Dwarfism in Alaskan Malamutes

A Disease Resembling Metaphyseal Dysplasia in Human Beings

RONALD D. SANDE, DVM, PhD,
JOHN E. ALEXANDER, DVM, MS,
G. ROGER SPENCER, DVM, PhD,
GEORGE A. PADGETT, DVM, MS,
and WILLIAM C. DAVIS, PhD

From the College of Veterinary Medicine, Washington State University, Pullman, Washington, and Michigan State University, East Lansing, Michigan

In a study of 300 Alaskan Malamutes, dwarfism was shown to be an autosomal recessive inherited disease with complete penetrance that resulted in disturbed endochondral bone formation. Osseous growth disturbance was manifest at the metaphyses of tubular bones. Clinical and radiographic changes were very similar to those of rickets, although appositional bone formation rates were normal. Serum calcium, phosphorus, and alkaline phosphatase were within normal limits. Urinary excretion of calcium, phosphate, and amino acids were normal. Excess matrix was formed in the zone of cartilage cell proliferation, and the matrix persisted in the growth plate. Normal stresses resulted in microfractures in the metaphyses with subsequent interference of vascular penetration into the zone of degenerated cartilage cells. (Am J Pathol 1982, 106:224–236)

DWARFISM in Alaskan malamutes is an inherited disturbance in endochondral bone formation that results in short-limbed, disproportionate dwarfism. Dogs with the disease have many clinical, radiographic, and histopathologic changes consistent with those found in rickets.[1,2] Characteristic signs of delayed and irregular endochondral bone formation develop while dogs are receiving an adequate amount of a balanced ration. The osseous changes that develop are refractory to treatment with supplemental calcium, phosphorus, and vitamin D.[1,2]

Dwarfism in the malamute was considered to be an inherited defect, and in 1969 a single autosomal recessive mode of inheritance was suggested.[3] Assuming that mode of inheritance, members of the Alaskan Malamute Club of America embarked on a test breeding program to eliminate dwarfism from the breed.[4] A subsequent report verified the mode of inheritance of the disease as a single autosomal recessive gene (gene symbol *dan*) with complete penetrance and no intermediate phenotypes.[5]

One group of investigators reported a hemolytic anemia as a pleiotropic effect in dwarf malamutes.[6-9] Subsequent reports by the same group described increased sodium concentration and water content in erythrocytes, with concomitant glutathione deficiency. These findings were considered similar to those in some human hemolytic anemias.[9,10]

Clinical evidence of dwarfism included short limbs with lateral bowing of the forelimbs, enlargement of the carpi, and lateral deviation of the forepaws (Figure 1).[1,11,12]

Radiographically, dwarfism was detectable at 7–10 days of age; and changes were pronounced after 3 weeks of age. Osseous lesions were evident in the growth plates and metaphyses of all tubular bones. Delayed ossification of cuboid bones and apophyses has been reported.[11] There was no evidence of irregular bone formation in the skull, mandibles, vertebrae, or pelvis.[11] Disruption of bone formation was present but generally less severe in the metaphyses of metacarpals, metatarsals, phalanges, femora, tibiae, and humeri. The most striking evidence of osseous change occurred at the distal

Supported in part by funds provided for biological and medical research by the State of Washington Initiative Measure No. 171 and the Graduate School Research Funds, by NIH Grant RR-00515, and by malamute breeders.

Accepted for publication September 22, 1981.

Address reprint requests to R. D. Sande, DVM, Department of Veterinary Clinical Medicine and Surgery, Washington State University, Pullman, WA 99164.

0002-9440/82/0210-0224$01.15

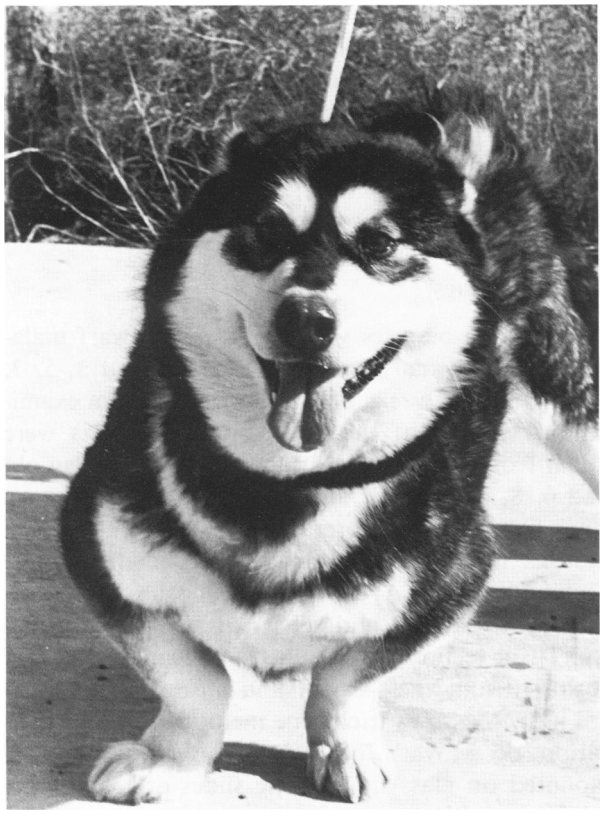

Figure 1—The clinical appearance of a dwarf malamute with shortening and valgus deformity of the forelimbs.

metaphyses and growth plates of the radius and ulna (Figure 2). It was postulated that the magnitude of osseous change in the distal end of the radius and ulna was related to weight distribution and growth characteristics in the canine forelimb.[11]

Materials and Methods

Genetic Study

Test animals used in the genetic study included adult malamutes and their progeny that were maintained in the genetic disease research facility at Washington State University. Also used were litters of malamute pups that were produced in cooperation with malamute breeders. Additional supporting data not contained herein were made available by malamute breeders.

Malamutes selected for breeding were considered initially to be either dwarf or normal phenotype. Those that were considered normal had no radiographic evidence of dwarfism while they were growing. Subsequent classification of "carrier" was made of dogs that were normal phenotype but were the progeny of a dwarf parent.

All breedings that produced pups considered in this study were witnessed by at least one investigator. No backcrosses were performed by mating parent to offspring. All dogs were housed in individual kennels and maintained under strict colony management.

Hematology and Serum Chemistry

Blood samples were collected from a total of 45 normal and 10 dwarf Malamutes at regular age intervals. Blood was first collected during the 6th week of age, and collections were continued at 2-week intervals through 18 weeks of age. Additional samples were collected at 6, 8, and 10 months of age.

Serum calcium (Oxford Titrator and Chemical Reagents, Scientific Products, Division of American Hospital Supply Corporation, McGraw Park, Ill)

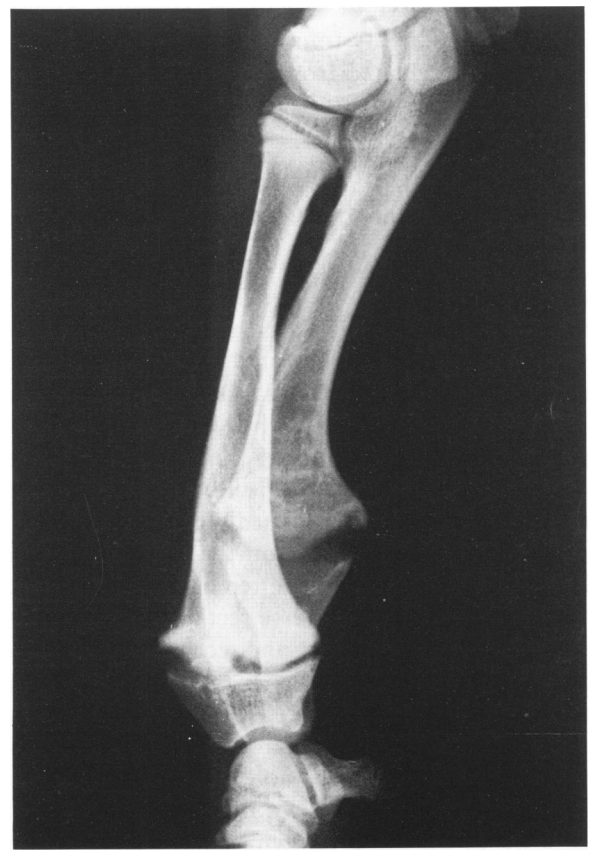

Figure 2—Radiographic appearance of the radius and ulna of a 12-week-old dwarf malamute. The metaphyseal borders are flattened and irregular, the growth plate is increased in width, and there is disorganized formation of osseous trabeculas in the metaphysis.

and inorganic phosphate (Hycel, Inc., Houston, Tex) concentrations were determined by methods using commercial reagents. Serum alkaline phosphatase activities were measured by a standardized commercial assay method (General Diagnostics Division, Warner-Chilcott Laboratory Division, Morris Plains, NJ).

