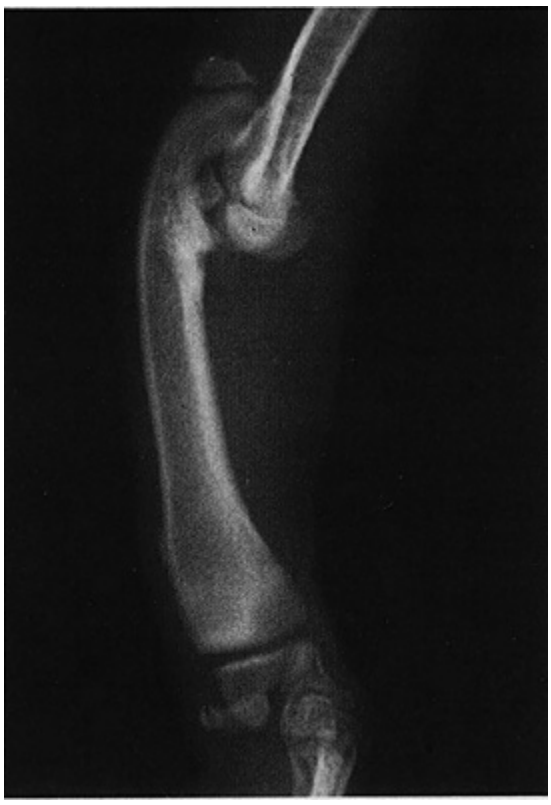

FIG. 57-6 Lateral radiograph of the forelimb of a kitten with radial aplasia. A marked increase in the diameter of the ulna is obvious.

Few reports of hemimelia in dogs and cats have appeared. (1,5,47,76) As in humans, radial agenesis appears to be the most common of these defects. I have seen numerous cases of this anomaly, primarily in cats. Affected animals have medially directed angular deformities of the affected limbs (Fig. 57-5). There may be complete or partial agenesis of either one or both radii with a compensatory increase in the diameter of the ulna (Fig. 57-6). Tibial agenesis is less common.(5) I have seen one litter of cats in which four of the five members were bilaterally affected. Three had complete agenesis bilaterally and the fourth had complete agenesis in one limb and a partial defect in the other (Fig. 57-7).The fibulae were markedly enlarged in the affected animals. A congenital, bilateral, terminal anterior hemimelia in two families of Chihuahua dogs has been reported and the pedigrees interpreted as being consistent with autosomal recessive inheritance.(1) However, one dog had a transverse limb reduction, which should therefore be termed an amelia, and its littermate had lesions I believe would be better described as ectrodactyly. The evidence for autosomal recessive inheritance was also not very strong, and no breeding studies were performed. Without further evidence to support the claim, the inherited nature of these abnormalities is dubious.

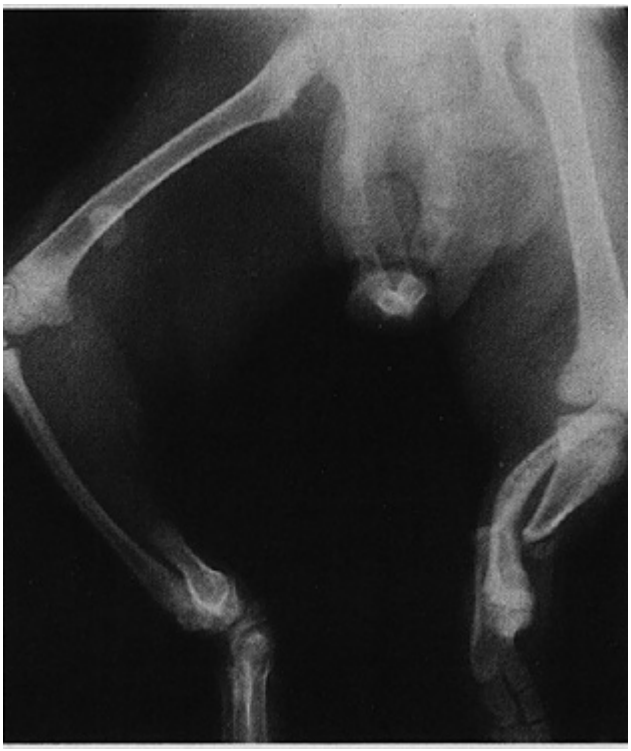

FIG. 57-7 Radiograph of the hindlimbs of a kitten with complete agenesis of one tibia and agenesis of the distal portion of the other. Both fibulae are markedly thickened, and that on the side with the partial defect of the tibia is bowed where the tibial fragment ends.

