Osteopetrosis in Cattle

H. W. Leipold, S. M. Dennis, *and* **R. Schalles**
Department of Pathology (Leipold and Dennis)
and the Department of Animal Science (Schalles)
Kansas State University
Manhattan, Kansas 66506, USA

Introduction

Osteopetrosis, a generalized defect of the skeletal system has been reported in U.S. and Canadian Angus calves[4 8 10 17 20 28 33] more recently in Hereford calves,[16 20] a Simmental calf in Kansas,[14] a Simmental calf in Holland,[3] and a Dutch Friesian calf in Holland.[3]

The pathology and genetic data of osteopetrosis in Angus and Hereford calves are reported here.

Materials and Methods

Pathologic Studies

All data were taken from a continuing study of bovine congenital defects for which the methods were previously outlined.[12 15 16] Herd histories were obtained by personal visits and mail inquiries. All cases were examined grossly. Heads or legs of selected cases were examined radiographically. Heads and bones were sawed in half and bone specimens were fixed in 10% neutral buffered formalin (BNF). Heads of selected cases were macerated. Cerebrum, cerebellum, spinal cord, pituitary, thyroid, parathyroids, adrenal glands, and samples of liver, kidney, spleen and lymph nodes were taken for routine histologic examination, fixed in 10% BNF, trimmed, embedded in paraffin, cut at 5 mμ, and stained with hematoxylin and eosin (H&E). Selected bone sections were stained with Alcian blue, Mason's trichrome, and periodic-acid Schiff (PAS). Sections of bone taken from long bones, phalangeal, carpal, vertebral, mandible, facial, and cranial bones were fixed in 10% BNF formalin and decalcified in an 8% sulfosalicylic acid decalcification solution.

Genetic Studies

Herd histories and pedigree information from herds in which osteopetrosis had occurred were collected by visits to the herds and by mail. The pedigrees were examined for common ancestry of affected calves. Two hundred and seven randomly selected pedigrees from the American Angus Association were used to compare the common ancestry of affected calves with that of the general Angus population.

Herd histories of affected Hereford calves were obtained by visits to the herds.

Breeding Trial

A breeding trial was initiated at Kansas State University utilizing a heterozygous bull (had sired osteopetrotic calves) (I_1), and four heterozygous cows who had each given birth to a calf affected with osteopetrosis ($I_{2\,5}$, figure 14). In addition, five Angus cows that had not produced defective calves (assumed homozygous normal), were bred to the heterozygous bull (I_1) once.

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Results

Pathologic Studies

All calves affected with osteopetrosis were premature stillbirth with exception of two born alive. These calves died within 12 hours after birth.

The gross and radiologic changes of osteopetrosis in Angus and Hereford calves were similar. All were small and weighed between 14 to 22 kg. The mandibles were up to 4 cm shorter than normal (figure 1). The mandibles were immobile, the mouth was open and the tongues protruded. Incisor teeth were partially covered by mucous membrane and molar teeth were irregular and impacted.

The cranial cavity was smaller than normal and appeared to crowd the brain. Each skull had a patent fontanelle, 1-3 cm in diameter. All facial and cranial bones were considerably thicker and denser than normal. Cranial and facial bones, as well as mandibles, lacked nutritive foraminas or they were stenotic. The bony accommodation of the optic chiasma was irregular and the optic canals were stenotic and compressed the optic nerves. Mandibles were compressed resulting in malocclusion. The mandibular rami were incomplete and did not articulate properly with the squamous temporal bones. The molar teeth were impacted.

All long bones were heavy and tough to cut but broke easily under lateral pressure. Upon longitudinal sectioning, long bones had a "solid bone within bone" appearance (figure 2). Bone marrow cavities were lacking and epiphyses, metaphyses and diaphyses were dense (figure 3). Facial bones and turbinates of the nose were dense and thicker than normal (figure 4). Vertebral bodies on longitudinal sectioning revealed a "butterfly" appearance (figure 5). Dense bone cones projecting against each other from the growth plate met with their apices in mid area. Macerated bone specimens revealed dense and thick bone and hypoplasia or aplasia of foramina (figure 6).

Radiographically, all vertebral bodies had a compressed sandwich-like appearance. All long bones had an internal dense bone appearance with little differentiation between

FIGURE 1. Angus calf affected with osteopetrosis. This was one calf born alive. Notice opisthotonus and also the short lower jaw. Angus calves affected with osteopetrosis were usually born dead and were about 3 weeks premature.