Urine Amino Acid Analysis and Chemistry

Twenty-four-hour paired urine samples were collected from normal-phenotype and dwarf malamute littermates. Four pairs of samples were collected from a total of 8 puppies.

Urine amino acid analyses were performed with the standard technique in an automatic amino acid analyzer (Technicon TSM Amino Acid Analyzer, Tehnicon Instruments Corporation, Tarryton, NY).

Twenty-four-hour total urinary calcium excretion was calculated from values determined with the use of a commercial reagent set and standard technique (Oxford Titrator and Chemical Reagents, Scientific Products, Division of American Hospital Supply Corporation). Twenty-four-hour urine phosphate excretion was calculated from values determined by a dilution technique using a commercial reagent (Hycel).

Double-Tetracycline-Labeled Ground Bone Sections

Five dwarf malamutes and three Malamutes with normal phenotype from three litters between 14 and 18 weeks of age were given intravenous injections of tetracycline hydrochloride at a dosage rate of 15 mg/kg body weight. Ten days following the initial injection, a second intravenous injection of tetracycline hydrochloride was made using the same dosage rate. Four days after the second injection, euthanasia was performed and followed immediately by necropsy.

At postmortem examination the right radius and ulna and right sixth rib were removed and dissected free of soft tissue. Transverse sections of bone were taken at the mid-diaphysis, and sections were ground to approximately 35 μ in thickness with the use of a rapid manual method of preparation.[13] The sections were stained with an osteochrome stain intended for use with fresh, mineralized bone sections.[14] Bone sections were mounted on glass microscope slides and examined by light and ultraviolet microscopy.

We measured 10 tetracycline-labeled osteons for each animal, using an eyepiece micrometer on a fluorescence microscope. The distance between tetracycline labels was measured at four equidistant points around the circumference of each osteon. Each measurement was made from the middle of the outer label to the midpoint of the inner label.

We obtained the appositional rate of bone formation by dividing the mean distance between osteon tetracycline labels by the time interval between injections (10 days).

Histopathology

Paired rib biopsies were taken from dwarf malamutes and normal phenotype littermates at 3, 5, 7, 12, 16, and 20 weeks of age. At postmortem examination sections of the right radius and ulna were taken from normal and dwarf malamutes 1 day old and 6, 8, 10, 16, 18, and 20 weeks of age. Tissues were fixed in 10% formalin and decalcified for 2 months in phosphate-buffered ethylenediaminotetraacetic acid (EDTA) at pH 7.4. Tissues were embedded in paraffin and sectioned at approximately 6 μ. Tissue sections were stained with hematoxylin and eosin, periodic acid–Schiff and alcian blue, colloidal iron, Masson's trichrome method, and a modification of Movat's pentachrome.[15] Sections were mounted on glass microscope slides and examined microscopically.

Histochemical Examinaton

The right ulna was removed from each of 2 dwarf and 2 normal 8-week-old malamute littermates at postmortem examination. Frozen sections were made of the growth plate, and the tissues were stained for acid phosphatase and for alkaline phosphatase (Sigma Chemical Company, Technical Bulletin No. 85, St. Louis, Mo). The tissues were examined microscopically to detect any difference in stain intensity.

Electron Microscopy

Growth plate specimens were obtained from 8 puppies of the same litter at 8 weeks of age. The litter consisted of 3 dwarf and 5 puppies of normal phenotype that were the progeny of a dwarf dam and a carrier sire. The distal epiphysis and growth plate, including a portion of the metaphysis, were removed surgically from the distal end of the right ulna to assure a fresh specimen.

Tissue specimens were longitudinally sliced into several sections 1 mm or less in thickness and placed in 2% phosphate-buffered (0.1 M $K_{(n)}$ PO_4, pH 7.3) glutaraldehyde containing 1% sucrose and 1% dimethysulfoxide. Following 2–4 hours' fixation, disks

of tissue 2 mm in diameter were punched from the sections in each zone of the growth plate, the epiphysis, and the metaphysis. The tissues were processed and embedded in a mixture of embedding resins (Epon-812 and Araldite-6005, Ernest F. Fullam, Inc., Schenectady, NY) according to a standard method.[16] Sections approximately 75 mμ in thickness were cut with a diamond knife in a Porter-Blum ultramicrotome. These sections were mounted on 200-mesh copper grids and poststained with uranyl acetate and lead citrate. Sections were examined in an electron microscope.

Results

Genetic Study

Table 1 summarizes the data accumulated and the matings performed in the study. Puppies examined in the genetic study were classified as normal phenotype or dwarf. Normal dogs developed no clinical or radiographic evidence of dwarfism by 12 weeks of age. Dwarf malamutes developed degrees of osseous growth disturbance varying from gross malformation of the limbs to transient radiographic evidence of uneven metaphyseal bone formation in the distal end of the radius and ulna. In spite of this variation, no intermediate phenotype was identified. A single autosomal recessive mode of inheritance was confirmed by these data.

Hematology and Serum Chemistry

White blood cell morphologic characteristics and differential counts in dwarf malamutes were similar to those in the normal and carrier malamutes. Erythrocyte indices of dwarf malamutes, however, indicated the presence of hypochromic, macrocytic anemia.

No difference was found at the 5% level of significance between the mean serum calcium concentrations in normal and dwarf malamutes. Mean serum calcium concentration in the dwarf varied from 9.5 mg/dl to 11.1 mg/dl. Similarly, the mean serum calcium concentration in normal pups varied from 10.1 mg/dl to 11.0 mg/dl (Table 2). Mean serum phosphate concentrations and mean serum alkaline phosphatase activities were usually greater in the dwarf malamute. Significant differences were found at the 5% level between mean serum inorganic phosphate concentrations of normal and dwarf dogs at 16 weeks of age, dwarfs having increased values (Table 3). Similarly, alkaline phosphatase activities were significantly higher in dwarf dogs at 10, 12, and 18 weeks of age (Table 4).

It should be noted, however, that absolute values for serum inorganic phosphate concentrations and serum alkaline phosphatase activities were not in excess of the normal limits established for canine sera.[17] With the approach of skeletal maturity, mean serum values for alkaline phosphatase activity and phosphate concentations decreased in the normal and dwarf malamute serum samples at a similar rate.

Urine Amino Acid Analysis and Chemistry

A total of 34 amino acid peaks were detected, and 13 of those peaks were identified, including proline, glycine, valine, citrulline, and threonine. Values were reported as micromoles per milliliter. No individual or comparative increase in the excretion of amino acids was detected in the urine of normal-phenotype or dwarf malamutes.

Excretion of calcium and phosphate in the urine was variable; however, no difference was found in paired samples between the dwarf malamute and its littermate with a normal phenotype.

