Feline Hypertrophic Cardiomyopathy

Gross Anatomic and Quantitative Histologic Features

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Gross anatomic features and the pattern and extent of cardiac muscle cell disorganization were studied in the hearts of 51 cats with spontaneously occurring hypertrophic cardiomyopathy. Each cat had a hypertrophied, but nondilated, left ventricle. Ventricular septal disorganization was extensive, involving 5% or more of the relevant areas of the tissue section, in 14 (27%) of the 51 cats. Marked septal disorganization occurred only in those cats with asymmetric septal hypertrophy (ventricular septal to left ventricular free wall thickness ratio of ≥1.1). Disorganization of cardiac muscle cells was uncommon and less extensive in the left ventricular free wall of the cats with hypertrophic cardiomyopathy. Disorganization involved the free wall of only 7 cats, each with asymmetric septal hypertrophy, and occupied >5% of the free wall tissue sections in just 3. Hence, about one fourth of this population of cats had hypertrophic cardiomyopathy resembling the human form of this disease, with asymmetric left ventricular hypertrophy and marked disorganization of cardiac muscle cells in the ventricular septum. The majority of cats (about 75%), however, demonstrated a form of hypertrophic cardiomyopathy characterized by symmetric ventricular hypertrophy and normal arrangement of cardiac muscle cells. (Am J Pathol, 1981, 102:388–395)

SINCE THE INITIAL PATHOLOGIC REPORT of primary myocardial disease in the cat was published in 1970,[1,2] certain clinical, hemodynamic, angiographic, and pathologic characteristics of feline hypertrophic cardiomyopathy have been defined.[3-10]

Disorganization of cardiac muscle cells in the ventricular septum, a characteristic finding in human patients with hypertrophic cardiomyopathy,[11-20] has been described in cats with this disease.[8-10] However, the prevalence and extent to which this histologic abnormality occurs in the left ventricular wall of a population of cats with hypertrophic cardiomyopathy, and its relation to asymmetric hypertrophy of the ventricular septum, has not been defined. Therefore, it is the purpose of this report to characterize the gross anatomic and quantitative histologic features of these abnormalities in cats with hypertrophic cardiomyopathy.

Materials and Methods

Selection of Cases

The cardiovascular registry of the Pathology Department of the Animal Medical Center from 1975 to 1977 was reviewed. During that period, 243 cats with cardiac disease were examined at necropsy; 51 of these cats were identified as having hypertrophic cardiomyopathy. This diagnosis was based on the presence of a hypertrophied (ie, heart weight increased above normal), nondilated left ventricle in a cat with no other cardiac abnormality capable of producing left ventricular hypertrophy.[21] Sixty-five cats with normal hearts or other cardiac diseases were selected for study as control animals (Table 1).

Measurement of Ventricular Wall Thickness

Measurements of ventricular wall thickness were made in fixed specimens in the following two areas: 1) the ventricular septum, at the point of maximum thickness, usually about one-half the distance between

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the base of the aortic valve and the apex of the left ventricle; and 2) the posterior left ventricular free wall, behind the caudal margin of the posterior mitral leaflet. In making measurements of ventricular wall thickness, we took care to avoid including trabeculas, papillary muscles, or crista supraventricularis.

Preparation of Tissue

In each of the 116 cats studied (51 with hypertrophic cardiomyopathy and 65 control animals), full wall thickness blocks were taken perpendicular to the long axis of the left ventricle[19] from: 1) the ventricular septum at the point of maximal thickness; 2) the posterior left ventricular wall about one-half the distance between the mitral valve anulus and left ventricular apex; and 3) the left ventricular wall about 1 cm lateral to the left anterior descending coronary artery (Figure 1). All tissue sections were embedded in paraffin, sectioned at a thickness of 6 μ, and stained with hematoxylin and eosin (H & E).

Definition and Classification of Cardiac Muscle Cell Disorganization

Cardiac muscle cell disorganization observed in the cats in this study was classified into four types as previously described in human patients with hypertrophic cardiomyopathy.[19]

Type I-A disorganization consisted of areas of myocardium in which adjacent cardiac muscle cells were aligned perpendicularly or obliquely to each other, usually forming tangled masses of "pinwheel" configurations (Figure 2). Type I-B disorganization consisted of broad bundles of muscle cells arranged at oblique or perpendicular angles to each other (Figure 3). Cells within these bundles showed normal arrangement. This type of disorganization gave the myocardium a "windmill" appearance. Both Types I-A and I-B primarily involved areas of ventricular septum in which the cardiac muscle cells were cut longitudinally, ie, appeared to be rectangularly shaped.