FIGURE 2. Bones, humerus and femur, from an Angus calf affected with osteopetrosis were bisected. Notice dense bone within bone appearance.

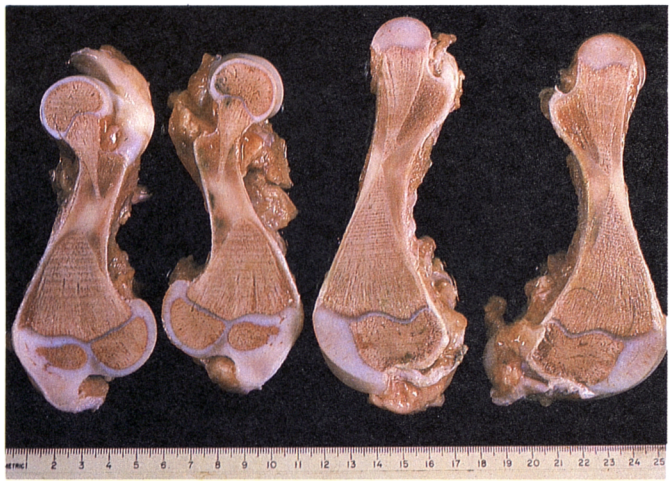


FIGURE 3. Humerus of a calf affected with osteopetrosis. Notice in the dense bone within bone appearance and lack of development of bone marrow cavity.

FIGURE 4. Cross section of facial bones and turbinates of an Angus calf affected with osteopetrosis. Notice thick turbinates.

FIGURE 5. Longitudonal bisection of thoraco-lumbar vertebral column of an Augus calf affected with osteopetrosis. Notice dense vertebral bone cones in vertebral bodies ("butterfly appearance").

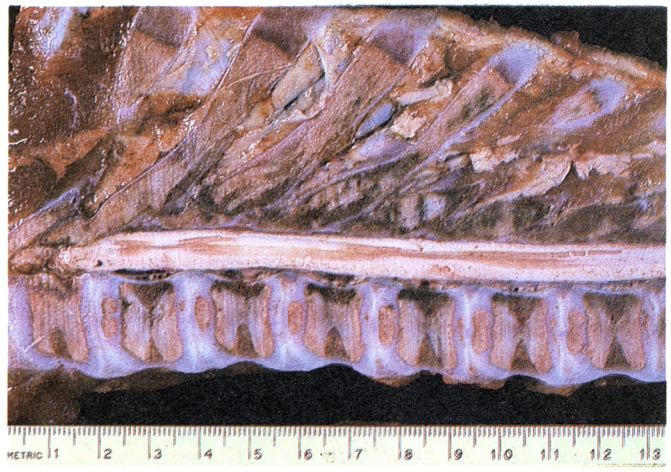


FIGURE 6. Macerated specimen of a sphenoid bone. Notice lack of foramina.

bone marrow cavity and cortex (figure 7). The cranial and facial bones were dense. The patent fontanelle was easy to visualize on x-rays (figure 8). Furthermore, the misshapen and shorter than normal mandible with impacted molar teeth were typical features in all cases of osteopetrosis (figure 8).

The central nervous system accommodated the osteologic defect; the cerebellum was compressed and the cerebral hemispheres appeared rectangular (figure 9).

Bone sections revealed the following histopathological changes. The nasal, frontal, temporal, parietal and maxilla bones were denser than normal with evidence of bone deposition on the outer surface but no bone removal from the inner surface. Pockets of marrow and small foci of fine connective tissue were interspersed throughout the bones. Median and paramedian sections of the cranial base has irregular intersphenoidal and spheno-occipital synchondroses. From both synchondrosesm, apices of wedge-shaped endochondral bone extended into solid cortical bone. The endochondral bone wedges consisted of calcified matrix and osteoid, occasional islands of resting chondrocytes and a few small foci of marrow. The sparsity of the vascular supply was striking. The growth plates of the vertebral bodies were irregular due to broad spicules of hypertrophied chondrocytes. Wedges of endochondral bone extended from the growth plates and their apices joined in the approximate center. Evidence of bone resorption was absent.

FIGURE 7. Radiograph of a hind leg of an Angus calf affected with osteopetrosis. Notice lack of development of bone marrow cavities in femur (a), tibia (b), metatarsus (c), and remaining bones.