Double-Tetracycline-Labeled Ground Bone Sections

Ground bone sections from dwarf limb bones and ribs had consistently thicker cortices than normal bone. Fewer Howship's lacunae and fewer active osteons were present in the cortex of dwarf bones. Bone

Table 1—Results of Matings Performed to Determine the Mode of Inheritance of Dwarfism in Alaskan Malamutes

Crosses performed	Litters produced	Total pups	Average litter size	Live pups	Normal phenotype	Dwarf
Normal to normal	6	50	8.3	49	49	0
Normal to carrier	5	39	7.8	34	34	0
Carrier to carrier	5	24	4.8	24	18	6
Normal to dwarf	18	123	6.8	103	103	0
Carrier to dwarf	10	46	4.6	46	29	17*
Dwarf to dwarf	3	18	6.0	14	0	14

* $\chi^2 = 3.14$, $P = .081$ for 1:1 normal to dwarf.

Table 2—*t*-Test Comparing Mean Serum Calcium Concentrations (mg/dl) in Dwarf and Normal Malamutes

	Age in weeks									
Group	6	8	10	12	14	16	18	24	32	40
Dwarf	11.0	10.7	9.5	10.6	10.6	10.4	10.1	10.8	10.2	10.9
n	7	2	2	2	2	4	8	3	4	2
Normal	10.5	11.0	10.4	10.3	10.6	10.8	10.1	11.0	10.3	10.3
n	29	22	7	9	5	11	6	7	7	5

from dwarf puppies had evidence of more active periosteal bone formation than normal except for the bone of one normal pup (Figure 3).

Mean appositional bone formation rate (Table 5) was slightly greater in bone from normal dogs than from dwarfs, but there were neither marked nor consistent differences between the rates of bone apposition at the double-tetracycline-labeled sites in normal and dwarf malamutes.

Histopathology

Newborn

There was little histologic difference in the growth plate and metaphyses of newborn dwarf and normal malamutes. The growth plate was narrow, and columns of cartilage cells were well organized. The zones of cartilage cell proliferation, hypertrophy, and degeneration were similar in sections from dwarf and normal pups. The zone of provisional calcification was regular; however, calcified matrix spicules in the primary spongiosa and ossified spicules in the secondary spongiosa were fewer but larger and more irregular in bone from dwarf malamutes (Figure 4).

Normal Phenotype

Although bone sections taken from newborn malamutes were quite similar, striking differences were found between growth plate sections from normal phenotype and dwarf malamutes during the growth period. In sections from the normal-phenotype growth plate, numerous cartilage cell stacks were produced in the zone of cartilage cell proliferation (ZCP), separated by narrow cores of matrix. Stacks of cartilage cells remained well aligned through the zone of cartilage cell hypertrophy (ZCH) and the zone of cartilage cell degeneration (ZCD), with occasional compression and lateral displacement of cells and lacunae. The three zones of cartilage cells were approximately equal in length, and vascular penetration of the degenerated cartilage cells occurred at a regular rate. Vascular penetration into the ZCD resulted in the removal of degenerated cartilage cells and exposure of the narrow cores of intervening calcified cartilage matrix. Osteoblasts proliferated and deposited osseous tissue on the exposed surfaces of the matrix spicules to form the osseous-matrix trabeculas of the secondary spongiosa. Therefore, narrow parallel osseous trabeculas, aligned with the bone growth axis, were formed in the metaphysis. Between these trabeculas, the vascular or marrow spaces remained in the area of the respective columns of degenerated cartilage cells that preceded them.

Dwarf

The cellular morphology of resting, proliferative, and hypertrophic cartilage cells appeared normal in the dwarf. Proliferation of cartilage cells in the ZCP resulted in short stacks of cells separated by broad cores of matrix. In some areas the abundant matrix displaced cartilage cell columns and gave the appearance that fewer cells were present. The ZCP and ZCH were normal in length and similar to the respective zones in the normal growth plate (Figure 5).

Arrangement of the cell columns and lacunae within the growth plate of the dwarf was variable. Cartilage cell stacks were found in relatively long, straight columns, whereas in the other areas columns were short and crooked. Linear arrangement of cells in the ZCH and ZCD was frequently lost, as cells were displaced laterally, forming confluent columns as many as five cells wide. Clusters of cartilage cells were found occasionally at the margins of the growth plate (Figure 6).

Table 3—*t*-Test Comparing Mean Serum Phosphate Concentrations (mg/dl) in Dwarf and Normal Malamutes

	Age in weeks									
Group	6	8	10	12	14	16	18	24	32	40
Dwarf	8.1	8.5	8.7	8.5	7.0	9.4	7.4	7.5	6.0	6.2
n	7	2	2	2	2	4	8	3	4	2
Normal	7.9	7.1	8.0	7.9	7.7	7.8	7.5	7.7	6.4	7.5
n	29	21	6	9	4	9	6	7	7	9

Table 4—*t*-Test Comparing Mean Serum Alkaline Phosphatase Activities (Bodansky Units) in Dwarf and Normal Malamutes

	Age in weeks									
Group	6	8	10	12	14	16	18	24	32	40
Dwarf	10.9	11.2	16.9	14.8	11.7	10.6	15.1	9.2	8.6	5.6
n	7	2	2	2	2	4	8	3	4	3
Normal	8.8	8.5	9.1	8.6	8.9	11.2	13.2	6.9	5.1	8.1
n	29	22	7	9	5	10	6	7	7	5

The abundant matrix that was present in the ZCP continued through the ZCH and the ZCD. The matrix in these zones was present in wide cores interconnected by transverse bands, which interrupted the columnar progression of cartilage cells or caused these columns to be deviated from the plane of the section.

In the ZCD broad longitudinal and transverse cores of matrix were interspersed among confluent stacks of intervening cartilage cells. In some areas vascular penetration from the metaphysis occurred normally. Exposed matrix cores were ossified, to become irregular longitudinal and transverse osseous-matrix spicules in the secondary spongiosa. These trabeculas were separated by wide vascular spaces similar to the confluent columns of cartilage cells which preceded vascular penetration into the ZCD.

Microfractures were frequent in the zone of provisional calcification. These fractures resulted in interruption of vascular penetration with hemorrhage, fibrosis, callus formation, and occasional thrombosis. In other areas there was evidence of healing, with renewed vascular penetration occurring distal to the microfracture. Occasional tongues of degenerative cartilage cells and unossified matrix extended into the metaphysis. These tongues of cartilage were found abutting the fibrous callus of a microfracture, whereas in adjacent areas of the same microfracture vascular penetration and osteogenesis were reinitiated (Figure 7).

