Chapter 2

Skeletal System

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Introduction and general comments

The skeleton probably receives less attention than all other organ systems during postmortem examination, even by experienced pathologists. Most organs are examined as part of the routine necropsy technique, but examination of the skeleton is more often confined to those occasions where the clinical history clearly indicates a skeletal problem. As a result, many skeletal disorders are likely to be missed. Furthermore, lack of familiarity with the normal appearance of skeletal structures commonly leads to misinterpretation in cases where a skeletal disease is suspected and a detailed examination of the skeleton is performed.

Complete examination of the skeleton at necropsy is both impractical and unnecessary but the standard procedure should include assessment of the shape, flexibility and breaking strength of readily accessible bones, such as ribs, cranium and key limb bones. Ideally, one or two representative long bones should be sectioned longitudinally to reveal the growth plates, the thickness of the cortex, and the amount and density of trabecular bone in metaphyseal and epiphyseal regions. If the clinical history suggests the possibility of a skeletal disorder, a more detailed assessment is required. Antemortem or postmortem radiographs may provide valuable information on the extent and severity of bone proliferation, lysis or demineralisation, but is an insensitive indicator of diffuse bone loss, as occurs in osteoporosis.

The manifestations of generalised skeletal diseases vary between bones and even within bones of the same animal. For example, lesions associated with metabolic bone diseases, such as rickets and fibrous osteodystrophy, will be most marked at sites of rapid bone formation. The growth plates of the distal radius, proximal humerus, distal femur and proximal tibia should therefore be targeted for gross and histological examination. Costochondral junctions of the largest ribs are also useful sites to examine in such cases. In osteoporosis, the depletion of trabecular bone is more rapid than that of cortical bone, presumably due to the greater surface area available for resorption in trabecular bone tissue.

This paper presents an overview of skeletal diseases of ruminants, with an emphasis on aetiology, pathogenesis and gross lesions.

Skeletal dysplasias

A diverse range of inherited disorders of bone and cartilage formation, referred to as skeletal dysplasias, has been reported in human beings and domestic animals. Only a small number of these have been described in any detail in ruminants.

Chondrodysplasias

Since most of the skeleton develops by endochondral ossification, where bone replaces a crude cartilage model, any abnormality in cartilage development can have a substantial effect on the skeleton. Most, but not all chondrodysplasias are characterised by disproportionate dwarfism, and the effect is usually generalised.

In **cattle**, the most severe form of chondrodysplasia is the lethal **bulldog type**, which is best known in the Dexter breed but also occurs in Holsteins and occasionally in the Charolais and Jersey breeds. Dexter cattle are considered short-legged derivatives of the Kerry breed, originating from Ireland, and are gaining in popularity in many countries because of the desirability of small, easily managed cattle for "lifestyle" farms. Some short-legged Dexters are heterozygous for an incompletely dominant gene which, when homozygous, gives rise to a bulldog calf. Bulldog calves may be carried to full term but are usually aborted before the seventh month of gestation and may not be detected by the owner. The skeletal abnormalities are severe and relatively consistent. As well as being much smaller than normal for the stage of pregnancy, they have extremely short limbs, which are usually rotated, a domed head with retruded muzzle and protruding mandible, and a large ventral abdominal hernia. The tongue is of normal size so protrudes markedly. The shortened limb bones consist of mushroom-shaped, cartilaginous epiphyses separated by a short, central segment of diaphyseal bone. Holstein bulldog calves are similar to those of the Dexter breed, but in Holsteins, the defect is characterised by autosomal recessive inheritance rather than incomplete dominance. The defective gene coding for chondrodysplasia in Dexter cattle has recently been identified and a test for carriers is now commercially available.

Brachycephalic ("snorter") type dwarfism was common in the Hereford breed during the late 1940's and early 1950's, but also occurred in other beef breeds, especially the Angus. Although inherited as an autosomal recessive trait, the defect appears to be partially expressed in heterozygotes, which are slightly smaller and more compact than normal. Selection for this phenotype most likely facilitated the spread of the chondrodysplasia gene in these traditional beef breeds and accounted for the high gene frequency. With a change in emphasis towards a larger frame score in beef cattle, and the introduction of programs to eliminate the defective gene, snorter dwarfism is now rare.

Snorter dwarfism is a much milder form of chondrodysplasia than the bulldog type. Affected calves have a short, broad head with bulging forehead, retruded upper jaw and a slightly protruding mandible. The vertebral column is shortened and the ventral borders of individual vertebrae are flattened, a useful diagnostic feature visible radiographically in young calves. Chronic ruminal tympany is a feature of snorter dwarfs, possibly as a result of reduced intra-abdominal space and impaired eructation. There is premature closure of basicranial synchondroses leading to compression of the cerebellum and shortening of the brain stem. The distal limb bones are proportionately shorter than proximal bones, the metacarpi showing the greatest degree of shortening. Interestingly, the width of long bones from brachycephalic dwarfs is comparable to, or greater than that of normal calves. The ratio of total metacarpal length to diaphyseal diameter is therefore a useful diagnostic indicator of this form of dwarfism. In snorter dwarfs the ratio is usually 4.0 or less, but in normal animals it is greater than 4.5.

In **sheep**, the most common form of chondrodysplasia is **spider lamb syndrome**, a semi-lethal condition of Suffolk and Hampshire sheep. Spider lambs were first recognised in North America in the late 1970's and the defect has since been introduced to Australia and New Zealand with imported Suffolk genetics. The trait is characterised by autosomal recessive inheritance with complete penetrance, but with variation in expressivity between individuals. The high prevalence of spider lamb syndrome in North America is probably due to selection for long-legged animals heterozygous for the "spider" gene.

Lambs with spider syndrome may be aborted or stillborn, but most are born alive showing skeletal deformities of varying severity. Some appear clinically normal at birth but develop typical signs of the disease within their first month of life, including disproportionately long limbs and neck, shallow body, scoliosis and/or kyphosis, sternal deformity, and valgus deformity of the forelimbs below the carpus, creating a "knock-kneed" appearance. Hind limb deformities may also be present, but are less severe than those involving the forelimbs. Facial deformities, including "Roman nose", deviated nasal septum and shortening of the maxillae are common, but not consistent. The deformities of the limbs and spinal column become progressively more severe with age. Diagnosis is best confirmed by demonstrating characteristic radiographic changes in the elbow, sternum and shoulder. Multiple, irregular islands of ossification are present consistently at these sites and there is malalignment and displacement of sternebrae.