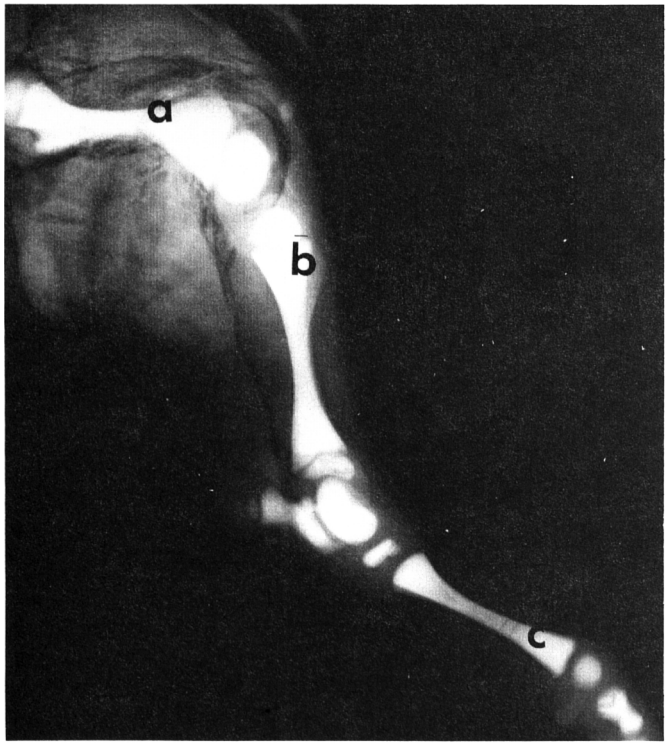


FIGURE 8. Radiograph of head of an Angus calf affected with osteopetrosis. Notice open fontanelle (a), and malformed, short lower jaw with impacted molar teeth (b).

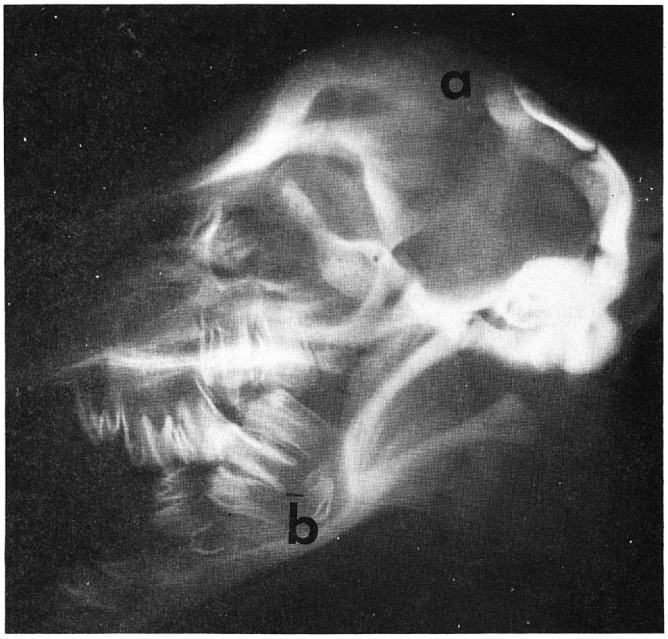
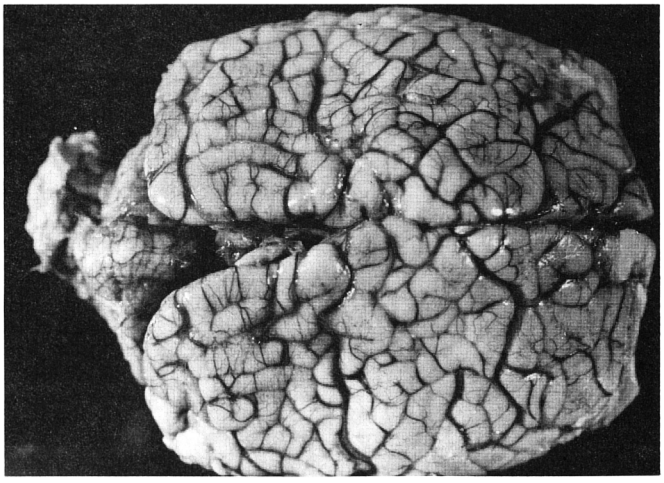


FIGURE 9. Brain of an Angus calf affected with osteopetrosis. Notice compressed, rectangular outline of brain.