Evidence of recent microfractures was present in

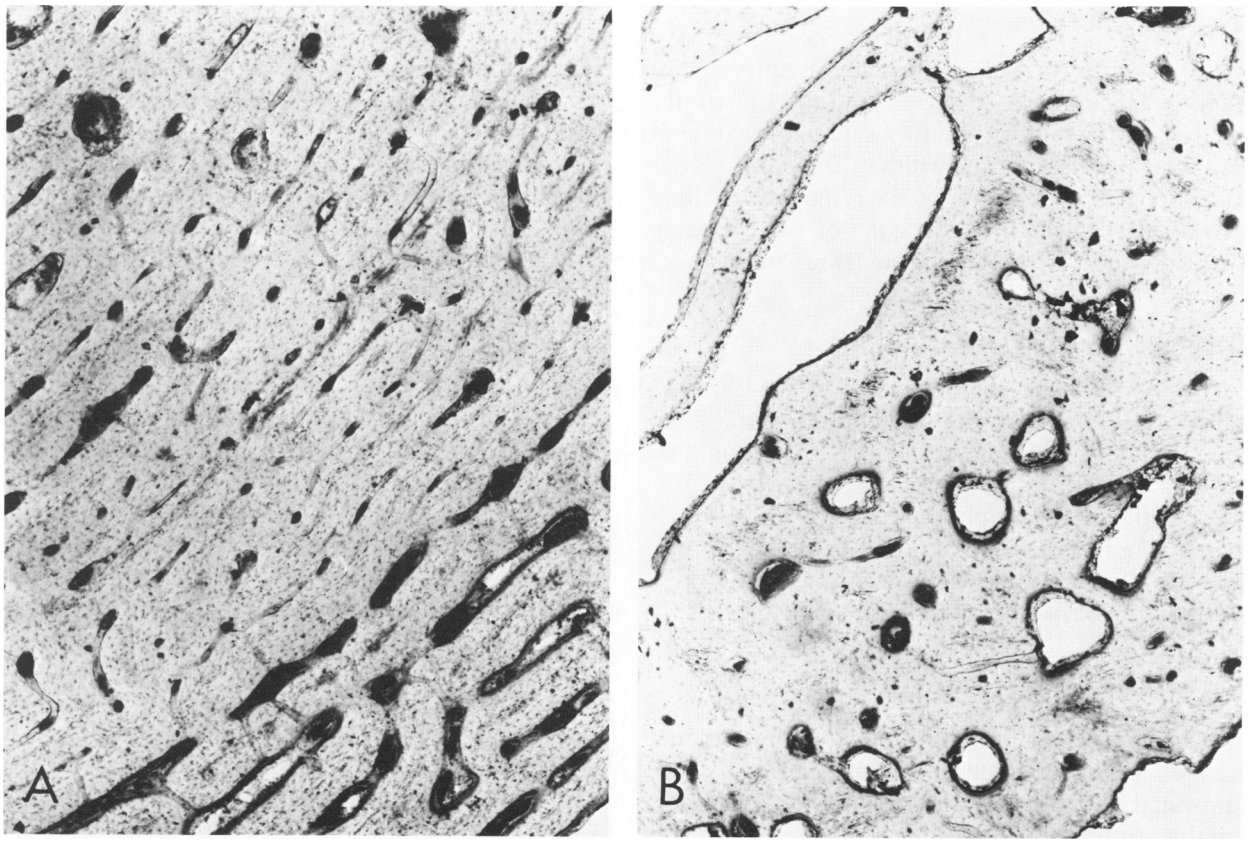

Figure 3—Transverse, ground rib sections from a dwarf (**A**) and a normal (**B**) malamute. Increased periosteal bone formation and reduced cortical bone remodeling were evident in the dwarf. (Villanueva's osteochrome, ×60) (With a photographic reduction of 4%)

Table 5—Double-Tetracycline-Labeled Bone Study for the Determination of Appositional Bone Formation Rate

Puppy number*	Age (weeks)	Sex	Appositional rate in microns/day	
			Normal phenotype	Dwarf
3-1	16	M		1.35
3-2		M	2.36	
3-3		F		2.01
3-4		M	1.37	
4-1	18	F		1.43
4-2		F		1.52
5-1	20	M	2.84	
5-2		F		1.58

* First number indicates litter number; second indicates puppy number.

the secondary spongiosa and metaphysis. Transverse bands of short trabeculas were interrupted by other transverse bands of fibrosis. The cartilage growth plate immediately distal to recent or healing microfractures was wide due to an increase in the length of the ZCD. In contrast, the growth plate was narrow, and zones of the growth plate were relatively normal distal to the secondary spongiosa, where there was no evidence of previous microfractures (Figure 8).

Histochemical Examination

No quantitative difference between intensity of staining reaction was detected among any of the tissue sections stained for either acid phosphatase or alkaline phosphatase. The width of the stained tissue corresponded to the width of the respective cartilage growth plate. Therefore, the zone of stain reaction was wider in tissue sections from dwarf pups.

Electron Microscopy

The morphologic characteristics of the cartilage cells were similar in dwarf and normal puppies. No abnormality in the structure of these cells could be detected.

Subjective examination indicated a possible difference in the fibrillar matrix found between cartilage cells. However, no conclusions regarding matrix were made on the basis of this study.

Discussion

The genetic data supported previous reports that the most probable mode of inheritance was a single autosomal recessive gene with complete penetrance, variable expression of dwarfness, and no intermediate phenotypes. A lethal factor was unlikely, because both the death rate among newborn puppies and reduced litter size were not consistent among litters produced by dwarf or carrier parents. The variation in litter size may have reflected physical problems encountered in breeding dwarf dogs. Furthermore, no allowance was provided in these data to adjust for the dwarf and carrier dams being usually primipara, whereas all normal dams were pluripara.

Samples obtained for urinalysis provided too few data to permit meaningful statistical analysis. The absence of overt differences in the urinary excretion of calcium, phosphorus, and amino acids suggested that no renal mechanism was involved in the disturbance of endochondral bone formation.

Fewer active osteons and fewer Howship's lacunae in the ground sections of dwarf bone indicated reduced cortical bone remodeling. Increased periosteal bone formation and reduced cortical remodeling may have been the result of mechanical factors associated with the broad, short, curved bones.

Alkaline phosphatase activity and inorganic phosphate concentration in the dwarf were not in excess of absolute values established for normal canine serum, although they were slightly higher than in normal control malamute serum. Increased serum phosphorus concentration in the dwarf was not considered unusual in the presence of normal serum calcium concentrations and increased osseous reorganization. Greater serum alkaline phosphatase activity in dwarf dogs might be expected in the presence of the marked osseous changes and bone remodeling that occurred, compared with normal malamutes. Serum values or inorganic phosphate and alkaline phosphatase activity progressively decreased with maturing endochondral ossification. These values were similar in normal and dwarf malamutes at skeletal maturity. In addition, no detectable differences in histochemical stain intensity could be found in endochondral ossification at the metaphysis of dwarf malamutes. These findings suggested that delay in endochondral ossification was not related to errors in alkaline or acid phosphatase metabolism.

The absence of a marked variation in serum calcium and phosphorus and the normal urinary excretion of calcium and phosphorus in dwarf malamutes suggested that vitamin D metabolism and the regulatory mechanisms involved in calcium and phosphorus homeostasis were not primary factors in the pathogenesis of the disease. The absence of a significant difference in the appositional bone formation rate added further support to the hypothesis that

