# X-Chromosomal Monosomy (77,X0) in a Doberman Pinscher With Gonadal Dysgenesis

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**A 6-month-old stunted female Doberman Pinscher was found to have a 77,X0 chromosomal complement. The ovaries were small, consisting primarily of interstitial-type cells and solid epithelial cords. The dam, sire, and a male littermate had normal karyotypes. (Journal of Veterinary Internal Medicine 1989; 3:90–95)**

MONOSOMY X (X0) is a condition occurring in a conceptus following the union of egg and sperm, wherein one sex chromosome per cell is missing. It is usually due to a failure of either the male or female (spermatocyte or oocyte) chromosomes of a mating pair to separate at anaphase during meiosis. This results in the production of a phenotypic female with an X0 genotype.[1]

Cases of X0 genotype have been reported in the human, Rhesus monkey, horse, sheep, pig, tammar wallaby, lesser bandicoot, Malayan black rat, mouse, and cat.[2–14] Among Canidae, this condition has been reported only in the Silver Fox.[15] Abnormalities observed in the various species vary considerably, and include those of the soma, and cardiovascular, urinary, and reproductive systems. Involvement of the genital tract is typically in the nature of small, afollicular ovaries, and hypoplastic uterine tubes, uterus, and vagina.

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In the bitch, the normal diploid chromosomal number is 76 autosomes plus two sex chromosomes (i.e., 78,XX). Only one of the two female (X) chromosomes is active in somatic cells and germ cells, except during oogenesis. The other X-chromosome becomes inactive and is recognized as sex chromatin (Barr body) in the nuclei of most somatic cells. In neutrophils, sex chromatin is recognized as a club-shaped nuclear appendage called a "drumstick."[1,16]

The present report describes a case of gonadal dysgenesis in a 77,X0 dog, the first for this species.

## Case Report

### *History*

A 6-month-old female Doberman Pinscher weighing 16.4 kg was presented for ovariohysterectomy. A male littermate weighed 30 kg. Intermittent dysuria, poor weight gain, increased respiratory sounds that had improved with chloramphenicol administration, and chronic intermittent diarrhea were historic problems. Thoracic radiographs, which were obtained when the respiratory signs developed at 4 months of age, showed pleural fissure lines and increased peribronchial markings. Appetite and activity levels were normal. The dog was coprophagic, and had eaten linoleum. Vaccinations were current. The dog had never shown signs of estrus.

### *Physical Examination*

The dog was of small stature, and was alert and responsive. Vital signs were normal. Physical abnormalities included increased bronchovesicular sounds noted on inspiration, thickened bowel loops, excessive skin in the ventrum of the neck,

mucopurulent vaginal discharge, and an enlarged friable clitoris that protruded approximately 2 cm beyond the vulva. A semisoft stool was observed on rectal examination. There were no parasite eggs observed on a direct smear. There was one supernumerary nail located just dorsal to the normal nail on each pelvic limb digit.

### *Diagnostic Tests and Procedures*

Hematologic and biochemical abnormalities included leukocytosis ($18.5 \times 10^3/\mu l$; normal, 6 to $17 \times 10^3/\mu l$), neutrophilia ($12.8 \times 10^3/\mu l$; normal, 3 to $11.5 \times 10^3/\mu l$), monocytosis ($1.7 \times 10^3/\mu l$; normal, 0.1 to $1.4 \times 10^3/\mu l$), hyperglycemia (114 mg/dl; normal, 63 to 105 mg/dl), hypercalcemia (13.3 mg/dl; normal, 5 to 12.9 mg/dl), and hyperphosphatemia (8.7 mg/dl; normal, 4.3 to 7.6 mg/dl). These changes were considered stress or age related. The urine was concentrated (specific gravity, 1.046); the urinalysis results were unremarkable. An electrocardiogram was normal.

A pediatric vaginoscope could not be passed beyond the vestibule, suggesting agenesis or stricture of the vagina. Contrast vaginography identified an os clitoris, but failed to demonstrate a vagina.