C. ECTRODACTYLY SYNDROME

Maldevelopment of the central rays of the limbs may produce longitudinal splitting of the extremities. Split hand or foot may be sporadic, but autosomal dominant and recessive forms of this condition, sometimes termed the "lobster claw" defect, have been described. The defect also occurs as part of several syndromes.

Several cases have been reported in cats and dogs.(10,17,37,64,65) Carrig and co-workers reported a series of 14 dogs with this defect.l7 Splitting was most commonly between the first and second metacarpals, although all variations were seen. Only one case was bilateral. Other abnormalities associated with the defect in this group were digit contractures, digit aplasia, and metacarpal hypoplasia and fusion. There was no breed or sex predilection noted. Studies of this defect in cats indicated that it was inherited as an autosomal dominant with variable expressivity.(65)

I. POLYDACTYLY

The presence of one or more extra digits is termed polydactyly. In humans, preaxial polydactyly involves an additional digit or digits cranial to the anatomical axis of the limb, that is, on the thumb or great toe side. In postaxial polydactyly, the extra digits are adjacent to the fifth finger or toe. Most cases are nongenetic, but several preaxial forms are inherited as simple autosomal dominant traits. Postaxial polydactyly is the more common form in humans. Both autosomal dominant and recessive forms have been reported. Polydactyly is also a feature of several more serious syndromes.

In dogs and cats, preaxial polydactyly is by far the more common form.(25,26,70) In cats, it is inherited as an autosomal dominant trait with variable expressivity.(25) A similar inheritance pattern appears to apply to the occurrence of multiple dewclaws in the dog, as is seen in the Great Pyrenees. Lateral polydactylism occurs less frequently but has been reported in two

members of a mixed breed litter.(36) There is no apparent clinical significance to these conditions, other than an increased propensity for traumatic injury of the partial supernumery digits.

J. SYNDACTYLY

This condition involves bony and/or soft tissue union of two or more digits, with varying degrees of involvement. Isolated syndactyly can occur sporadically or as a genetic entity. Several types with varying modes of inheritance have been described. Generally, genetic forms are bilateral and symmetrical, while sporadic cases are usually unilateral.

Few cases of syndactyly in dogs and cats have been reported in the literature.(7,12,23,42,46,61) This syndrome is probably more common than would be assumed from the reported cases, since few clinical problems are associated with the malformation. I have seen a few cases, including two of nine Irish setters in a litter. The radiographic appearance of a typical case is shown in Fig. 57-8.

CHROMOSOMAL ABERRATIONS

(Specific disorders not listed): primary metabolic abnormalities

11. COMPLEX CARBOHYDRATES AND MUCOPOLYSACCHARIDOSES

These disorders result from deranged degradation of glycosaminoglycans and belong to the general category of lysosomal storage diseases. At present, these disorders in humans are grouped into six major classifications, with several subgroups.(49,51,60) Each subgroup is characterized by the clinical manifestations, by the types of glycosaminoglycans excreted in the urine, and by a specific enzyme defect. Like most lysosomal storage diseases, the mucopolysaccharidoses are rare disorders in humans. In the past few years, two such disorders have been delineated in cats and two have also now been described in dogs.