Other gross lesions that may be detected at necropsy include: elongation of occipital condyles in a craniocaudal direction and dorsal deviation of the sternum between the second and sixth sternebrae. The caudal sternebrae often fail to fuse across the midline. Cervical and thoracic vertebral bodies contain excessive quantities of cartilage with disorganized arrangement, often accompanied by abnormalities in shape and symmetry. The olecranon and distal scapula also contain an excess of cartilage surrounding the multiple, irregular-shaped islands of

ossification. Severe degenerative arthropathy, particularly involving the atlanto-occipital, elbow and carpal joints, is present in lambs older than 3 months.

A point mutation in ovine FGFR3 (a receptor for fibroblast growth factor) has been identified as the underlying defect in spider lamb syndrome. The gene encoding this receptor has largely been cloned and sequenced, and an accurate test for detecting heterozygous individuals is now available.

A chondrodysplasia characterized by disproportionate dwarfism and varus deformity of the forelimbs has recently been recognised in **Texel sheep** in New Zealand. The syndrome appears to be inherited as an autosomal recessive trait, but with variable expression. Affected lambs appear normal at birth, but by 2-4 weeks of age show evidence of reduced growth rate, shortened neck and legs, varus forelimb deformities and a wide-based stance. Severely affected lambs show progressive reluctance to walk, respiratory difficulty following exercise, and often die within the first 4 months of life. In such cases, the articular cartilage on major weight-bearing surfaces of the hip and shoulder joints may be completely eroded, exposing the subchondral bone. The trachea is flaccid, sometimes kinked, and tracheal rings are partially flattened. The biochemical defect has yet to be characterised but presumably involves the synthesis of either type II collagen (the major type of collagen in cartilage) or glycosaminoglycans.

Osteogenesis imperfecta

This disease is characterised clinically by joint laxity and excessive bone fragility due to a genetic defect in type I collagen. Several forms of varying in severity are recognised in human beings, where it is one of the most common inherited disorders of connective tissue. Most reports in animals are in calves and lambs and appear analogous to the most severe form of the disease in humans. There is convincing evidence to support an autosomal dominant mode of inheritance, even though the sire and dam of affected animals are clinically normal. The disease results from new mutations in gonadal germ cell lines and may therefore occur in "outbreak" form, depending on the degree of gonadal mosaicism and the number of offspring sired.

In **cattle**, the disease has occurred in Australia, USA and Denmark in the offspring of three clinically normal, unrelated **Holstein-Friesian** bulls, and in **Charolais** calves in Denmark. The manifestations of the disease in each report in calves have been similar, but minor variations exist, suggesting that different mutations may be involved. Affected calves are usually born alive and are of normal size, but most are unable to stand due to marked hypermobility of the joints and, in some cases, the presence of limb fractures. Some affected Holstein-Friesian calves are able to stand and can walk with difficulty, but have a characteristic crouched stance with pasterns almost touching the ground. As in some forms of the human disease, calves with osteogenesis imperfecta have

small, translucent pink-gray teeth, which are barely erupted at birth and may fracture in calves that survive for a few weeks. In some calves the sclerae are distinctly blue, but this is more evident during postmortem examination following enucleation of the eye. Skin fragility is not a feature of the disease in calves although bone fragility has been reported in Belgian calves with dermatosparaxis.

The main findings during postmortem examination of calves with osteogenesis imperfecta relate to the skeleton. The bones are essentially normal in shape, but are extremely brittle and can usually be broken with little effort. Acute fractures are common in the mandibles and major limb bones; the latter probably occurring during attempts to stand. Severely affected calves may have multiple, well-developed calluses on their ribs, indicating intrauterine fractures. Tendons are thinner than normal and discolored pink.

In **sheep**, severe forms of osteogenesis imperfecta have occurred in two flocks in New Zealand and one in the United Kingdom. In both New Zealand reports, one of which involved the **Romney** breed, affected lambs died either during parturition or soon after. The Romney lambs had a domed head with brachygnathia inferior, dark blue sclerae, fragile, pink teeth and marked joint laxity. A feature of the disease in Romneys, which involved about 50 lambs, was the presence of marked skin fragility. In affected lambs, the bones could be easily bent or cut with a knife and were often abnormally shaped with thickened diaphyseal regions. Most lambs had recent fractures surrounded by hemorrhage and older (*in utero*) fractures with poorly formed calluses, especially involving the ribs.

Type I collagen is the predominant collagen type in bone, dentine, ligaments, tendons and in the ocular sclera, thus accounting for the characteristic distribution of lesions.

Osteopetrosis

Osteopetrosis (marble bone disease) is a group of rare disorders occurring in humans and animals, characterised by defective osteoclastic bone resorption and the accumulation of primary spongiosa in marrow cavities.

In **cattle**, osteopetrosis is best studied in the **Angus** breed, where it is inherited as an autosomal recessive trait. Affected calves are small, premature (250-275 days of gestation) and usually stillborn. Clinically, they show brachygnathia inferior, impacted molar teeth and protruding tongue. The long bones are shorter than normal and easily fractured. Radiographically, the medullary cavities are dense, without clear differentiation between the cortex and medulla. Vertebrae are shortened, frontal and parietal bones are thick, and the bones of the cranial base are thick and dense. On cut surface, the metaphyses and diaphyses of long bones, are filled with dense, unresorbed cones of primary spongiosa extending from the metaphysis to the center of the

diaphysis. In spite of their increased density, the bones are more fragile than normal and fractures are sometimes detected at necropsy, but the fragility is much less marked than in osteogenesis imperfecta.

Osteopetrosis also occurs in the **Hereford** and **Simmental** breeds, but in affected Herefords the frontal bones are markedly thickened and filled with cystic spaces. The domed forehead of these calves could be misinterpreted as hydrocephalus unless the skull is sectioned.

Osteochondrosis

Osteochondrosis is most common and important as a disease of pigs, horses and large breeds of dog, but it also occurs in cattle, sheep and farmed deer. Young, fast growing animals are most susceptible to osteochondrosis, especially breeds selected for rapid growth. It is characterized by multifocal abnormalities in endochondral ossification involving articular-epiphyseal cartilage complexes (the immature cartilage covering the ends of growing long bones) and growth plates. Other synonyms for the disease are **osteochondrosis dissecans** and **osteochondritis dissecans**. Such differences in terminology are due, at least in part, to the variation in lesions when examined at different stages. Severe degenerative joint disease is a common sequel to osteochondrosis and is one of the most common causes of lameness in domestic animals.