At surgery, small ovaries ($0.5 \times 0.4 \times 0.5$ cm in size) were attached to the kidneys by connective tissue. There was one grossly normal uterine horn (4 mm in diameter) and a remnant left uterine horn. The os clitoris was excised in hope of resolving dysuria that might have been the result of distortion irritation of the vulva. The supernumerary nails were removed. Excessive intraoperative bleeding prompted evaluation for Von Willebrand's disease. Factor VIII-related antigen was less than 7% of the normal value. Blood was submitted for karyotyping, but was damaged during shipping. The dog was treated with ampicillin (20 mg/kg three times daily) for 10 days to prevent postoperative infection. Dysuria resolved postoperatively.

Histologically, the ovaries contained a well-vascularized cortex and medulla. The ovarian surface contained a mixed simple squamous to cuboidal epithelium, with frequent short epithelial cord and tubular invaginations typical of the dog ovary.[17] Numerous long epithelial cords extended through the cortex into the medulla (Fig. 1A). A small aggregate of cuboidal cell-lined cavities resembling rete ovarii were present in the medulla. One of these was continuous with what appeared to be a medullary cord (Fig. 1B). No ovarian follicles or remnants of follicles or corpora lutea were observed. Ovarian interstitial cell masses were noted (Fig. 1C). Histologic studies made of ovaries from three approximately 6-month-old dogs (Doberman Pinscher × Collie; Husky; and Schnauzer) showed many primordial and larger follicles (Figs. 2A and 2B) and occasional degenerate tertiary (Graafian) follicles (Fig. 2C). Minimal uterine glandular development (Fig. 1D), similar to that observed previously in an X0 cat, was found in the normal-appearing uterine horn.[14]

Serum collected before ovarihysterectomy was submitted for testosterone, estradiol, progesterone, luteinizing hormone (LH), and thyroxine ($T_4$) determinations. The testosterone concentration was elevated at 1.02 ng/ml (normal, <0.4 ng/ml). The estradiol concentration was 47.80 pg/ml, the progesterone concentration was 0.28 ng/ml, and the LH concentration was 2.5 ng/ml. The $T_4$ concentration was elevated at 3.52 μg/dl (normal, 1.5 to 3.0 μg/dl).

The dog was presented 2 months later for an intestinal obstruction, which was related to ingestion of parts of a couch. This obstruction was corrected through multiple enterotomies, without excessive bleeding. A repeated Von Willebrand's test showed 23% of normal levels of Factor VIII-related antigen.