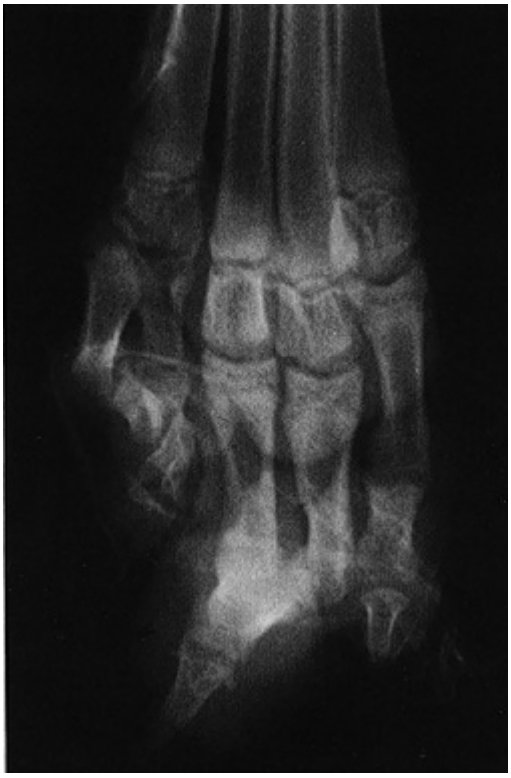

FIG. 57-8 Dorsal-palmar radiograph of the forepaw of a young Irish setter with syndactyly. Fusion of the distal portions of the first and second digits and the third and fourth digits is present.

A. MUCOPOLYSACCHARIDOSIS TYPE I (MPS l; (a-L-iduronidase deficiency)

Three syndromes have been associated with a-L-iduronidase deficiency in humans. The most severe form is known as the Hurler syndrome, which becomes clinically evident early in life. Affected children usually develop normally for a few months and then deteriorate mentally and physically. Although these children may be unusually large initially, dwarfism accompanied by abnormal faces and dysmorphia ensues. Progressive corneal clouding occurs, and the liver and spleen are enlarged. There are cardiac abnormalities associated with deposition of glycosaminoglycan in the coronary arteries and the heart valves. Mental development regresses after a few months, and retardation may be profound. Death occurs before the end of the second decade, usually as a result of cardiac failure or respiratory problems associated with thoracic deformity, abnormalities of bronchiolar cartilages, and frequent infection.

The habitus of patients with Hurler syndrome is characteristic. The head is large and features are generally coarse, with a depressed nasal bridge, hypertelorism, large lips and tongue, stubby malformed teeth, and a short neck. Short stature and stiff joints, especially in the hands, are present, as is kyphosis with a thoracolumbar gibbus. Radiographic findings include early closure of skull sutures resulting in scaphocephaly, an enlarged sella turcica, shallow orbits, widening of the medial end of the clavicle, oar-shaped ribs, shallow acetabulae, diaphyseal enlargement of long bones, and vertebral abnormalities. Vertebrae at the apex of the gibbus are hypoplastic, with cranial beaking.

Characteristic of Iysosomal storage diseases, material accumulates within Iysosomes. This appears as vacuolation of parenchymal and mesenchymal cells under light microscopy. The primary defect in this disorder is decreased activity of a-L-iduronidase, which blocks the normal degradation of dermatan and heparan sulfates. Partial degradation of these substances by endoglycosidases results in excretion of large fragments of the molecules, which can be identified in the urine.

A mild form of a-L-iduronidase deficiency characterized by severe corneal clouding, coarse faces, normal stature and intelligence, claw hands and stiff joints, and aortic valve disease occurs (Scheie syndrome). Carpal tunnel syndrome is common in these patients. A third, intermediate, form of this disorder also occurs and is known as the Hurler-Scheie syndrome. Affected persons have short stature, corneal clouding, deafness, stiff joints, and valvular heart disease. They also have severe dysostosis multiplex and micrognathism. Patients with this condition were originally believed to be compound heterozygotes of the Hurler and Scheie syndromes but are now considered to represent homozygotes of a different allelic mutation at the iduronidase locus. Other mutations at the same locus are also thought to exist because of the varying clinical features seen in some patients with proven a-L-iduronidase deficiency.