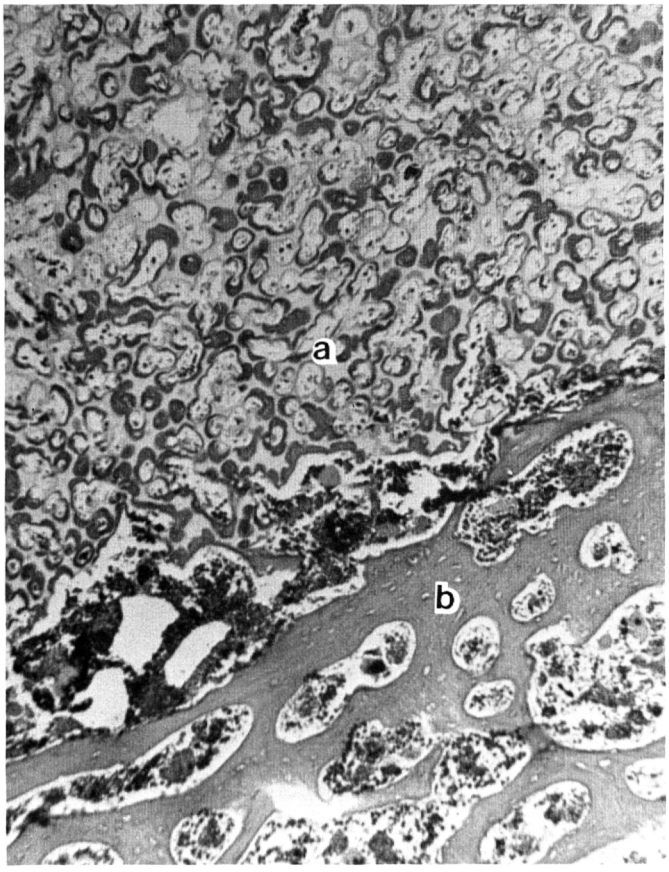


The long bones had similar microscopic features. The articular surfaces were normal. The epiphyses consisted of primary spongiosa, and the epiphyseal plates were irregular due to spicules of hypertrophied chondrocytes protruding towards the metaphyses. Islands of hypertrophied chondrocytes were present in metaphyses. Calcified matrix arising from epiphyseal plates was dense and persisted throughout the endochondral bone core. Marked osteoid seams were formed around the calcified cartilagenous matrix. The metaphyses contained calcified cartilagenous matrix, osteoid, and osseous tissue. Some osteoclasts were observed but appeared inactive. Few penetrating vessels were observed. Marrow spaces were limited, visible blood

vessels were few and dilated and hematopoietic tissue was sparse. Numerous areas of potential pockets of marrow cavities were replaced by a network of fine connective tissue. Cross-sections of bone in the metaphyseal and diaphyseal areas revealed narrowing of marrow spaces by cartilagenous matrix and osteoid, and by surrounding encroaching cortical bone. Upon transverse and longitudinal sections, the central areas of diaphyses had dense compacted cortical bone, which contained a few foci of marrow and loose connective tissue. The center of the diaphyses contained a narrow core of endochondral bone. Signs of bone resorption and remodelling were absent. Longitudinal sections of phalangeal bones had a wedge of endochondral bone, the apex of which met distally with dense cortical bone in a V-shaped line (figure 10).

Petechial hemorrhages were present in the cerebrum and cerebellum. The hypothalamic area revealed calcified blood vessels and neurons. A few smaller blood vessels, specifically dural vessels over the cerebellum, were calcified. The parathyroid glands were small but not histologicaly different from parathyroids of normal neonatal calves. The liver, spleen, and lymph nodes contained numerous foci of extramedullary hematopoiesis. Other tissues were normal

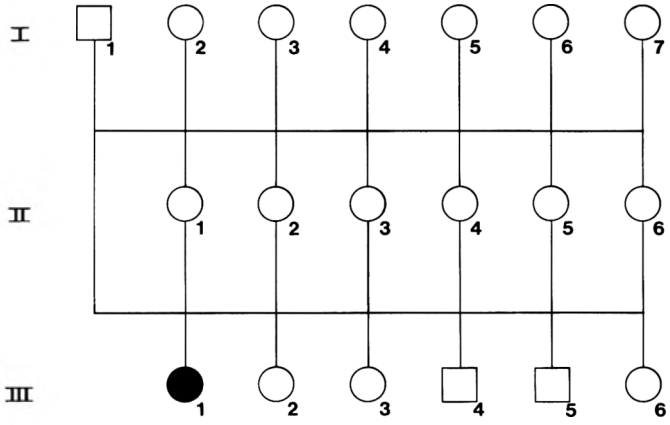
FIGURE 10. Histopathologic section of long bone of an Angus calf affected with osteopetrosis. Section was taken at mid-shaft area. Notice chondro-osseous matrix (a) and cortical bone (b). H&E, 120x.