The aetiology and pathogenesis of osteochondrosis are poorly understood and have been the subject of considerable recent debate. The aetiology is multifactorial, but most likely involves the effect of trauma or biomechanical factors on cartilage that has been weakened by nutritional or hormonal imbalances, vascular disruption, or genetic factors. Whatever the cause, the initial lesion in the articular-epiphyseal cartilage complex of each species where detailed studies have been performed are remarkably similar, suggesting a common pathogenesis, most likely involving ischemic damage to the growing cartilage.

Although there are only occasional reports of osteochondrosis in **cattle**, the disease is likely to be much more common in this species than is currently recognised. Due to financial constraints and difficulties in detailed radiologic examination, many lame cattle are sent for slaughter without definitive diagnosis. In a survey of middle-aged bulls slaughtered for non-medical reasons, lesions of osteochondrosis were detected in the stifle joint of 3 of 25 animals in the absence of clinical lameness. Degenerative joint disease was detected in the stifle of 14 of the 25 bulls and although these lesions were too advanced to accurately determine their origin, the fact that the lesions identified as osteochondrosis, and those of degenerative joint disease both had a predilection for the lateral trochlear ridge, suggested that at least some cases of degenerative joint disease in this population of bulls were secondary to osteochondrosis. Other predilection sites for osteochondrosis in cattle are the humeral head, distal radius, elbow joint, and the tibial tarsal and occipital condyles.

Early gross lesions of osteochondrosis appear as thickened, white or cream foci of articular cartilage, which are sharply demarcated from adjacent normal areas of cartilage. In more advanced lesions the affected cartilage usually shows evidence of separation and underrunning, and there may be nodules of cartilage reflecting attempts at repair. In other cases, underrun segments of articular cartilage may be detached completely, leaving a deep ulcer with exposure of subchondral bone.

In farmed red **deer** and wapiti x red deer hybrids in New Zealand, a strong association is recognized between osteochondrosis and copper deficiency. On some farms, more than 30% of the fawns are affected. Lameness may be noticed as early as 1 month of age, but more commonly, the problem is not noticed until weaning at around 4 months-of-age. Epiphysiolysis of the femoral head is a common manifestation of the disease and may be bilateral. Animals with this lesion are severely lame and may adopt a "bunny-hopping" gait or "cow-hocked" stance. Other predilection sites are the carpal, hock, and stifle joints. The lesions are usually bilateral. Affected deer invariably have low serum and/or liver copper concentrations and the disease can be prevented by copper supplementation of pregnant hinds.

Osteochondrosis appears to be rare in **sheep**, but has been reported as a cause of lameness in young, rapidly growing, Suffolk ram lambs. It is likely that the incidence of osteochondrosis in sheep will increase with continued selection for rapid growth. Valgus and varus limb deformities are common in ram lambs in feedlots and test stations in the USA and also occur in other countries. Grossly, some affected rams have thickening of the distal radial physis, similar to the growth plate lesions of osteochondrosis in other species, but joint changes are absent. Vascular and growth plate lesions mimicking osteochondrosis can be produced experimentally in lambs by procedures that increase weight bearing. Epiphysiolysis of the distal radial growth plate, associated with deformity of the forelimbs, is reported in 3-month-old lambs, supporting the concept that the physeal lesions of osteochondrosis may be one cause of angular limb deformity in sheep.

Localised skeletal dysplasias

Syndactyly, a defect characterized by partial or complete fusion of functional digits, occurs in several breeds of cattle, including Holstein-Friesian, Angus, Chianina, Hereford and Simmental. Inheritance is autosomal recessive with incomplete penetrance and variable expression. The disorder became widespread in the Holstein-Friesian breed following extensive use of a heterozygous bull by artificial breeding, but is rare in other breeds. In Holstein-Friesians, the disorder seldom affects all 4 digits. The right forelimb is most frequently affected, followed by the left forelimb then the right hindlimb. In contrast, the defect in Angus cattle usually affects all 4 digits. The lesions of syndactyly may vary from complete horizontal fusion of paired phalanges to fusion of only one or

none of the phalanges, but fusion of interdigital soft tissues. Vertical fusion of phalanges is reported in some affected Angus cattle. **Polydactyly,** an increase in the number of digits, is an inherited trait in various bovine breeds but the inheritance pattern is poorly understood. In most cases, it is the medial digit (digit 2) that is duplicated and although all 4 feet may be affected, the anomaly is more frequently confined to the forelimbs. A polygenic mode of inheritance requiring a dominant gene at one locus and two recessive genes at another is postulated in Simmental cattle.

Hemimelia refers to the partial absence of one or more limbs and occurs as a recessively inherited lethal defect in Galloway calves. Affected calves have bilateral agenesis of the tibial bones and patellae. Other bones of the hind limbs are apparently normal, highlighting the localized nature of the defect. A similar syndrome characterized by tibial hemimelia, meningocele, retained testicles and abdominal hernia is reported in Shorthorn calves and is also believed to be transmitted as an autosomal recessive trait

Brachygnathia inferior, shortening of the mandibles, and **brachygnathia superior**, shortening of the maxillae, may occur alone or in combination with other skeletal defects. Brachygnathia inferior is commonly encountered in otherwise normal domestic animals and, while not life-threatening, is an undesirable characteristic. Genetic and teratogenic aetiologies have been suggested and both are likely to occur. Brachygnathia superior occurs in association with degenerative joint disease as a lethal genetic defect in Angus calves. In addition to brachygnathia superior, affected calves have other skull changes similar to those of brachycephalic dogs and degenerative changes are present in articular cartilage throughout the body.

Porphyria

Red-brown discoloration of the teeth and bones, caused by a recessively inherited defect in porphyrin metabolism (**congenital erythropoietic porphyria**), is reported in several breeds of cattle, including Hereford, Holstein, Ayrshire, Shorthorn, and Jamaica Red and Black. A deficiency of uroporphyrin III cosynthetase leads to the accumulation of uroporphyrin I and coproporphyrin I in blood, bone and a variety of other tissues. The urine may also be red-brown or turn red on exposure to sunlight. The action of sunlight on porphyrins accumulated in the skin results in photodynamic dermatitis. The teeth, bones and urine of affected animals show bright cherry-red fluorescence on exposure to ultraviolet light in a darkened room. Congenital erythropoietic protoporphyria in Limousin cattle, caused by a deficiency of the mitochondrial enzyme ferrochelatase, is associated with photosensitivity but no discoloration of the bones or teeth.