Mucopolysaccharidosis I has been recognized in both cats and dogs. The feline disease was first recognized in domestic short-haired cats and is characterized by facial dysmorphia with a large head, short ears, wide-spaced eyes and a broad nose, and larger than normal body size. Diffuse corneal clouding is present, and mitral insufficiency is common. Excessive urinary excretion of dermatan and heparan sulfates occurs, and (a-L-iduronidase is deficient in all tissues tested, including peripheral white blood cells. Leukocytes are routinely used to identify affected and carrier animals. Radiographic features include bilateral coxofemoral subluxation, fusion and widening of cervical vertebrae, and mild pectus excavatum. Affected animals have hindlimb gait abnormalities and appear to have some joint pain associated with the disorder. The disease is transmitted as an autosomal recessive trait and is most similar to the Hurler-Scheie syndrome in humans.(40,41)

The canine form of MPS I was recognized in a family of Plott hounds. The affected dogs were dwarfed and had progressive motor and visual defects. Joints were swollen and painful. Glossoptosis and corneal clouding were present. Radiographically, there was epiphyseal dysgenesis and periarticular bony proliferation. The femoral diaphyses were also enlarged. Increased granulation of lymphocytes was noted. Fibroblasts had deficient a-L-iduronidase activity, and excessive amounts of dermatan and heparan sulfates were excreted in the urine.

Pedigree analysis indicated an autosomal recessive mode of inheritance.(69,71)

E. MUCOPOLYSACCHARIDOSIS TYPE VI (MPS VI; arylsulfatase B deficiency)

This disorder is also known as the Maroteaux-Lamy syndrome. It has been separated into two subgroups, severe and mild forms, based on clinical manifestations. Both are characterized by growth retardation, hypertelorism, corneal clouding, a depressed nasal bridge, hepatosplenomegaly, and normal or near-normal intelligence. Cardiac valvular disease similar to that of MPS I also occurs. Hydrocephalus and atlantoaxial subluxation, consequent to hypoplasia of the odontoid process, are frequent complications. Radiographically, the disease is characterized by severe dyostosis multiplex. Prominent lesions include localized constriction of metaphyses, irregular epiphyseal ossification, paddle- shaped ribs , a hypoplastic odontoid process, hypoplastic cervical vertebrae, and a shoe-shaped sella turcica. Alder-Reilly bodies are present in the majority of leukocytes. Arylsulfatase B is deficient in all tissues, and partially degraded dermatan sulfate is excreted in excess in the urine. Mildly affected patients are often not diagnosed until adulthood, when decreased joint mobility becomes a problem.

Thus far this disorder has been recognized only in cats of Siamese ancestry.(21,44) Affected animals have hypertelorism, a depressed nasal bridge, and a flattened face. They are smaller than normal littermates and have short ears, a short tail, and large feet. There is a diffuse corneal clouding and usually a noticeable pectus excavatum. Locomotion deteriorates progressively, most noticeably in the hindlimbs, and affected cats have a characteristic "waddling" gait. Exostoses at the thoracolumbar junction produce hind limb paresis and paralysis in severely affected animals.(38) Hydrocephalus is common. Radiographic changes are most profound in the axial skeleton, with a hypoplastic odontoid process, widening and fusion of cervical vertebrae, and caudal beaking and frequently fusion of thoracolumbar vertebrae. There is a variable, generalized osteoporosis, with sclerosis of vertebral end-plates and articular facets. The long bones have marked epiphyseal dysplasia accompanied by severe degenerative joint disease. There are irregular acetabulae, and the coxofemoral joints are subluxated. These lesions become progressively worse with age, as can be appreciated in the radiograph of the 5l/2-year-old cat shown in Figure 57-9.