Herd Histories

Two grade Hereford herds affected with osteopetrosis were located in Western Kansas in an area with an annual rainfall of about 12 inches. The first herd consisted of 20 adult grade cows, each of which had more than one normal calf previously. The calf crop from the adult cows was normal in that year and there were perinatal losses or abortions. In addition, there were six grade replacement heifers, all daughters of the herd sire. The first heifer had an abnormal female calf (III-1). The other five heifers had normal calves (III-2 to III-6, figure 11). Feeding and management practices were typical for the area. The cows were fed bailed Sumac cane and grazed corn and milo stubbles. Block salt and protein blocks were available *ad lib*.

FIGURE 11. Genealogy of osteopetrosis in a Hereford herd. An osteopetrotic calf resulted from father x daughter matings. Bull I-1 had been bred to six of his daughters (II-1 to II-6). One affected female calf (III-1) resulted and three normal females (II-2, II-3, and II-6) and two normal males (II-4 and II-5).



The abnormal calf was born during the night and found next morning by the owner. The calf was unable to rise and was taken to the local veterinarian who diagnosed fracture of each proximal tibia. The calf was transported to Kansas State University and died during the night and was submitted for necrosy examination.

In the second herd, a male Hereford calf had been aborted about 3 weeks prematurely. The calf died shortly after birth and was submitted for necropsy examination. The calf resulted from a half-sib mating. Further history was not available. The pathologic changes in these Hereford calves were similar to the ones observed in Angus calves (figures 12 and 13).

Pedigree Analysis

Pedigree analyses of osteopetrotic Angus calves revealed that three Angus sires were common (X, A, and B). Bull X was a common ancestor of all osteopetrotic calves examined. However, the bull also appeared in either paternal or maternal lines or both of 206 cattle (99.52% of

FIGURE 12. Bisection of a femur of a Hereford calf affected with osteopetrosis. Notice lack of development of bone marrow cavity (a).

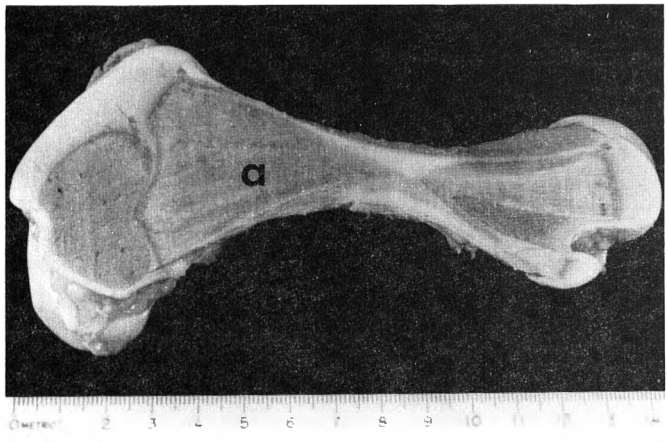
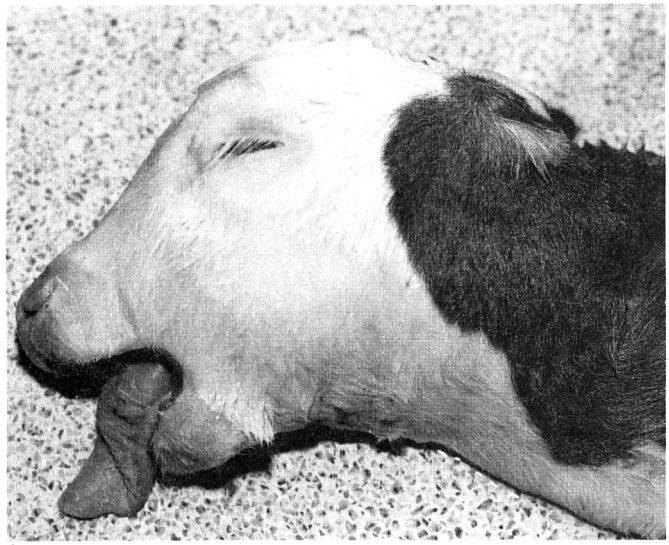


FIGURE 13. Head of Hereford calf affected with osteopetrosis. Notice short lower jaw and protruding tongue.