Acquired porphyria with pink discoloration of bones was recognized at slaughter in approximately 300 of 390 *crossbred lambs in Australia.* Similar "outbreaks" have also occurred in lambs and young deer in New

Zealand. The discoloration was most prominent in the cortex of long bones and fluoresced on exposure to ultraviolet light, but teeth were not affected. On cut surface of long bones in a sample of affected lambs and deer, the pink discoloration was confined to areas of bone that had formed in the weeks prior to death, in particular the outer cortex. This reflects the fact that porphyrins are only deposited at sites of active mineralisation. In congenital porphyria, the constant availability of porphyrins during dental and skeletal mineralisation results in diffuse discoloration of all mineralised tissues. The extraction of coproporphyrin and protoporphyrin from the bones of lambs in the Australian outbreak suggested an enzyme block towards the end of the heme synthetic pathway, most likely induced by a toxin. Although lead toxicity can induce porphyrin accumulation, no lead was detected in affected lambs. Toxicity caused by some chlorinated hydrocarbons can also result in impaired heme synthesis and the detection of 1,2,4-trichlorobenzene in fat samples supported this possibility in the lambs. This compound is a major metabolite of lindane, an organochlorine insecticide that was widely used in parts of Australia and New Zealand before being banned. The occurrence of acquired porphyria in grazing animals may therefore reflect environmental contamination due to leakage from chemical dumpsites.

Acquired abnormalities in skeletal development

It is important to recognise that skeletal abnormalities do not always have a genetic basis. Many teratogenic agents have been shown to mimic genetic diseases of the skeleton and other organ systems, and unless there is clear evidence that the problem is inherited, or it resembles an established genetic disorder, any temptation to attribute a genetic aetiology should be resisted. Bone growth and maturation is a complex process, requiring an interaction between genetic factors, local and systemic hormones, dietary nutrients and mechanical forces. Anything that interferes with the synthesis of proteoglycans or collagen by chondroblasts or osteoblasts, the differentiation of precursor cells, or the resorption of bone by osteoclasts can result in a skeletal abnormality. The expression of an abnormality depends on many factors, including the phase of skeletal development that is altered, the severity of the defect, the age of the animal at the time of the insult, and how long it persists. As a result, the range of possible skeletal defects is huge, and a single aetiology may vary considerably in its manifestations. An accurate aetiological diagnosis is not always possible in an animal with a skeletal defect, particularly since the inciting cause is often no longer present at the time of examination.

Manganese deficiency

Manganese is essential for the activation of xylosyltransferase, the first enzyme in the biosynthetic pathway of sulfated glycosaminoglycans. A deficiency of manganese causes decreased production and increased

degradation of cartilage glycosaminoglycans and therefore potentially affects all bones that develop by endochondral ossification.
Manganese deficiency has been incriminated as the cause of skeletal deformities in newborn calves and other farmed livestock. The deficiency does not appear to affect adult animals but calves born to cows fed on manganese-deficient rations during pregnancy may show varying degrees of skeletal deformity. The abnormalities include shortening and twisting of limbs, enlarged, mushroom-shaped epiphyses and reduced breaking strength. Tracheal rings may be thickened and collapsed in severe cases.

Copper deficiency

Copper deficiency has been incriminated as a cause of **osteoporosis** and, in some species, **osteochondrosis**, but full appreciation of the role of this trace mineral in skeletal development is lacking. As a component of the enzyme lysyl oxidase, copper is required for cross-linkage of collagen molecules. This is an important step in strengthening the matrix elements of bone tissue, cartilage, and other connective tissues that rely on collagen for support. It is not surprising therefore that increased fragility of bone, and possibly cartilage, is a feature of copper deficiency. Studies in dogs and swine have demonstrated reduced osteoblastic activity in animals with copper deficiency, leading to narrow cortices of long bones and reduced deposition of bone on persistent spicules of mineralised cartilage in the primary spongiosa. These metaphyseal changes resemble those of vitamin C deficiency, which is not surprising since both deficiencies interfere with collagen synthesis and cross-linkage.

In calves (but not lambs), copper deficiency has been associated with grossly visible focal thickenings in rapidly growing growth plates, but the mechanism for this lesion is not clear. It is possible that the stress of weight bearing causes microfractures of fragile trabeculae in the primary spongiosa with local disruption of the metaphyseal blood supply and impaired invasion of the mineralized cartilage. These growth plate lesions bear a strong resemblance, grossly and histologically, to those of rickets and osteochondrosis. Differentiation from rickets may be further complicated by the possibility of spontaneous long-bone fractures in copper-deficient animals due to osteoporosis and increased bone fragility.

Copper deficiency may be either primary, due to inadequate dietary copper, or secondary to increased dietary levels of copper antagonists, such as molybdenum, zinc and iron.

Fluorosis

Fluorine is an essential trace element but, when present in chronic excess, is capable of inducing characteristic dental and/or bony changes. All species are susceptible but because of the manner in which chronic poisoning occurs, fluorosis is most common in herbivores, cattle being more susceptible than sheep.

The characteristic changes of severe fluorosis occur in teeth and bones and are accompanied by shifting lameness, loss of production and a variety of non-specific signs of debility. The mildest gross evidence of dental fluorosis is the presence of small foci with a dry, chalky appearance compared to the normal glistening surface of enamel. In more severe cases, all the enamel in affected teeth may be chalky, opaque and show various degrees of yellow, dark brown or black discoloration, which is virtually pathognomonic for fluorosis. Affected teeth show accelerated wear and may develop chip fractures. In chronic cases, they may be worn to the gum line. The pigment is present in the enamel layer and possibly in the dentin, and may reflect oxidation of the organic matrices of the teeth. Unlike the pigment of food stains and tartar, it is not limited to the surface and cannot be removed by scraping.

The dental lesions develop only if intoxication occurs while teeth are in the developmental stages and enamel is forming. Ameloblasts and odontoblasts are extremely sensitive to fluorine, which causes them to produce a matrix that mineralises abnormally and is reduced in quality and quantity.