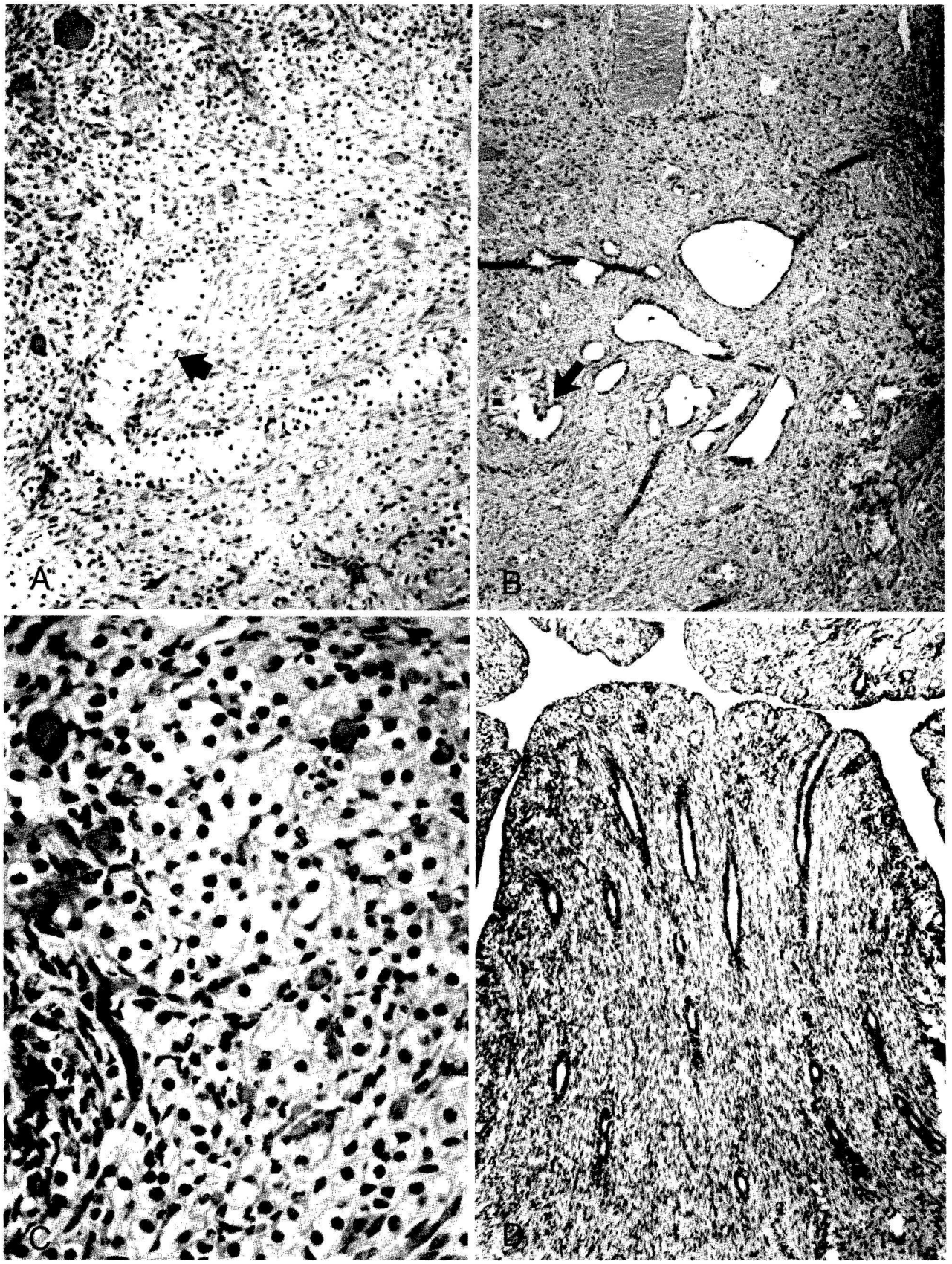
Heparinized blood and a skin biopsy specimen were collected for cytogenetic and neutrophil drumstick evaluations using techniques described previously.[18] A karyotype of 77,X0 (monosomy-X) was found in both the blood and skin (Fig. 3), while the dam, sire, and male littermate had normal karyotypes. A normal bitch should have a 78,XX karyotype with approximately 4% drumsticks.[16] Neutrophil drumsticks (inactivated X-chromosome) were not observed in the dog.