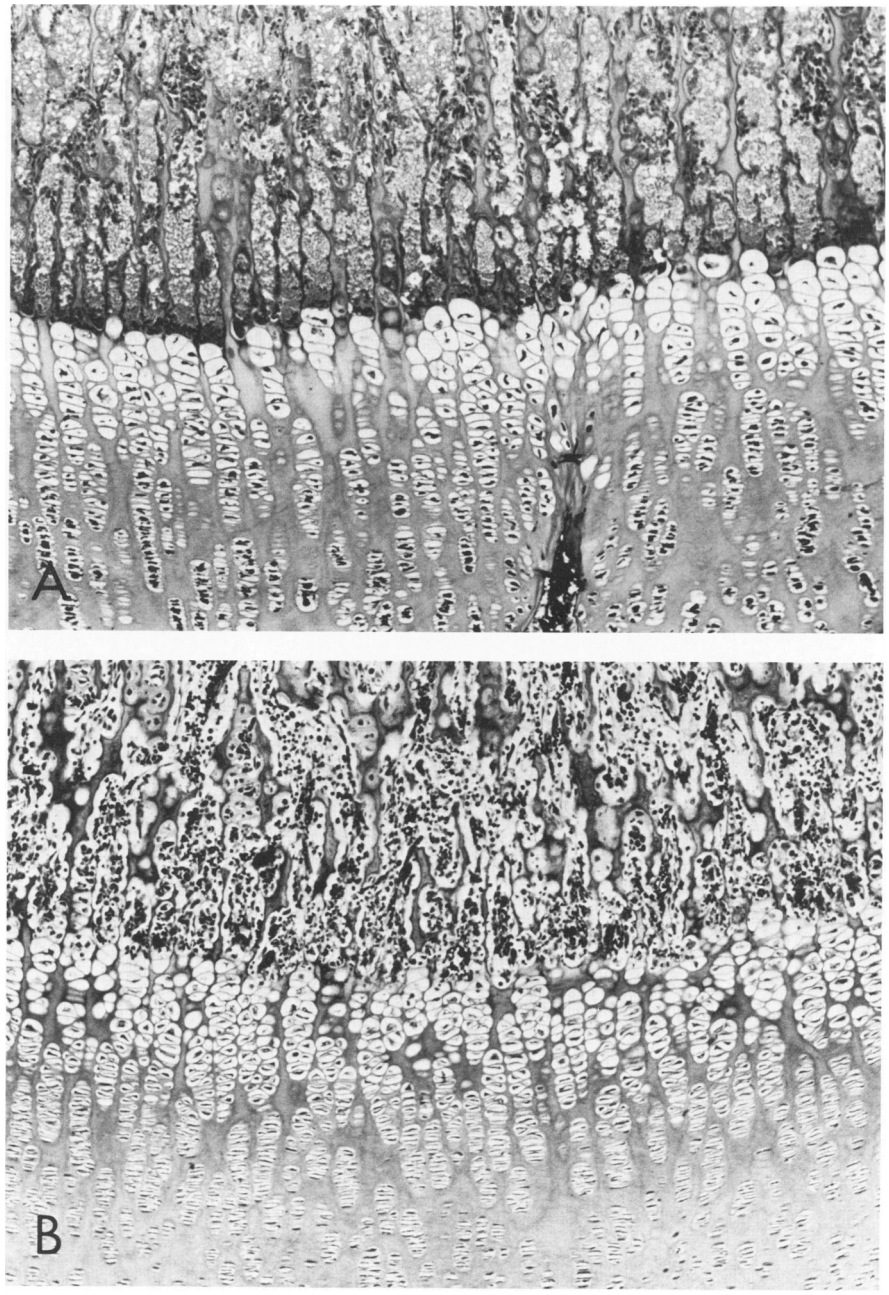

Figure 4—Photomicrographs comparing sections from the growth plate of normal (**A**) and dwarf (**B**) newborn malamutes. Fewer and more irregular trabeculas were present in the secondary spongiosa and metaphysis of the dwarf. (Movat's pentachrome, ×90)

general factors associated with mineralization of bone were normal.

Histologic findings in the growth plate of normal-phenotype malamutes were consistent with normal columnar endochondral bone formation. No indications of cellular or structural differences were found that would distinguish the heterozygous condition.

Histopathologic findings in the dwarf growth plate did not reveal morphologic abnormalities of cartilage cells, vascular components, or osteoblasts. Large cores of exposed matrix in the zone of provisional calcification resulted in less total surface area for ossification. As a result of this weakness, normal stresses resulted in trauma and fractures in the zone of provisional calcification. Vascular penetration with resorption of degenerated cartilage cell lacunae were interrupted, and irregularities in the healing of microfractures resulted in additional vascular interference. The ZCP was not affected by these changes, and cartilage cells continued to proliferate, hyper-

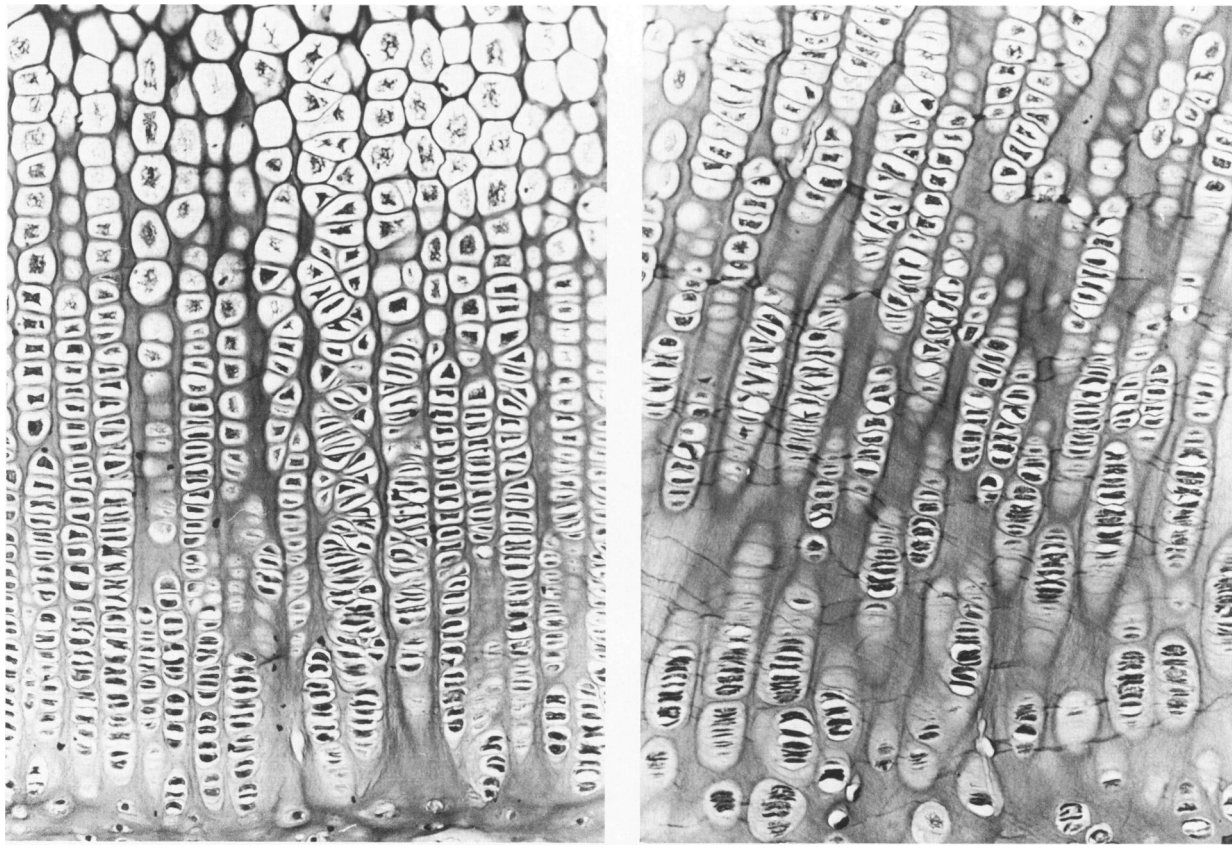

Figure 5—Photomicrographs comparing growth plates from a normal (**A**) and a dwarf (**B**) malamute at 12 weeks of age. Matrix was more abundant and cartilage cell columns appeared fewer in the dwarf. (Movat's pentachrome, × 180) (With a photographic reduction of 4%)

trophy, and degenerate. Therefore, increase in the length of the ZCD and unevenness in the cartilage growth plate were the result of mechanical interruption in vascular penetration and osteogenesis.

The subtle difference between the growth plates of newborn dwarf and normal malamutes did not provide a reliable means of determining either the phenotype or the genotype. This observed difference, however, suggested an inborn cellular error in dwarfs with the presence of a structural weakness at birth that required mechanical factors to bring about the clinical manifestation of dwarfness. The first osseous change seen on radiographs of dwarf malamutes occurred at 7–10 days of age. These changes were consistent with a pathogenetic mechanism involving trauma. In other dogs, evidence of bone resorption at the site of a fracture became apparent at 7–10 days following the initial trauma.