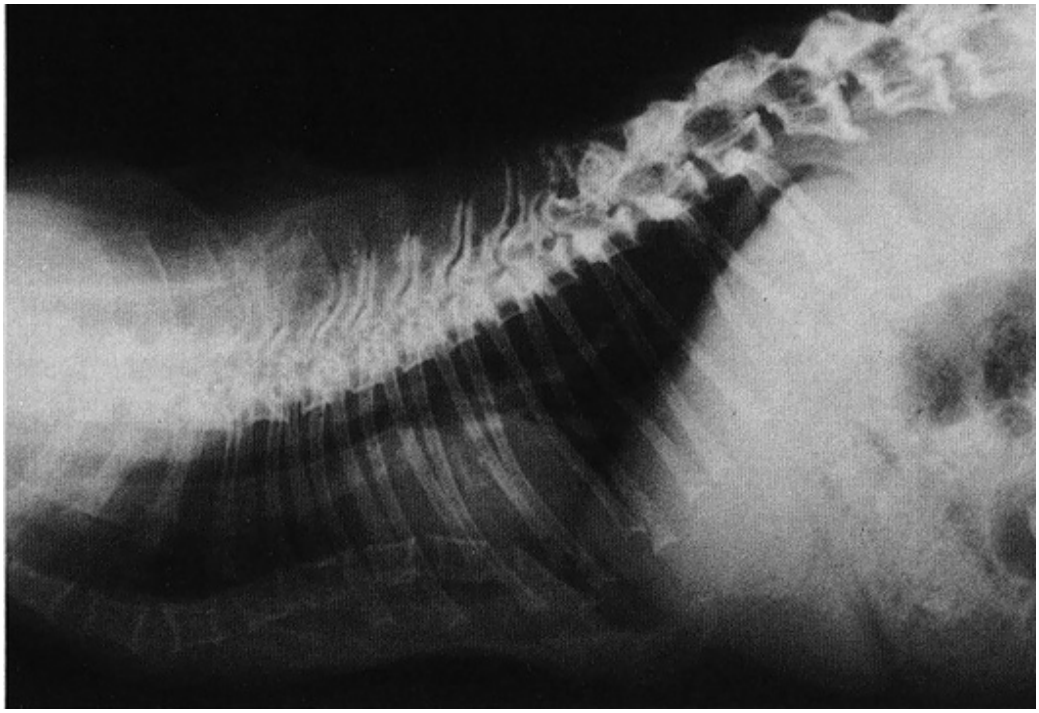

FIG. 57-9 Lateral radiograph of the thorax of a 5 1/2-year-old Siamese cat with mucopolysaccharidosis Vl. Osteoporosis and caudal breaking of vertebrae with sclerosis of the end-plates are seen. A marked pectus excavatum is present.

Almost all polymorphonuclear leukocytes have excessive coarse granulations that stain metachromatically with toluidine blue. Arylsulfatase B is deficient in all tissues. Dermatan sulfate, sometimes accompanied by chondroitin sulfate, is excreted in excessive amounts in the urine. The trait is transmitted as a simple autosomal recessive, but recent evidence indicates that more than one defective allele is present in the affected population. This latter finding probably accounts for the variable degree of severity of lesions that has been observed in affected cats.

At the time this chapter was written, approximately 20 naturally occurring cases had been identified throughout the United States and Canada. If one surveys the older literature on bony disorders in cats, several more probable cases can be identified, including several diagnosed as having hypervitaminosis A.(6,43,66,67) In Seawrights' studies of vitamin A toxicity,(68) which are discussed in detail in Chapter 58, he was never able to produce lesions as severe as those seen in some naturally occurring "cases" in Siamese cats. The bony lesions seen in those cats are virtually identical with those in our MPS VI cats, and almost certainly at least some of the animals had this disorder. Also in an article on rarefying osteodystrophy in the kitten, Barton showed a picture of a Siamese kitten with the typical appearance and stance of an MPS VI cat.(6) That cat was also reported to develop paraplegia "as a result of some minor injury" that was actually probably the natural progression of its metabolic disorder.(38)

F. MUCOPOLYSACCHARIDOSIS, Type VII (B-glucuronidase deficiency)

This is an extremely rare disorder in humans, with only about 15 cases having been reported. There has been great variability in the severity of clinical manifestations in these few patients. Severe manifestations include coarsened faces, corneal clouding, thoracolumbar gibbus, hepatosplenomegaly, and severe mental, motor, and growth retardation. Metachromatic inclusions are present in granulocytes. Radiographic changes include hypoplasia of vertebral bodies, spatulate ribs, epiphyseal dysgenesis, and pectus carinatum. B-Glucuronidase is deficient in cultured skin fibroblasts, and there is a variable chondroitin sulfaturia.(51)