## Discussion

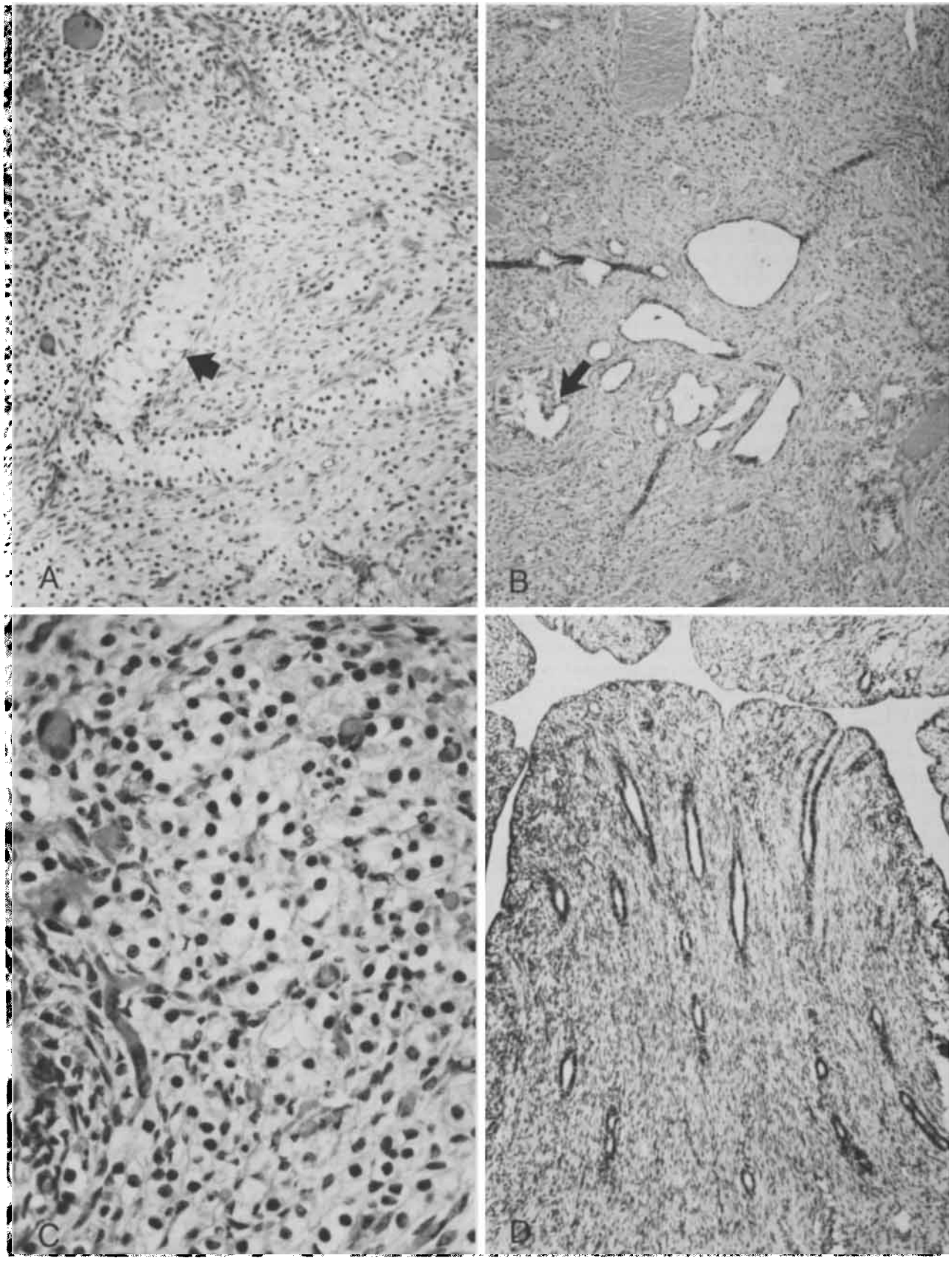
Many of the morphologic abnormalities in this dog can be attributed to the X0 genotype. Small stature and hypoplasia of the genital system is commonly reported in animals of other species with monosomy-X. Metabolic causes for stunted growth were not supported by our laboratory test results. Webbing of the neck also is commonly observed in women with the X0 chromosome complement.[19] Supernumerary nails have not been reported in other cases of monosomy-X. However, women with an X0 chromosome complement may have hypoplastic nails, and 50% have short fourth metacarpals.[19] The presence of an os clitoris has not been described previously with this condition and would suggest elevated testosterone concentrations during development. This is supported by the increased serum testosterone values observed. The source of testosterone is not apparent.

The dysuria was believed to be due to the enlarged clitoris, causing distortion and irritation of the vulva. The dysuria resolved following partial amputation of the clitoris and removal of the os clitoris. Von Willebrand's disease, a condition common in the Doberman Pinscher,[20] probably accounted for the excessive bleeding during the first surgical procedure. The increase in the percentage of Factor VIII-related antigen on the second test may reflect either laboratory variation, a true age-related increase,[20] or patient variability.

The elevated $T_4$ concentration in this dog is probably a normal variant. The estradiol concentration suggested proestrus. This was not supported by histopathologic evaluation of the ovaries. The dog was not exhibiting proestrus behavior and there was no genital tract bleeding. Cytologic evaluation of a smear from the vestibule revealed no abnormalities. Possible causes for these near-normal findings would include ectopic functional gonadal tissue, unobserved follicles in either ovary, or laboratory error. The progesterone concentration was compatible with anestrus, proestrus, or estrus. The LH concentration could reflect normal endogenous pulsatile activity in an anestrus bitch, or a high baseline level due to gonadal insufficiency.