Among the "cartilage-preformed bones" formation of bone from elongated columns of cartilage cells was characteristic of the tubular bones. The structural architecture of this type of endochondral bone formation was more susceptible to trauma and the subsequent effects of vascular interruption. Vascular interruption with irregularities in healing and development of unequal vascular penetration into the zone of degenerated cartilage cells resulted in an uneven rate of bone formation at the metaphysis. In rickets the initial source of weakness was inadequate calcification of matrix spicules in the primary spongiosa. Variations in the composition, quantity, or deposition of cartilage matrix may have had a similar effect. It was likely that focal interruption of vascular penetration into the growth plate from any cause could have produced a similar manifestation in growing bone. Therefore, in the dwarf malamute the occurrence of marked irregularities in bone formation at the metaphyses of tubular bones and the apparent absence of interference with other types of endochondral bone formation did not preclude the possibility of a generalized cartilage defect. Delayed ossification in cuboid bone and apophyses in

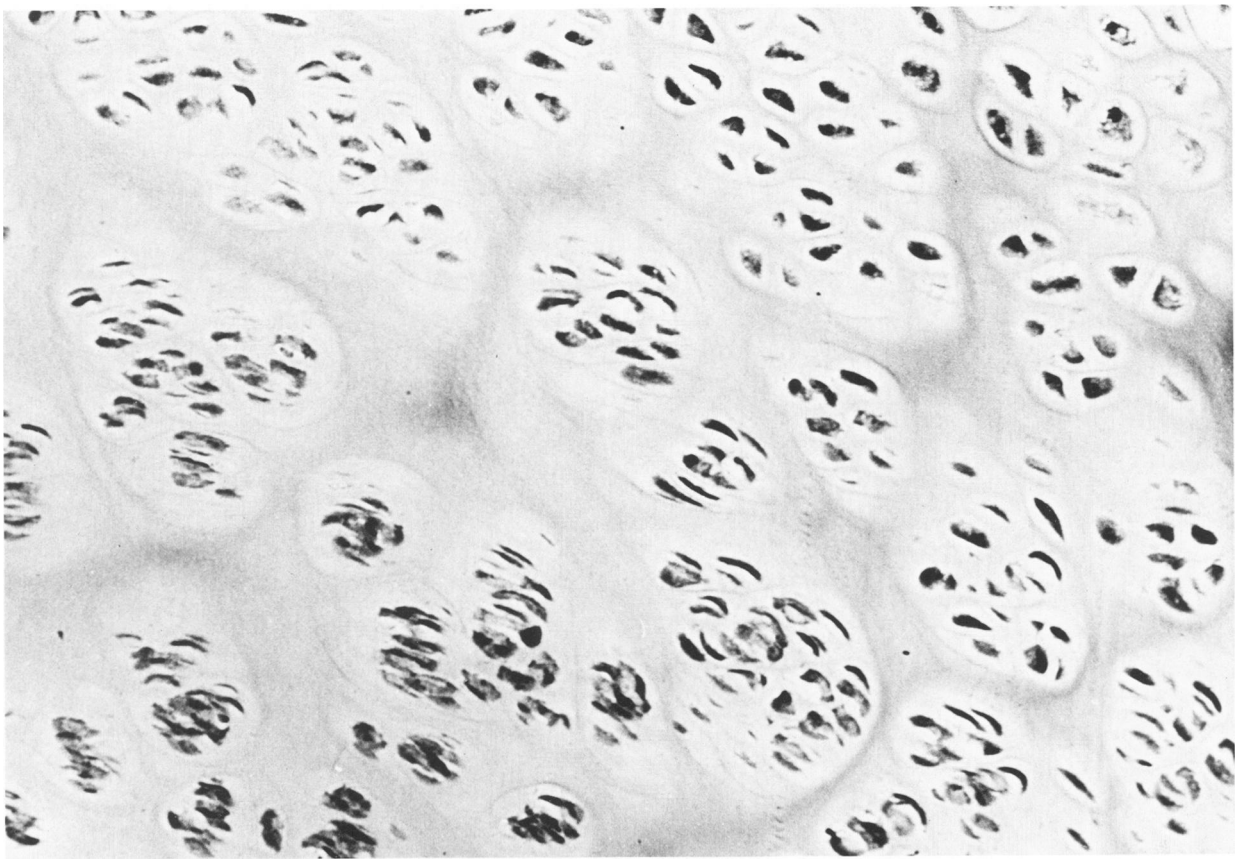

Figure 6—Photomicrograph of the growth plate from the rib of a 12-week-old dwarf malamute. Cartilage cells were occasionally found in confluent columns and clusters. (Movat's pentachrome, ×400) (With a photographic reduction of 3%)

malamute dwarfs supported the hypothesis that a generalized defect in cartilage is present.

Excessive cartilage matrix or structural weakness of the cartilage matrix or a combination of both could have led to greater displacement of plastic flow of matrix while the cartilage was under stress. This could have led to distortion of the columns of cartilage cells with displacement of cells and subsequent increase in width of cartilage cell columns. Microfractures that were observed in the primary spongiosa could have been produced by mechanical stress acting on the zone of provisional calcification, made weaker by the development of fewer and larger calcified cores of abnormal matrix. Excess matrix was first observed in the zone of cartilage cell proliferation, and irregular cores of matrix persisted in all three zones of the growth plate, to become equally irregular ossified spicules in the metaphysis. These findings suggested an alteration in the collagen-gel composition of the cartilage matrix.

Ultrastructural defects have been found in the cartilage cells of some human dwarfs.[18-22] Electron-microscopic examination of cartilage cells from malamute dwarfs failed to reveal a storage defect in the rough endoplasmic reticulum. No other ultrastructural defects were found in cartilage cells, and no conclusions were made regarding the fibrillar matrix surrounding these cells. Subsequent ultrastructural studies have revealed defects of growth plate chondrocytes, which include fewer ruthenium red granules present in the interterritorial matrix of dwarf malamutes and some dilation of the rough endoplasmic reticulum in proliferating cartilage cells.[23]

Dwarfism in the malamute is a chondroosseous defect with characteristics similar to the metaphyseal dysplasias in human beings. The similarities may be summarized as follows:

1) Both diseases have a marked resemblance to rickets.[1,2,11,24-28]
2) Both diseases have been mistaken for vitamin D-resistant rickets.[1,24,29-32]