This disorder has recently been identified in a family of mixed breed dogs. The affected dog had a large head with a shortened maxilla and protruding mandible. There was glossoptosis, and his teeth were peg-shaped and wide-spaced. Diffuse corneal clouding was present. He had progressive hindlimb paresis from 8 weeks and was unable to walk by 6 months. His rib cage was dorsoventrally compressed, and his limbs were short and curved. Joints were lax, swollen, and crepitant. Neurologic examination was normal within the limits imposed by his severe skeletal disease. Radiographic changes included platyspondyly, caudal beaking of vertebrae, and a generalized epiphyseal dysplasia. Lesions in the hips were marked, with large lucent areas in the femoral heads, irregular acetabulae, and bilateral coxofemoral luxation. Femoral diaphyses were markedly widened. Most peripheral lymphocytes and granulocytes contained cytoplasmic granules that stained metachromatically with toluidine blue. ,B-Glucuronidase was deficient in cultured fibroblasts, and chondroitin sulfates were excreted in excess in the urine.(39)

Bone abnormalities secondary to disturbances of extraskeletal systems (This category was deleted in the 1977 revision, but is included here.)

A. ENDOCRINE DISTURBANCES

1. PANHYPOPITUITARISM OR GROWTH HORMONE DEFICIENCY

These conditions result in retardation of skeletal maturation and short stature. An autosomal recessive form of this disorder occurs in German shepherds.(3) As Wynne-Davis and Fairbank (78) succinctly wrote, "Apart from the failure of maturation there is little of note to find in the skeleton" of these patients.

2. CONGENITAL HYPOTHYROIDIS

This condition in children (cretinism) can result in severe osseous changes, since thyroid insufficiency leads to reduced bone formation and remodeling. Clinical features of this condition include lethargy, apathy, constipation, disproportionate dwarfism, hypotonia, and mental retardation. Radiographically, there is delayed closure of fontanelles, delayed appearance of epiphyses, which, when they do appear, are irregular and fragmented, and cortical thickening of long bones. There is a thickened cranial vault in older children, and vertebrae are abnormal, with "hook-shaped" thoracolumbar vertebral bodies and kyphosis. In the rare untreated adult, there is severe dwarfing with scoliosis, unjoined epiphyses, and severe osteoarthritis resulting from disorganization of articular surfaces.

Congenital hypothyroidism has rarely been reported in dogs or cats. A recent report documented a congenital goiter in an 8-month-old mixed breed dog due to an organification defect.(18) The affected animal was disproportionately dwarfed, with a large head and short limbs. Generalized muscle weakness and apathy were noted. The hair coat was thin and juvenile, and a thorocolumbar kyphosis was present. Exophthalmos, lateral strabismus, and glossoptosis were also noted. Radiographic findings included lack of epiphyseal ossification, metaphyseal flaring, shortened facial bones, and open suture lines in the skull. The disorder appeared to be inherited as a simple autosomal recessive trait.

A case of congenital hypothyroidism in an 8-monthold female Boxer has also been reported.(33) She was dwarfed, with disproportionately short limbs and had a short broad skull with myxedematous facial features. She was apathetic and lethargic and had a juvenile hair coat, anemia, and hypercholesterolemia. Radiographically, there was undermineralization and dysgenesis of the epiphyses and metaphyseal flaring. Since that report, I have seen eight cases of apparently identical congenital hypothyroidism in Boxers. Affected dogs were 5 weeks to several years old when first seen. The typical appearance of an older affected dog is shown in Figure 57-10. The myxedematous features, thoracolumbar kyphosis, juvenile hair coat, and disproportionate dwarfism are characteristic. Marked epiphyseal dysgenesis was seen in all but the oldest dog. Long bones were typically short and wider than normal, with metaphyseal flaring, which was especially noticeable in the femur (Fig. 57-11). The vertebral bodies were malformed, with a caudal beaking not unlike that seen in the mucopolysaccharidoses (Fig. 57-12). Serum thyroid hormone levels were not elevated by administration of exogenous thyroid stimulating hormone. All dogs responded well to L-thyroxine supplementation, but degenerative changes were present in many bones and joints of most dogs after supplementation, especially in the vertebrae. One dog has had episodes of hindlimb paresis and ataxia secondary to bony impingement on the lumbar spinal cord, but the rest have been essentially asymptomatic after treatment. Pedigree analysis is consistent with inheritance of this trait as a simple, autosomal recessive.