FIGS. 1A–1D. (A) Ovarian cortex of a Doberman Pinscher with X-chromosomal monosomy, showing solid epithelial cords (H & E, ×150). (B) Ovarian medulla of a Doberman Pinscher with X-chromosomal monosomy. Arrow shows continuity between apparent medullary cord and rete ovarii structures (H & E, ×100). (C) Ovarian cortex of a Doberman Pinscher with X-chromosomal monosomy, showing ovarian interstitial cell masses (H & E, ×350). (D) Endometrium of a Doberman Pinscher with X-chromosomal monosomy. Note low uterine surface epithelium and minimal uterine glandular development (H & E, ×150).

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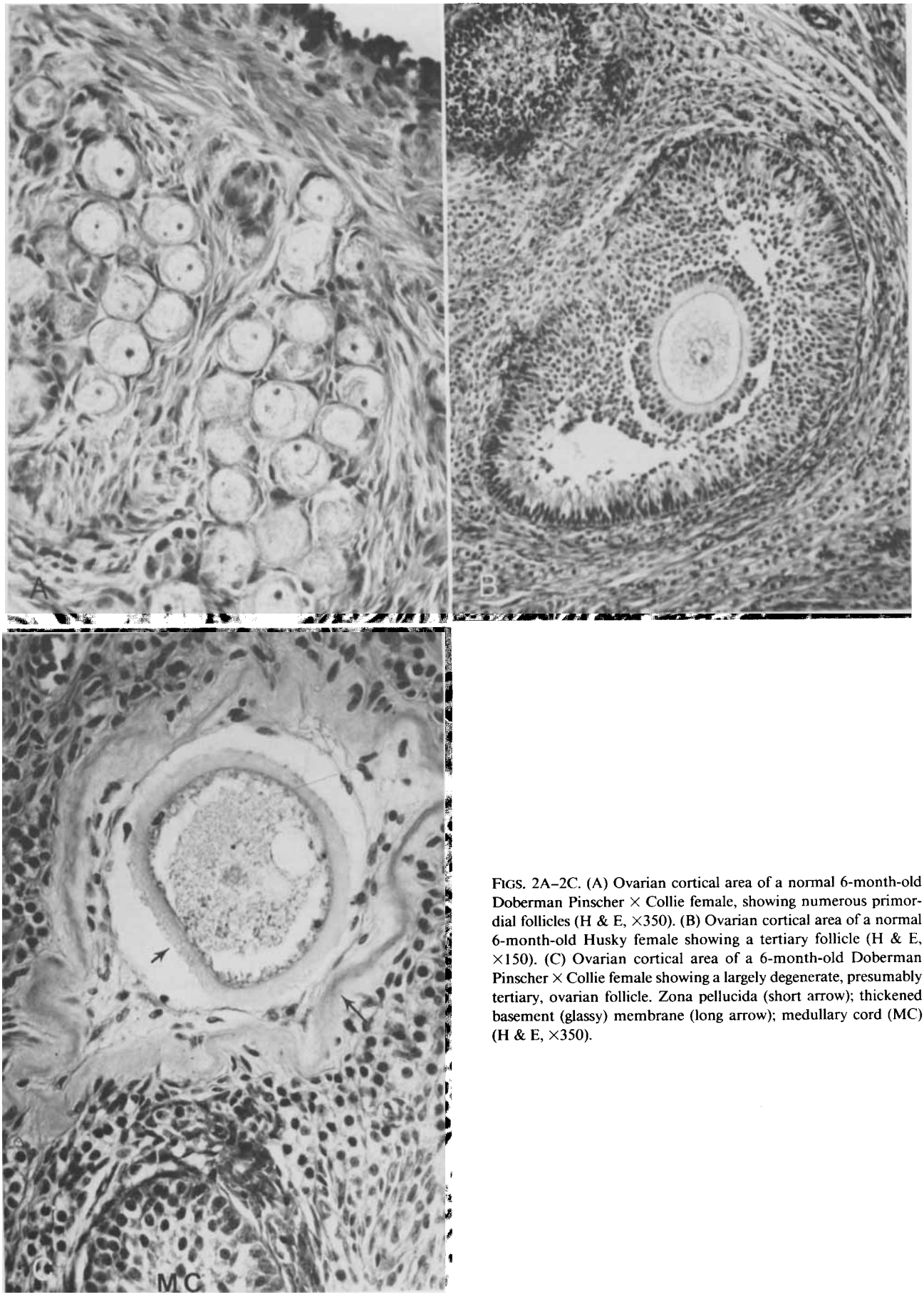
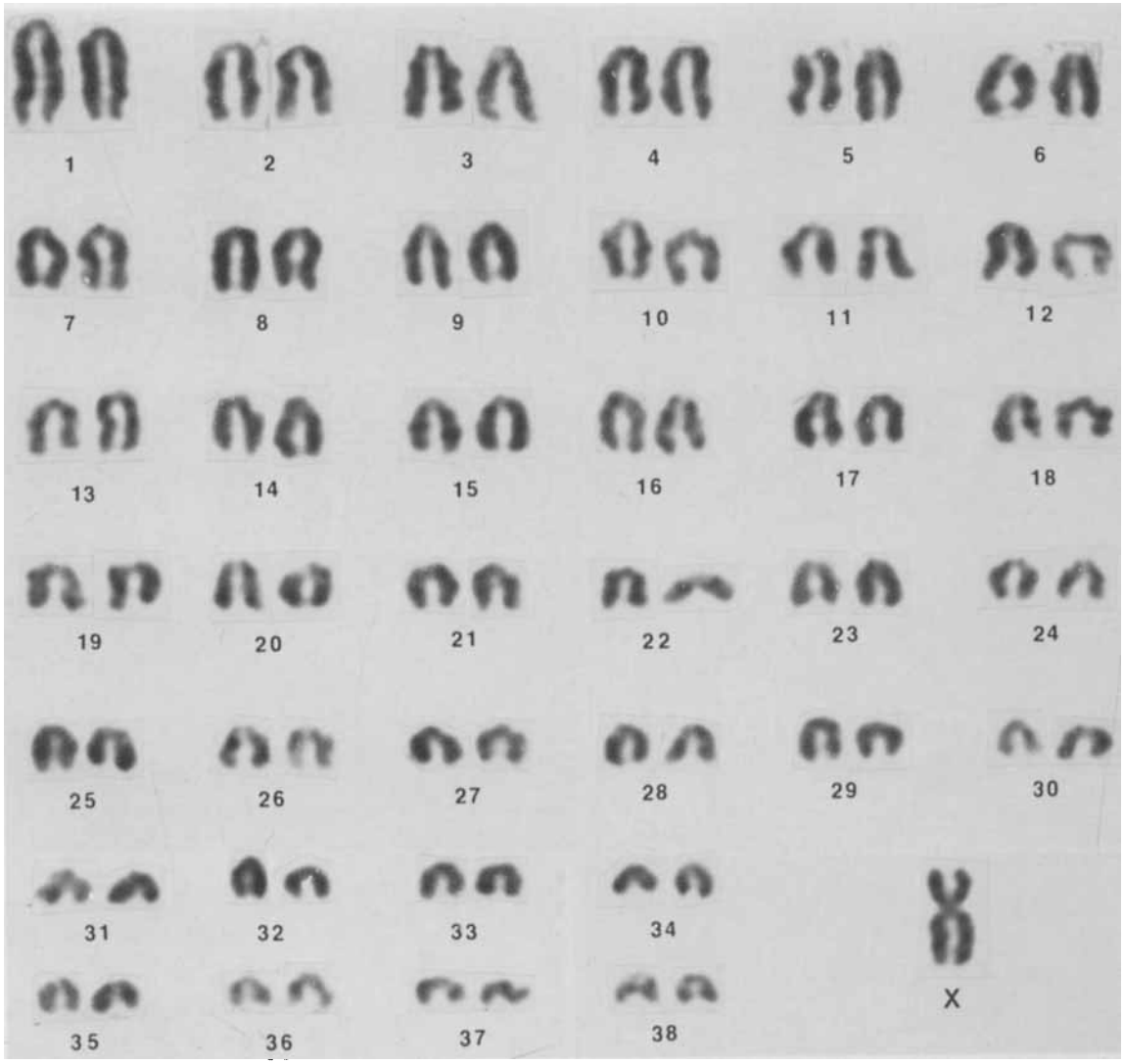



FIGS. 2A–2C. (A) Ovarian cortical area of a normal 6-month-old Doberman Pinscher × Collie female, showing numerous primordial follicles (H & E, ×350). (B) Ovarian cortical area of a normal 6-month-old Husky female showing a tertiary follicle (H & E, ×150). (C) Ovarian cortical area of a 6-month-old Doberman Pinscher × Collie female showing a largely degenerate, presumably tertiary, ovarian follicle. Zona pellucida (short arrow); thickened basement (glassy) membrane (long arrow); medullary cord (MC) (H & E, ×350).