The bone lesions of fluorine toxicity are generalized but not uniform and, in severe cases, are characterized grossly by the formation of periosteal hyperostoses.

Lead toxicity

Lead toxicity is better known as a cause of CNS lesions, but it may also cause bone lesions. The characteristic lesion is a band of sclerosis, referred to as a **"lead line"**, visible radiographically and grossly in the metaphyses of developing bones. This is a relatively early morphological lesion in children with lead poisoning, and also occurs in animals. The sclerosis is due to persistence of mineralised cartilage trabeculae in the metaphysis because of impaired osteoclastic resorption. The metaphyseal sclerosis associated with lead toxicity radiographically and grossly resembles that seen in association with some cases of intrauterine bovine viral diarrhea virus infection, which also interferes with osteoclast function or number.

Plant toxicities

Many plant species are known, or suspected, to cause skeletal abnormalities, either by inducing a teratogenic effect on the developing foetus, or influencing skeletal remodeling in young growing animals. Those with a teratogenic action typically exert their influence early in pregnancy and require ingestion by the dam during a specific stage of foetal development. The classic example is ***Veratrum californicum***, which causes **cyclopia** in the progeny of ewes that consume the plant on day 14 of gestation.

A syndrome referred to as **crooked-calf disease** occurs when pregnant cows ingest certain **wild lupins**, including *Lupinus caudatus, L. sericeus*

and *L. formosus*, especially between days 40 and 80 of gestation. Malformation of the limbs, notably the forelimbs, is the most common alteration, but the axial skeleton may also be involved. The limb abnormalities consist of flexion contracture and arthrogryposis associated with disordered growth of joints, in addition to shortening and variable rotation of the bones. Torticollis, and either scoliosis or kyphosis are common, involvement of the thoracic spine being associated with costal deformities. Possible abnormalities in the skull include cleft palate and brachygnathia superior. Affected calves are usually born alive and may survive, depending on the nature and severity of their malformations, but growth is retarded and the malformations persist, often becoming more severe with age.

Various plant toxicities (and other aetiologies), have been incriminated in a limb deformity syndrome of lambs referred to as "**bentleg**". In Australia, the syndrome has been associated with ingestion of *Trachymene ochracea* (white parsnip), *T. cyanantha* and *T. glaucifolia* (wild parsnip) by ewes, which preferentially graze the inflorescence of *Trachymene sp.* The toxic principle is unknown, but the deformity may be either be congenital, due to exposure of lambs *in utero*, or may develop during postnatal growth, probably following exposure of lambs through the milk. Gross deformities are usually most prominent in the forelimbs, and include outward bowing, flexion and lateral rotation of the carpal joints and medial or lateral rotation of the fetlocks. Similar syndromes are described in New Zealand (where it is called "**bowie**") and South Africa, but plant toxicities are not suspected. In both of these conditions, calcium deficiency and osteoporotic bone disease play a major role in the weakening and deformity that develop.

Metabolic bone diseases

Metabolic bone diseases, also referred to as **osteodystrophies**, are the result of disturbed bone growth, modeling or remodeling due to either nutritional or hormonal imbalances. The manifestations are generally most severe in young animals where the skeleton is undergoing rapid turnover, but lesions also occur in adults due to an effect on the quality or quantity of bone formed during remodeling. In addition to variations with age, there are variations between species in the manifestations of dietary mineral imbalances.

Metabolic bone diseases are traditionally classified as **rickets**, **osteomalacia**, **fibrous osteodystrophy** or **osteoporosis**. Although these are distinct morphological entities with characteristic pathogenesis and lesions, they can occur in combination in the same individual. This may create confusion diagnostically. Furthermore, their aetiology can vary between species. For example, calcium deficiency in sheep is likely to result in osteoporosis, but in a rapidly growing pig, fibrous osteodystrophy is a more likely result. Also, each of these disorders can be caused by more than one dietary or endocrine imbalance.

Since bone matrix is composed largely of calcium and phosphate ions in the form of hydroxyapatite crystals, any dietary or physiological factors affecting the metabolism of calcium and/or phosphorus can interfere with the formation of bone tissue and cause an osteodystrophy.

Osteoporosis

Osteoporosis is easily the most common of the metabolic bone diseases, both in man and animals. Rather than being a specific disease, it is a lesion characterised by a reduction in the quantity of bone, the quality of which is normal. In effect, osteoporosis represents an imbalance between bone formation and resorption in favour of the latter, resulting in bone that is structurally normal but with reduced breaking strength.

Many mild cases of osteoporosis in animals remain undetected, even at post mortem examination, as the shape of individual bones is not altered and unless there have been pathological fractures, lameness is not likely to have been observed clinically. The occurrence of a bone fracture without evidence of excessive trauma may be the first indication that an animal is suffering from osteoporosis. In farmed livestock, there may be an unusually high incidence of fractures in the herd or flock, suggesting increased bone fragility.

Most cases of osteoporosis in farm livestock are **nutritional** in origin and may be due to deficiency of a specific nutrient, such as calcium, phosphorus or copper, or to **starvation**, where there is restricted intake of an otherwise balanced ration. Starvation is relatively common in grazing animals in areas prone to drought or due to overstocking in seasons when pasture growth is below expectations. Poor quality milk replacers fed to young calves or other young animals may also result in starvation due to inadequate digestibility and absorption of nutrients. In starved animals, the mechanism of osteoporosis is complex, but the lack of dietary protein and energy most likely contribute, either directly or indirectly. The effects of starvation on the skeleton are greater in young growing animals than in adults. **Growth arrest lines** may be evident in the metaphysis, reflecting intermittent periods of premature physeal closure followed by reactivation of growth. **Serous atrophy of medullary adipose tissue** is a common feature of starvation-induced osteoporosis in animals.

Calcium deficiency, in the presence of adequate dietary levels of phosphorus and vitamin D, causes osteoporosis experimentally in mature and immature animals, but rarely if ever occurs as a natural disease. Unless the deficiency is extremely severe, physeal growth and mineralisation of cartilage are normal. Rickets is not a feature of uncomplicated calcium deficiency because calcium resorption from bone ensures that this mineral is not a limiting factor at sites of mineralisation.

Phosphorus deficiency produces osteomalacia in adults and rickets in growing animals, both under natural and experimental conditions. However, under some circumstances it causes osteoporosis. The reasons

for this are not clear, but it may be related to the anorexia that often accompanies phosphorus deficiency, the age and growth rate of the animals, and the severity and duration of phosphorus deficiency.