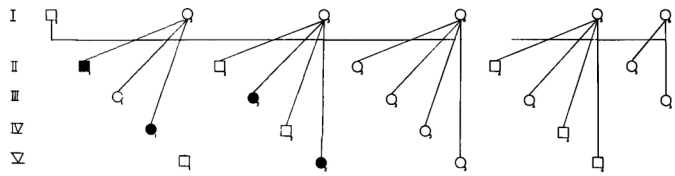


the population) of 207 randomly selected pedigrees. He was a paternal and maternal ancestor of 188 cattle (90.82% of the population). Bull A was a common paternal and maternal ancestor of all affected calves for which pedigrees were available. All calves traced back to bull A through several pathways. The average number of generations to bull A was 9. When 20 randomly selected pedigrees from the original 207 were examined, bull A was a common ancestor of 17 (85%). Bull B, a son of bull A, was a common paternal and maternal ancestor of all affected calves for which pedigrees were available. Bull B was a common ancestor of 70% of the 20 randomly selected pedigrees.

Breeding Trial

The results of the breeding trial conducted are given in figure 14. Calves sired by the heterozygous bull (I_1) from five assumed homozygous normal Angus cows were all normal. The heterozygous Angus cow ($I_{2\ 6}$) mated to the heterozygous bull (I_1) produced 18 calves, 4 of which were osteopetrotic (figure 14). With the hypothesis of a simple autosomal recessive trait, one-fourth of the calves would have been expected to be affected. The 3:1 ratio was not rejected ($P<.05$). The herd pedigree records that were available also support the simple autosomal recessive trait.

FIGURE 14. Breeding trial of osteopetrosis in Angus cattle. Circle denotes female, square denotes male, solid figures denotes animals affected with osteopetrosis.



Discussion

Osseous anomalies comprise a considerable part of the whole spectrum of congenital defects in cattle. They may be restricted to certain regions of the body or may be generalized. The defect described here is generalized and is readily recognizable by such gross features as brachygnathia inferior and impacted molars and lack of bone morrow cavities. In another description,[20] Hereford calves had greatly thickened cystic frontal bones with resulting domed foreheads, similar to some cases of hydrocephalus.

Some congenital osteologic defects affecting bone are restricted to the jaws; others are generalized. Hereditary brachygnathia inferior resulting from a disparity in length of the jaws has been described in several breeds; agnathia, a hereditary lethal, also has been noted.[12 14] A similar condition has appeared in Milking Shorthorns in the United States, New Zealand, and Great Britain under the name of "impacted molars" as reviewed recently.[14] The bones of affected cattle were neither radiographed nor examined grossly. Whether the two congenital diseases (brachygnathia inferior with malformed, impacted molars) and that described here are the same remains to be clarified.

Osteopetrosis has been described in man,[1 2 19 22 24 26 32] in dogs,[9 23] and described in laboratory animals.[18 21 29 31]

Gross and microscopic lesions described in the present paper correspond to those encountered in human congenital osteopetrosis. Although, the condition appears to be an imbalance between bone formation and bone resorption, the basic mechanism is still not clarified.[26]

In the pedigrees of the field data, bull X is an ancestor of most Angus cattle today and probably is not responsible for the recessive gene for osteopetrosis or it would have been more widespread. Bull A was a relatively unimportant ancestor of the Angus breed in 1955.[27] Bull B had less influence on the breed than bull A or bull X and is more closely related to the affected calves. Bull B seems to be the

logical choice as the source of the mutant gene.

The breeding trial (figure 14) confirmed simple autosomal recessive transmission of osteopetrosis in Angus cattle. The field data support this hypothesis. The same gene appears to be involved in both Angus and Hereford cattle.

Summary

Osteopetrosis is inherited as a simple autosomal recessive trait in Angus and Hereford cattle. It is characterized by premature stillbirth, 10 days to one month prior to term, brachygnathia inferior, impacted molar teeth, and easily fractured long bones. Other pathologic findings included absence of bone marrow cavities with replacement by primary spongiosa. The fetal-like, abnormal intramedullary bone consisted of chondro-osseous tissue. Long bones had the shape of two bone cones with their bases at the epiphyseal plates and their apices meeting at the midshaft. Foraminas of the skull and nutrient foraminas of bones were hypoplastic or aplastic. Cranial bones were thickened and compressed the brain into a rectangular shaped cerebrum and coned cerebellum. Extensive mineralization was present in vessel walls and neurons of the brain of the hypothalamus. The defect differed only slightly by breed.

Acknowledgements

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