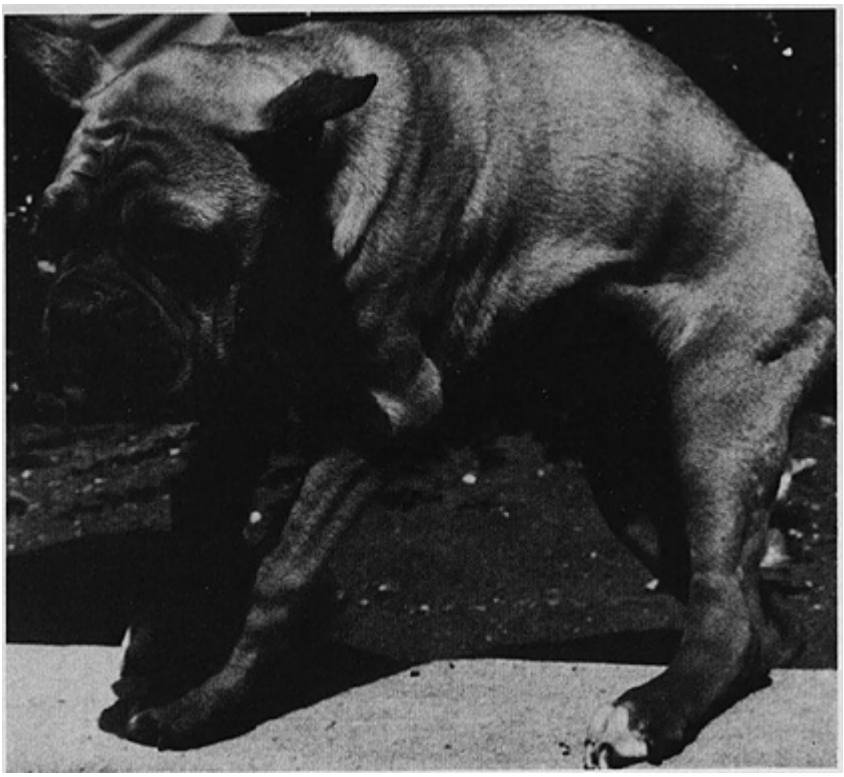

FIG. 57-10 Photograph of an 18-month-old Boxer dog with congenital hypothyroidism. Characteristic features include wrinkled facial skin, juvenile hair coat, a large head relative to the body, and thoracolumbar kyphosis.

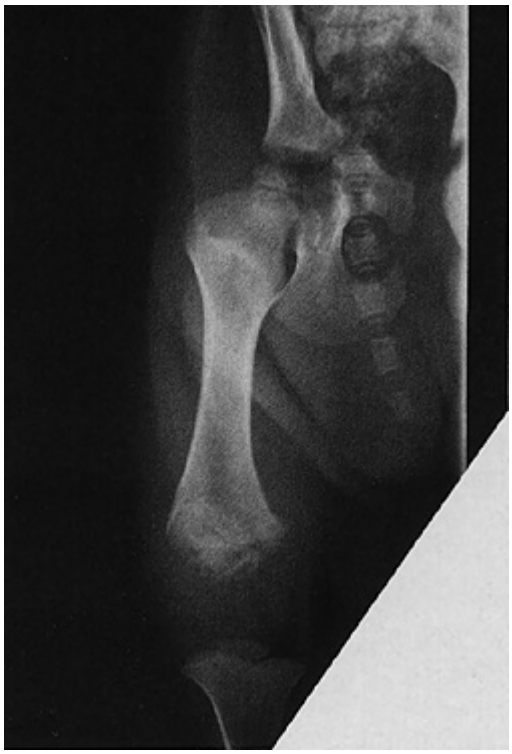

FIG. 57-11 Radiograph of a femur and its articulations m a congenitally hypothyroid Boxer dog. The femur is short and widened. The epiphyses are underossified and appear dysplastic. The physes are unfused. The stifle joint appears to be excessively wide owing to the lack of epiphyseal mineralization.