Osteoporosis is recognised as a feature of naturally occurring and experimental **copper deficiency** in lambs and calves. As a component of the enzyme lysyl oxidase, copper is required for the cross-linkage of collagen and elastin. Deficiency of this enzyme is probably responsible for the reduced osteoblastic activity observed in swine and dogs with copper deficiency, while the impaired cross linkage of collagen in bone matrix most likely accounts for the increased bone fragility in copper-deficient animals when compared to animals with osteoporosis of other causes. As mentioned above, copper deficiency may also predispose to osteochondrosis (in some species) and induce physeal lesions resembling those of rickets.

Osteoporosis is often present in animals with severe **gastrointestinal parasitism.** Although malabsorption is likely to be a factor, the mechanism may be more complex and probably involves the generation of pro-inflammatory cytokines such as interleukin-1 and interleukin-6, both of which induce bone resorption and inhibit its formation. There is also evidence that some nematodes, e.g *Trichostrongylus colubriformis,* may induce phosphorus deficiency. In another study, osteoporosis in lambs with subclinical *Ostertagia circumcincta* infestation was linked to reduced availability of protein and energy for bone matrix production. Increased production of endogenous corticosteroids may also be involved. The importance of parasite-induced osteoporosis in grazing animals is unknown but it is undoubtedly much more common than is recognised and may be responsible for some of the unexplained cases of spontaneous bone fractures encountered in cattle and sheep.

The gross lesions of osteoporosis are generally most marked in bones, or areas of bones, consisting predominantly of cancellous bone. This is presumably because cancellous bone has a greater surface area to volume ratio than cortical bone and is resorbed more rapidly. Vertebral bodies in particular are affected early in the disease in human patients and animals with osteoporosis and may contain pathological fractures. Flat bones of the skull, scapula, ilium and the ribs may also be severely affected and the breaking strength of the ribs, as assessed during necropsy, may be noticeably reduced. Cancellous bone in the metaphyses and epiphyses of long bones may be reduced in amount and more porous than normal. Trabeculae that are most concerned with transmission of weight-bearing stress are relatively spared and may become more prominent. In advanced stages of osteoporosis, the medullary cavities of long bones are enlarged and the cortices extremely thin.

Rickets and Osteomalacia

It is convenient to consider these two diseases together as they have a similar aetiology and pathogenesis, differing only in the age at which they occur. **Rickets** is a disease of the developing skeleton in young animals and is accompanied by abnormal endochondral ossification at physes, in addition to defective bone formation. **Osteomalacia** occurs only in adults and although there are no lesions associated with growth cartilages, the bone changes are the same as those that occur in rickets. Both diseases occur in all ruminant species, including wildlife, but there are differences between species in the circumstances under which they occur, and in the most likely cause.

The pathogenesis of both rickets and osteomalacia involves **defective mineralisation**. In young animals with rickets, this includes cartilage matrix at sites of endochondral ossification, as well as newly formed osteoid. In adults, where skeletal growth by endochondral ossification is no longer occurring, the defective mineralisation affects only the osteoid formed during skeletal remodeling.

Anything that interferes with the mineralisation of cartilage or bone matrix may cause rickets or osteomalacia, but most cases in animals result from dietary deficiencies of either vitamin D or phosphorus. Calcium deficiency on its own causes either osteoporosis or fibrous osteodystrophy, but not rickets.

Vitamin D deficiency may occur in grazing animals where the combination of relatively high latitudes and temperate climates allow them to be pastured for much of the year. Such conditions occur in parts of the United Kingdom, South America, New Zealand and southern Australia. Photobiosynthesis is a more important source of vitamin D than diet in grazing animals, but may be inadequate during the winter months in some regions. When the winter sun is at an angle of less than 30 degrees to the horizontal, the short-wavelength ultraviolet rays required for the activation of 7-dehydrocholesterol in the skin are reflected into the atmosphere and dermal synthesis of previtamin D_3 is impaired. Mature grass and sun-cured hay are relatively good alternative sources of vitamin D_2, but the levels present in immature pasture are likely to be inadequate. This may be further compounded by the anti-vitamin D activity of carotenes present in lush pasture and green cereal crops. The extra demands of pregnancy and lactation during winter and early spring may also contribute significantly to the development of clinical osteomalacia. It is likely that many grazing animals are vitamin D deficient for a period during the winter, but clinical rickets or osteomalacia are only likely to develop if the deficiency is marked or persists for longer than usual. Problems may also occur if vitamin D deficiency is combined with deficiencies of other essential nutrients, such as phosphorus or copper.

Sheep appear to be more susceptible to vitamin D deficiency than **cattle**, possibly because a dense fleece covers much of their skin. The concentration of vitamin D in blood increases following shearing. **Alpacas** and **llamas** may be even more susceptible to vitamin D deficiency than sheep. Rickets has been diagnosed in young camelids in New Zealand, South Australia and northern regions of the United States of America. The disease occurs during winter months and is accompanied by low blood concentrations of both 25-hydroxyvitamin D and phosphorus. In the New Zealand report, lambs grazing the same pasture had normal serum phosphorus concentrations and the phosphorus content of the pasture was normal. The natural environment for alpacas and llamas is at high altitude near the equator, where solar irradiation is intense. Their dense fibre and pigmented skin may have evolved as a protective mechanism to prevent excessive solar irradiation reaching the skin. This could prove to be a disadvantage in animals moved to lower altitudes, especially at latitudes with limited solar irradiation during the winter.

Rickets and osteomalacia due to **phosphorus deficiency** are uncommon, but do occur in animals grazing pastures low in phosphorus. There are many areas of the world, including South America, South Africa, northern Australia and New Zealand, where soil phosphorus levels are very low and successful livestock production requires application of phosphorus either to the soil or the animals. **Cattle** appear to be more susceptible than **sheep** to phosphorus deficiency. Rickets has also been diagnosed in farmed red **deer** grazing phosphorus deficient pastures in New Zealand.

Signs of phosphorus deficiency develop slowly, especially in the mature skeleton, and many animals with subclinical osteomalacia no doubt remain undiagnosed. Clinical disease is most likely to occur in cows where the deficiency is exacerbated by the extra demands of pregnancy or lactation. Such animals lose condition, develop transient, shifting lameness and show an increased susceptibility to fractures. They may crave phosphorus-rich materials, and osteophagia and pica are characteristic signs of the deficiency. Hypophosphatemia develops early but also returns to normal rapidly if the animals are supplemented. Serum calcium concentrations are usually normal or increased. The presence of normal serum phosphorus concentration in an animal with osteodystrophy does not therefore exclude phosphorus deficiency as the cause.