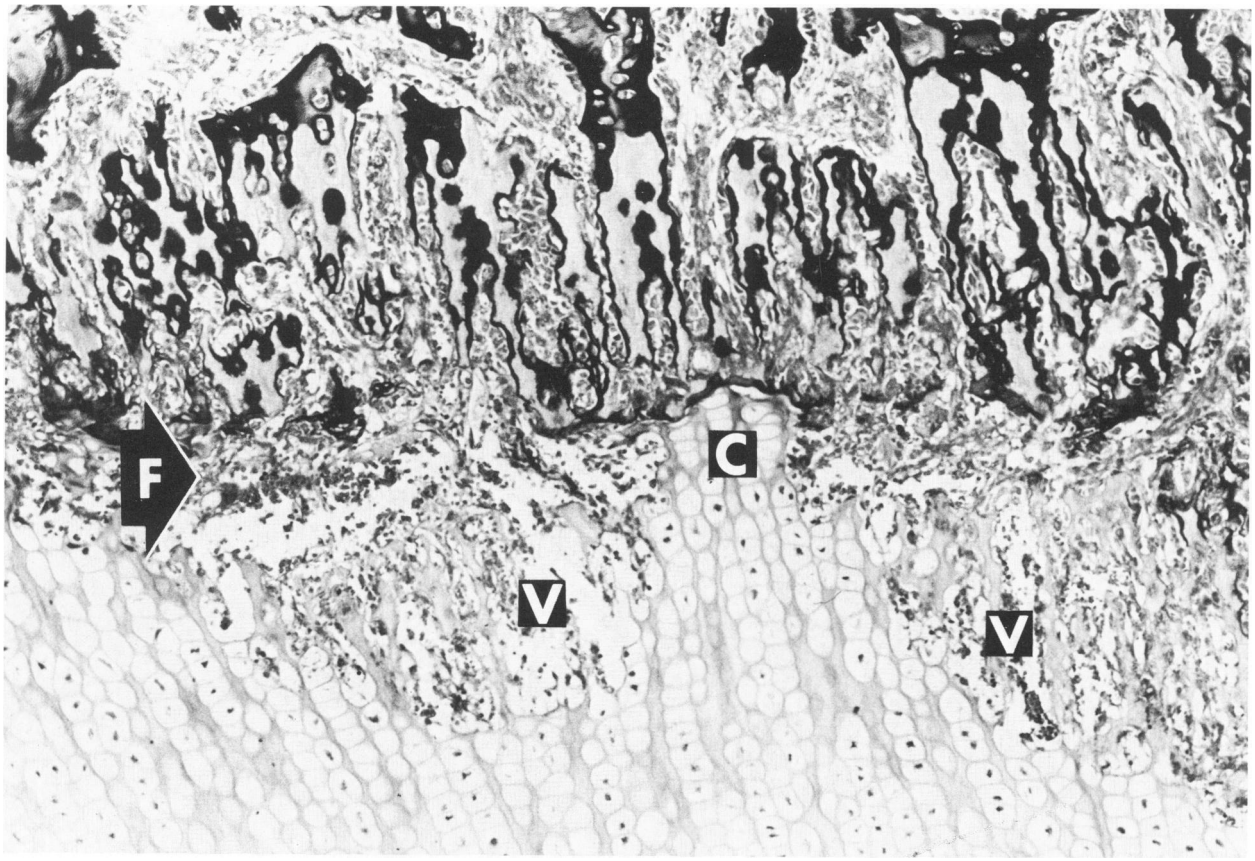

Figure 7—Photomicrograph of a healing microfracture in the growth plate from the distal radius of a 20-week-old dwarf malamute. The zone of provisional calcification distal to the microfracture (*F*) was uneven. Vascular penetration (*V*) and osteogenesis were evident on either side of a tongue of degenerated cartilage (*C*). (Movat's pentachrome, × 120) (With a photographic reduction of 3%)

3) Patients were short in stature, and osseous changes were usually restricted to the long tubular bones.[1,2,11,24–27,31,33–35]
4) Retarded ossification of cuboid bones have been suggested.[1,36,37]
5) Bones of the spine and skull had no noticeable change.[1,2,11,25,26,28,31,33,35]
6) Transmission of these diseases was considered hereditary.[1–5,24–27,31,33,34,35,38]

Literature citing dwarfism in human patients is frequently confusing, due to inconsistencies in classification and and nomenclature. In recognition of this problem, attempts have been made to develop a more standard nomenclature.[36,39] An effort to classify dwarfism in the malamute should consider the following: 1) dwarfism is transmitted by an autosomal recessive gene; 2) manifestation of the cartilage–osseous defect occurs during the growth period following birth and is not grossly evident in the newborn; 3) the disease does not appear to be intrinsic to bone or osteogenetic precursor cells; 4) dwarfism is not influenced by nutritional factors involved in osteogenesis; and 5) the osseous change appears to be a function of the cartilage cell or the matrix formed by cartilage cells. Applying these findings to one method of classification, malamute dwarfism may be considered to be a form of metaphyseal dysplasia.[36] Using another nomeclature, one may classify this disease as osteochondrodysplasia.[39] It is not the purpose of this study to rename dwarfism in malamutes; therefore, it is suggested that the name "canine chondrodysplasia,"[2] or more simply, "dwarfism in Alaskan malamutes," be retained until the biochemical mechanisms are discovered. It should be stressed, however, that chondrodysplasia in the malamute is completely unlike familial canine chondrodystrophia fetalis (achondroplasia).[40] In addition, this disease is unlike dyschondroplasia as is described in some human dwarfs.[41]

Marked variation in the expression of dwarfness occurs among malamutes. Although this variation is not as great as that which occurs among human dwarfs, it should be recongized that affected dogs are the product of a relatively small genetic pool. In addition, these dogs are maintained in more standard

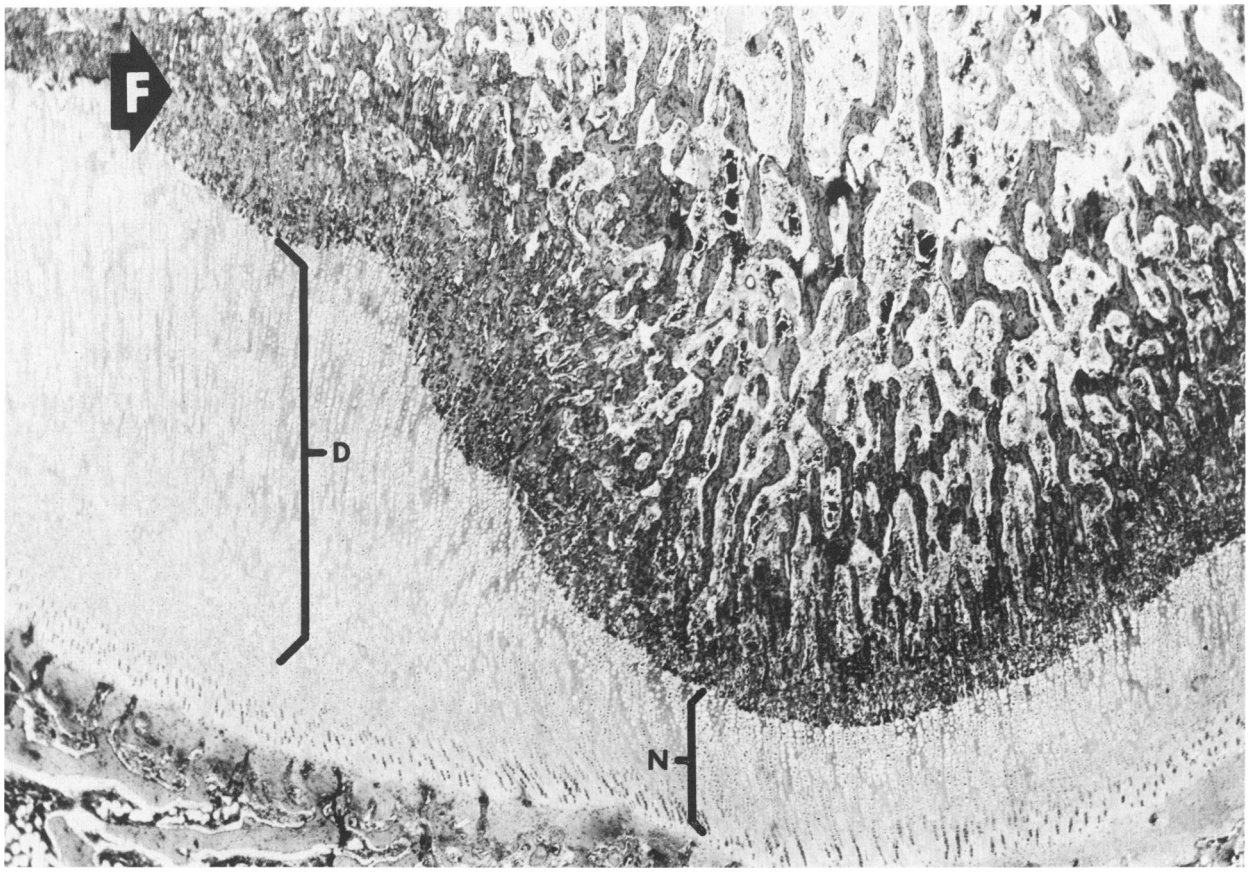

Figure 8—Photomicrograph of the growth plate from the distal radius of a 20-week-old dwarf malamute. Columns of degenerated cartilage cells (*D*) were longer distal to microfractures (*F*) in the metaphysis. The growth plate (*N*) was relatively normal distal to the metaphysis, where no microfractures were present. (Masson's trichrome, × 16) (With a photographic reduction of 2%)

conditions of environment and diet than their potential human counterparts. Dwarfism occurs sporadically among the general canine population; however, little effort has been made to document individual cases. This has resulted in an unfortunate void in the comparative study of dwarfism among dogs.