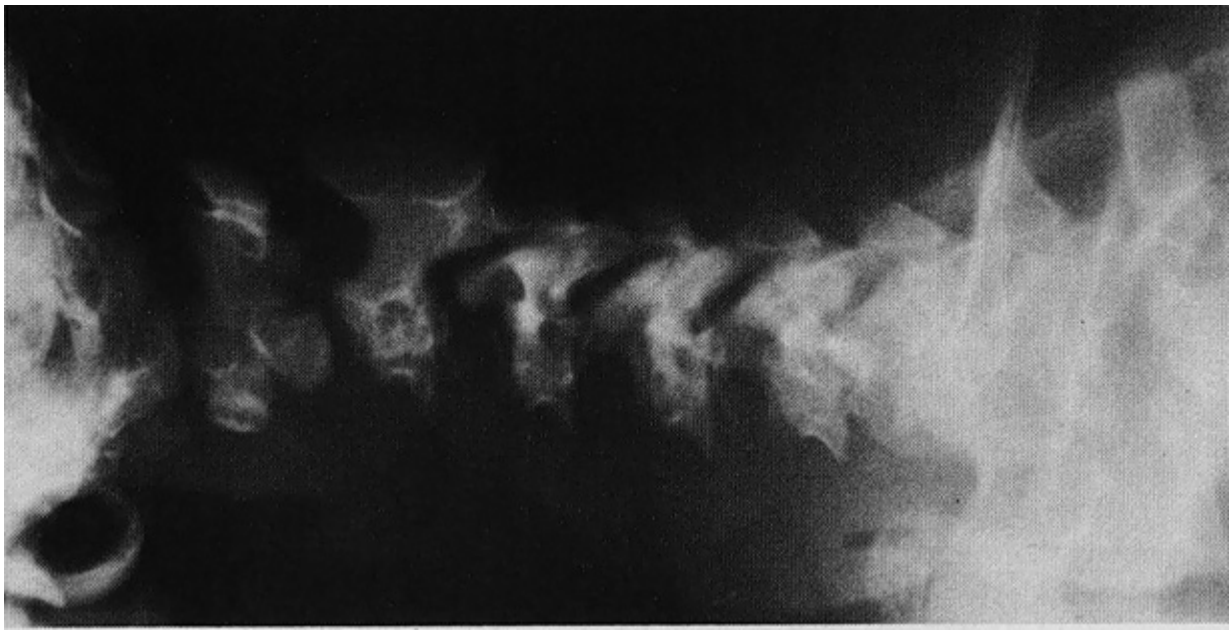

FIG. 57-12 Lateral radiograph of the thoracic spine of a Boxer dog with congenital hypothyroidism. The epiphyses are underossified and the intervertebral spaces appear widened. Caudal beaking of the vertebral bodies is present.

In addition, I have seen numerous other isolated cases of congenital hypothyroidism in both dogs and cats. The clinical features have not differed significantly from those reported above. Hydrocephalus has been present in some animals and has appeared to be clinically significant in a few, although it is difficult to separate the effects of hydrocephalus from those of the hypothyroidism. Constipation has been a prominent feature in some animals and was the cause for presentation of two affected kittens. When presented with a dwarfed young animal with lethargy and a juvenile hair coat, the veterinarian should always consider congenital hypothyroidism. Radiographic features as described above provide further evidence for the nature of the defect. Thyroid-stimulation tests should be performed, keeping in mind age-related differences in resting thyroid levels observed in dogs. Differentiation from other disorders such as the mucopolysaccharidoses is important, since therapy of hypothyroid animals instituted early in development results in essentially normal development. Even after prolonged lack of therapy, the response to therapy is rewarding, and residual mental retardation does not appear to be as severe as that observed in human patients.

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