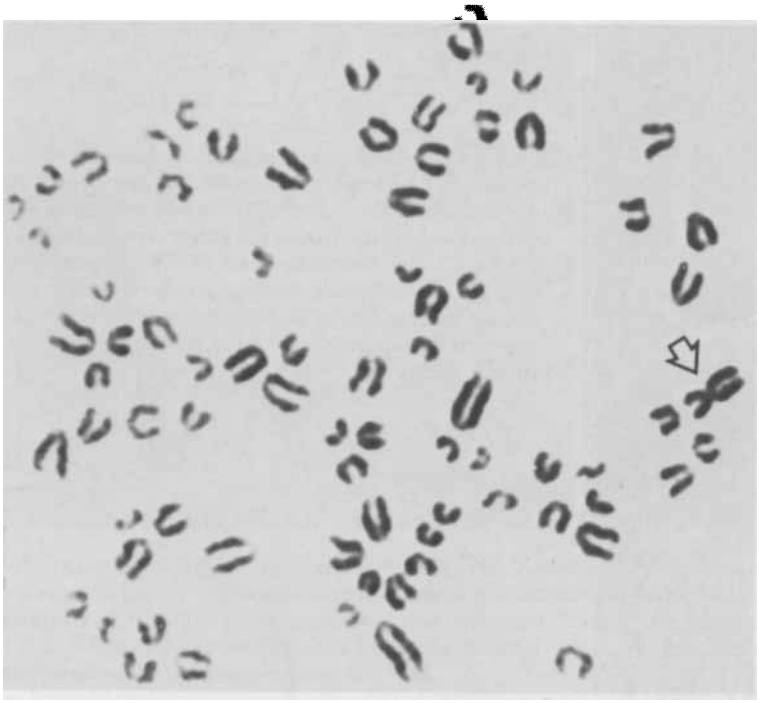



FIG. 3. Karyotype (above) and chromosome spread (below) of a Doberman Pinscher with X-chromosomal monosomy (77,X0). Arrow in chromosome spread shows X-chromosome (Giemsa stain).

A point of interest in this report of monosomy-X (77,X0) in a 6-month-old dog is whether or not follicular development occurred postnatally. The presence of afollicular cortical epithelial cords and surface epithelial invaginations along with medullary cord and rete-like structures suggests that ovarian follicular development may not have continued normally (Figs. 2A–2C), but instead, early postnatal dysgenesis ensued.

One of the initial explanations for the pathogenesis of gonadal dysgenesis was that low X-gene dosage has a deleterious effect on oocytes. Therefore, follicular formation occurs early, but follicular atresia develops gradually postnatally.[21] Consequently, X0 rodents with a shorter reproductive span would be fertile initially, while in larger species, such as humans, sterility would occur long before puberty.[22] However, the reports of occasional fertile X0-women and sterility in the X0-cat contradict this theory.[14,23] Miklos originally,[24] and Burgoyne and Baker,[25] and Speed[26] more recently, suggested that meiotic cells are selectively spared by some mechanism when homologous chromosomes are acrocentric in type. This is explained on the basis that in such a chromosome, nonhomologous ("fold-back") pairing of sister chromatids onto themselves may occur resulting in the X-chromosome forming a "hairpin" configuration. Thus, X0-oocytes from species with acrocentric X-chromosomes (e.g., mouse) would be spared. In the human, horse, dog, fox, and cat, which have metacentric X-chromosomes, fold-back pairing would be less able to occur. Thus, oocyte atresia would occur earlier in these species. If atresia occurred sufficiently early in the case reported here, evidence of a prior existence of follicular structures, as observed in normal development (Fig. 2C), would be lost. The epithelial aggregates of the second proliferation, which would form the definitive follicles, would remain as afollicular cords rather than subdividing into follicles. The presence of such afollicular cords, plus large aggregates of interstitial cells of the ovary, is what characterized the ovarian sections of the Doberman Pinscher in this report.

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