The clinical, radiographic, and histopathologic characteristics of dwarfism in the Alaskan malamute have been described. Identification of the biochemical disease mechanism and additional ultrastructural studies are necessary before the ultimate classification of this disease can be made. It appears that this disease might provide a valuable model with which to study similar chondroosseous disease in human beings.

References

1. Sande RD, Alexander JE, VanHoosier G: Vitamin D resistant rickets in the malamute (Abstr 207). Fed Proc 1970, 29:283
2. Fletch SM, Smart ME, Pennock PW, Subden RD: Clinical and pathological features of chondrodysplasia (dwarfism) in the Alaskan malamute. J Am Vet Med Assoc 1973, 162:257-361
3. Padgett GA, Alexander JE, Sande RD: Dwarfism: An inherited metabolic defect in malamutes. AMCA Newsletter, November 1969
4. Pearson D: The master plan for control and elimination of the condition known as "dwarfism" in the Alaskan malamute. AMCA Newsletter, November 1971
5. Subden RE, Fletch SM, Smart ME, Brown RG: Genetics of the Alaskan malamute chondrodysplasia syndrome. J Hered 1972, 63:149-152
6. Fletch SM, Pinkerton PH: An inherited anaemia associated with hereditary chondrodysplasia in the Alaskan malamute. Canad Vet J 1972, 13:270-271
7. Fletch SM, Pinkerton PH: Inherited erythrocytic macrocytosis in the purebred Alaskan malamute. (Abstr) Bull Am Soc Vet Clin Pathol 1972, 1:18
8. Fletch SM, Brueckner PJ, Pinkerton PH: Hereditary Hemolytic anemia and chondrodysplasia in the dog (Abstr 3398). Fed Proc 1973, 32:821
9. Fletch SM, Pinkerton PH: Animal model: Inherited hemolytic anemia with stomatocytosis in the Alaskan malamute dog. Am J Pathol 1973, 71:447-480
10. Pinkerton PH, Fletch SM, Brueckner PH, Miller DR: Hereditary stomatocytosis with hemolytic anemia in the dog. Blood 1974, 44:557-567
11. Sande RD, Alexander JE, Padgett GA: Dwarfism in

the Alaskan malamute: Its radiographic pathogenesis. J Am Vet Rad Soc 1974, 15:10–17
12. Smart ME, Fletch SM: A hereditary skeletal growth defect in purebred Alaskan malamutes. Canad Vet J 1971, 12:31–32
13. Frost HM: Preparation of thin undecalcified bone sections by rapid manual method. Stain Technol 1958, 33: 273–277
14. Villaneuva AR: An improved stain for fresh, mineralized bone sections: Useful in diagnosis of certain metabolic diseases of the bone. Am J Clin Path 1967, 47:78–84
15. Russell KH Jr: A modification of Movat's pentachrome stain. Arch Pathol 1972, 94:187–191
16. Mollenhauer HH: Plastic embedding mixtures for use in electron microscopy. Stain Technol 1964, 39:111–114
17. Laird CW: Representative values for animal and veterinary populations and their clinical significances. Hycel, Inc., Houston, Texas, 1972
18. Cooper RR, Pedrini-Mille A, Ponseti IV: Metaphyseal dysostosis: A rough surfaced endoplasmic reticulum storage defect. Lab Invest 1973, 28:119–125
19. Cooper RR, Ponseti IV: Metaphyseal dysostosis: Description of an ultrastructural defect in the epiphyseal plate chondrocytes. J Bone Joint Surg 1973, 55-A: 485–495
20. Cooper RR, Ponseti IV, Maynard JA: Pseudoachondroplastic dwarfism: A rough-surfaced endoplasmic reticulum storage disorder. J Bone Joint Surg 1973, 55-A:475–484
21. Maynard JA, Cooper RR, Ponseti IV: A unique rough surfaced endoplasmic reticulum inclusion in pseudoachondroplasia. Lab Invest 1972, 26:40–44
22. Phillips SJ: A rough endoplasmic reticulum storage disease in chondrocytes. Anat Rec 1970, 166:363
23. Bingel SA, Sande RD, Newbrey JW: Dwarfism in the Alaskan malamute: Ultrastructural features of developing growth plate chondrocytes. Calcif Tissue Int (In press)
24. Stickler GB, Maher FT, Hunt JC, Burck EC, Rosevear JW: Familial bone disease resembling rickets (hereditary metaphyseal dysostosis). Pediatrics 1962, 29:996–1004
25. Miller M, Paul W: Roentgen observations in familial metaphyseal dysostosis. Radiology 1964, 83:665–673
26. Dent CE, Normand ICS: Metaphyseal dysostosis, type Schmid. Arch Dis Child 1964, 39:444–454
27. Stelling FH: General affections of the skeletal system: Bone dysplasias, dystrophies, and dysostoses. Ped Clin North Am 1967, 14:359–396
28. Maroteaux P, Savart P, Lefebvre J, Royer P: Les formes partielles de la dysostose metaphysaire. Presse Med 1963, 71:1523–1526
29. Daeschner DW, Singleton EB, Hill LL, Dodge WF: Metaphyseal dysostosis. J Pediatr 1960, 47:844–854
30. Evans R, Caffey J: Metaphyseal dysostosis resembling vitamin D-refractory rickets. AMA J Dis Child 1958, 95:640–648
31. Lenk R: Hereditary metaphyseal dysostosis. Am J Roentgenol 1956, 76:569–575
32. Ruppercht E, Hinkel GK: Beitrag zum metaphysär dysostotischen Minderwuchs. Z Kinderheilkd 1968, 103:73–80
33. Schimd F: Beitrag zur dysostosis enchondralis Metaphysaria. Monatsschr Kinderheilkd 1949, 97:383–397
34. Spahr A, Spahr-Hartmann I: Dysostose metaphysaire familiale: Etude de 4 cas dans une fratrie. Helv Paediatr Acta 1961, 16:836–849
35. Taybi H, Mitchell AD, Friedman GD: Metaphyseal dysostosis and the associated syndrome of pancreatic insufficiency and blood disorder. Radiology 1969, 93: 563–571
36. Rubin P: Dynamic Classification of Bone Dysplasias. Chicago, Year Book Publishers, Inc., 1964
37. Kozlowski K, Zychowicz C: Metaphyseal dysostosis of mixed type in the female child. Am J Roentgenol 1962, 88:443–449
38. Goor M, Sauvage D, Toursel F, Farriaux JP, Fontaine G: Contribution a l'étude de la dysostose metaphysaire. Rev Pediatr 1970, 6:531–542
39. European Society of Pediatric Radiology: Nomenclature internationale des maladies osseuses constitutionnelles. Ann Radiol 1970, 13:455–464
40. Gardner DL: Familial canine chondrodystrophia foetalis (achondroplasia). J Pathol Bacteriol 1959, 77:243–247
41. Fairbank HAT: Dyschodroplasia. J Bone Joint Surg 1948, 30-B:689–708