Animals with rickets are generally stiff or lame, and in severe cases are reluctant to stand. The limbs, especially the forelimbs, may be bowed. Swelling of the carpals and other joints, due to enlarged ends of long bones, may lead to an initial suspicion of arthritis.

Gross lesions of rickets are most prominent at sites of rapid growth, including metaphyseal and epiphyseal regions of long bones and costochondral junctions of the large middle ribs. Enlargement of costochondral junctions is a classic feature and is referred to as the

"rachitic rosary". In rickets, the metaphysis of the rib is often wider than the cartilaginous portion and on sagittal section, the chondro-osseous junction is irregular, with tongues of unresorbed cartilage extending into the metaphysis. The normal architecture of the metaphysis is replaced by a mixture of disorganised trabeculae, irregular tongues and islands of cartilage, fibrous tissue and sometimes haemorrhage. Similar changes may be evident in sagittal sections of long bones, especially at sites of most rapid growth, such as distal radius, proximal humerus, distal femur and both ends of the tibia. Irregular thickening of physes at one or more of these sites is the hallmark of rickets. Metacarpal and metatarsal physes are also likely to show gross changes. The severity of lesions between different physes may vary considerably, even within the same animal. This emphasizes the importance of examining sagittal sections of several bones during postmortem examination. The enlargement of the ends of long bones is due partly to flaring of the metaphysis and partly to compression caused by weight bearing on metaphyseal bone of reduced strength. Also, there is accumulation of poorly mineralised osteoid, which is not removed efficiently by osteoclasts.

Pathological fractures may be present in the limbs, ribs or vertebrae in severe cases. When the deficiency is relatively recent but severe, a distinct zone where abnormal bone formation commenced may be present in the metaphysis. This reflects a change from adequate to inadequate dietary phosphorus or vitamin D and may of value in relating the disease to a particular change in diet or environment.

The lesions of **osteomalacia** are similar to those of rickets but since they occur in adult animals, growth plates are not involved. Pathological fractures are common in advanced cases. In affected cattle, fractures are most common on the ribs, pelvis, and long bones.

Fibrous osteodystrophy

Fibrous osteodystrophy is caused by persistent elevation of parathyroid hormone concentrations and in herbivores is almost invariably due to an imbalance in dietary levels of phosphorus and calcium. Nutritional secondary hyperparathyroidism may be associated with either low dietary calcium or excess dietary phosphorus and its effects are most marked in young, growing animals.

Severe fibrous osteodystrophy is relatively common in **goats** fed rations high in concentrates, but there are no convincing reports of the disease in either **sheep** or **cattle**, suggesting species variation in susceptibility. In goats, fibro-osseous enlargement of the mandibles and maxillae is a characteristic clinical feature. Respiratory distress may be present due to encroachment by swollen maxillary bones on the nasal cavity. The relative severity of lesions in bones of the skull in goats and certain other species may be related to the mechanical stimulus associated with chewing. The bones of the limbs are also affected in goats with fibrous osteodystrophy and may be markedly bowed.

Inflammatory diseases of bones and joints

Bacterial infections of bones are very common in young ruminants, particularly following neonatal bacteraemia or septicaemia in animals with inadequate passive immunity. Since the route of infection is usually haematogenous, most are centred on the medullary cavity and are referred to as **osteomyelitis**. Bacterial osteomyelitis is most likely far more common than is diagnosed. Affected animals often die of septicaemia before the bone lesions become evident and the skeleton is generally not closely examined at necropsy unless clinical signs have suggested a skeletal disorder.

During bacteraemia or septicaemia, bacteria can become localised in many organs and at many sites. In bones, there is a strong predilection for sites of active endochondral ossification within the **metaphyses** and **epiphyses** of long bones and **vertebral bodies**. This reflects the unique nature of the vascular architecture at the physis, and at the equivalent site in expanding epiphyses. Capillaries invading the mineralised cartilage make sharp loops before opening into wider sinusoidal vessels that communicate with the medullary veins. The capillaries are fenestrated, thus permitting ready escape of bacteria into the bone marrow. Localisation of bacteria in the vessels of cartilage canals is also common in haematogenous infections of young animals. As the skeleton matures, the vascular morphology at chondro-osseous junctions alters to make it less suitable for bacterial localisation and there is probably only a narrow window during which bacteria are able to establish in bones. If the infection is not controlled by host defences or antibiotic therapy, the likely sequelae are localised bone destruction and/or **sequestration**. Large sequestrae are not resorbed and become walled off by an **involucrum**, but interfere with healing and harbour bacteria. The clinical manifestations of osteomyelitis may not develop until several months later when the bone lesion becomes extensive enough to cause pain, disfigurement of the bone, or perhaps result in a pathological fracture.

Vertebral osteomyelitis is a relatively common manifestation of bacterial osteomyelitis in young ruminants. Following localisation in the epiphysis or metaphysis of a vertebral body, or adjacent to a growth plate in a developing vertebral arch, the infection causes progressive destruction and weakening of the affected vertebral bone. As in long bones, sequestration and abscessation may occur. The most common sequela is pathological fracture and collapse of affected vertebrae with dorsal displacement of pus and necrotic bone fragments into the spinal canal. Such an event is accompanied by the sudden onset of neurological signs (e.g. hind limb paralysis) caused by compression of the spinal cord.

Mandibular osteomyelitis ("lumpy jaw") caused by *Actinomyces bovis* is well known in **cattle**, and occurs occasionally in other ruminants. *A bovis* is probably an obligate parasite of the oropharyngeal mucosa in a number of animal species, and most infections involve the buccal tissues. The organism is not particularly virulent, and in most, perhaps all cases,

the surface tissues must be injured by some other agent or by a foreign body for invasion to occur. *A bovis* may invade bone directly though the periosteum, but osteomyelitis usually develops from periodontitis, presumably via lymphatics, which drain into the mandibular bone. Once in the bone, *A bovis* causes a chronic, pyogranulomatous inflammatory reaction. Suppurative tracts permeate the medullary spaces leading to multiple foci of bone resorption and proliferation. Large sequestra do not develop, even when the cortex is invaded, probably because of the slow, progressive nature of the disease. Fistulae often extend into the overlying soft tissue and may discharge through the skin or mucous membranes. Periosteal proliferation is excessive and the bone may become enormously enlarged, the normal architecture of the mandible being destroyed. On cut surface, the affected mandible has a "honeycomb" appearance with reactive bone surrounding pockets of inflammatory tissue. The pus often contains many 1-2 mm diameter, soft, light yellow granules referred to as **"sulfur granules"**. These consist of an internal mass of tangled, gram-positive filaments mixed with some bacillary and coccoid forms, and a periphery consisting of closely packed, club-shaped, gram-negative bodies.

Localisation of bacteria infection in the highly vascular synovial membrane of joints during bacteraemia is very common, resulting in **polyarthritis**. The arthritis is more readily apparent clinically than osteomyelitis, but most animals that develop arthritis in the neonatal period will also have multiple foci of osteomyelitis. The prognosis is therefore poor unless affected animals can be treated with appropriate antibiotics very early in the disease process.

Acutely inflamed joints are swollen, hot and painful. Fibrin clots may be floating free within the joint fluid, attached to the synovial membrane or lodged within recesses of the joint. Sheets of yellow fibrin sometimes cover the synovial membrane, which is often oedematous and hyperaemic or studded with petechiae. Synovial villi, which are barely noticeable in normal joints, may become prominent due to the oedema and hyperaemia. The synovial fluid is increased in volume and may be either slightly turbid and mucinous or thin and cloudy, the latter implying septic inflammation. Complete resolution of septic arthritis is possible if the infection is eliminated spontaneously or by antibiotic therapy before erosion of cartilage occurs, but if the inflammatory process persists, the joint and adjacent structures will be severely altered. Cartilage degeneration occurs mainly at sites of weight bearing or at the articular margins, the latter in association with pannus formation. Erosion of the degenerate cartilage may allow infection to enter the subchondral bone, resulting in purulent osteomyelitis with extensive underrunning and separation of the articular cartilage. In such cases, it may be difficult to determine whether the arthritis preceded the osteomyelitis or *vice versa*, or whether the infectious agent gained access to both sites independently. Granulation tissue originating in the subchondral bone may grow out over the degenerate articular surface and predispose to ankylosis.

The suppurative process may extend from the joint to involve adjacent tendon sheaths and outwards from the synovial membrane of the articular capsule to produce cellulitis in periarticular tissues. The articular region is then greatly enlarged and the proliferation of fibrous tissue in response to inflammation, or during the healing process, results in permanent joint stiffness. In some cases, localisation of the cellulitis into a periarticular abscess may be followed by fistulation to the skin.

A range of opportunistic bacteria may be involved in neonatal osteomyelitis and polyarthritis in ruminants including: *Streptococcus spp, Escherichia coli, Arcanobacterium pyogenes, Staphylococcus aureus* and *Salmonella spp.* Other organisms, such as *Erysipelothrix rhusiopathiae, Mycoplasma spp* and *Chlamydia spp* have a strong predilection for the synovium and cause polyarthritis in the absence of osteomyelitis in lambs or kids and infection with such organisms is usually not related to neonatal septicaemia.

Degenerative diseases of joints

Degenerative joint disease is relatively common in **cattle** and is an important cause of wastage of stud bulls and bulls in artificial breeding centres. The **hip**, **stifle** and **hock** joints are most frequently involved. Although an inherited aetiology is suspected in the Friesian and Jersey breeds it is likely that most cases are secondary to poor conformation, traumatic damage to ligaments during fighting or mounting, or as a sequel to osteochondrosis. Osteochondrosis is probably most important in young, fast-growing bulls of large beef breeds that have been fed on concentrate rations in preparation for shows or sales.

By the time an affected joint is examined at slaughter, the lesion is usually too advanced to determine its cause. In chronic cases the cartilage may be completely eroded from weight-bearing surfaces, exposing eburnated subchondral bone, and any surviving cartilage is usually yellow and fibrillated. Exostoses may surround the articular surface and, in severe cases, there may be ossification of joint capsules and tendon sheaths. If the degenerative joint disease is secondary to trauma it is likely to involve a single joint while multiple joint involvement is a feature of osteochondrosis. It is a good idea to open several joints as healed lesions of osteochondrosis may still be apparent, even in joints that did not appear to be clinically affected.

Spondylosis (spondylosis deformans, ankylosing spondylosis) is a degenerative disease of the vertebral column characterised by the formation of osteophytes at the ventral and lateral margins of vertebral bodies adjacent to intervertebral spaces. The osteophytes may appear as spurs growing towards the adjacent vertebral body or as complete bony bridges with fusion of vertebrae.

Spondylosis is common in **bulls** kept in artificial breeding centres where it is presumably related to repeated traumatic damage to intervertebral

disks during semen collection. Lesions are found in almost any animal past middle age. Osteophytes develop mainly on the posterior end of thoracic vertebrae and the anterior end of lumbar vertebrae, and their incidence and size tends to decrease in either direction from the thoracolumbar junction. Although is a common incidental finding in breeding bulls, the disease is sometimes associated with mild or severe clinical signs. Affected bulls may show posterior weakness and ataxia, or even paralysis, after dismounting from service. They may continue to be mildly ataxic or recover, only to be affected again later. The onset of signs is usually associated with fracture of the vertebral bodies and of the ankylosing new bone, which is dense, but tends to be brittle. There is little displacement of the fractured ends in most cases and trauma to the spinal cord is usually mild. Paralysis is usually secondary to either haemorrhage or repeated trauma.

Tumours of bones and joints

Primary and secondary tumours of the skeleton are rare in ruminants and there are few reports in the literature. Chondromas and chondrosarcomas are occasionally found on flat bones (e.g. sternocostal complex, scapula, ilium) of aged ewes at slaughter. Most pathologists have seen isolated cases of tumours such as osteoma, osteosarcoma and fibrosarcoma involving the bones of ruminants, but there are too few cases to establish reliable information on their prevalence or behaviour.

The juvenile form of sporadic **lymphosarcoma** commonly involves the bones of calves. Large pale tan or yellow infarcts, associated with tumour cell infiltration, contrast sharply with the normal red, haematopoietic marrow on sectioning of long bones. Multiple bones are usually involved and the tumour also involves other tissues, including lymph nodes, liver, and kidney.

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