Type II-A disorganization consisted of relatively narrow (usually one or two cells wide), longitudinally cut bundles of cells that were interlaced in various directions among larger groups of transversely cut cells (Figure 4). This type of disorganization gave the myocardium a "swirled" appearance. Type II-B was similar to Type II-A disorganization, except that the narrow, longitudinally cut bundles of cells were more linear. The two forms of Type II disorganization involved both longitudinally and transversely cut cardiac muscle cells.

Nonparallel arrangements of cardiac muscle cells were not considered to represent true disorganization if present at the junction of the ventricular septum with the left or right ventricular free wall, within trabeculations, within or adjacent to areas of fibrosis, surrounding blood vessels, or at points of convergence of major muscle bundles.

Quantitation of Cardiac Muscle Cell Arrangement

A technique previously described in detail[19] was used to quantitatively assess the extent of cardiac muscle cell disorganization in tissue sections of ventricular septum and left ventricular free wall. In brief, tissue sections in which cardiac muscle cell disorganization was judged to be present qualitatively were photographed, and the images enlarged into 30 × 40-inch

Table 1—Cardiac Diseases in 65 Control Cats

Disease	Number of cats studied	Number of cats with septal disorganization
Dilated (congestive) cardiomyopathy[9]	16	0
Ventricular septal defect	5	0
Supravalvular aortic stenosis	2	0
Congenital malformation of mitral valve complex[9]	3	0
Congenital dysplasia of tricuspid valve[9]	3	0
Normal	36	3
TOTAL	65	3 (4%)

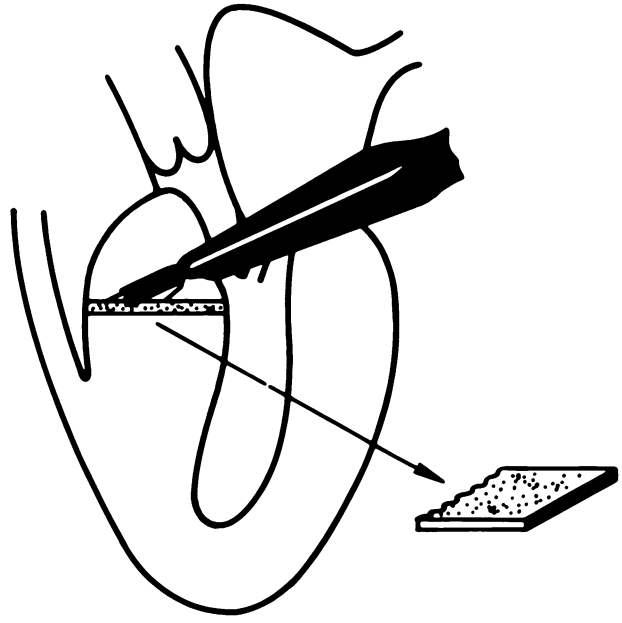

Figure 1—Transverse section of ventricular septum obtained in a plane perpendicular to the long axis of the left ventricle.

positive prints, resulting in an average magnification of about 2000 times the original tissue section. A transparent cellulose overlay was then placed over the print, and the areas of myocardium occupied by disorganized cardiac muscle cells were outlined with a marking pen on the transparent overlay (Figure 5). Although it was often possible for us to make the assessment from direct examination of the print, we frequently found it necessary to reexamine the original tissue section with a light microscope to localize the disorganized area. Areas in which cardiac muscle cells were cut either longitudinally or transversely were also demarcated. Large areas of fibrosis, artifacts of tissue preparation, or large interstitial spaces with blood vessels were identified and excluded from the analysis. The transparent overlay was removed from the print and photographed and the image reproduced as a 5 × 7-inch print. Each area into which the tissue section had been divided was outlined separately with a fine-point marking pen on ordinary tablet paper and quantitated by the use of a video planimetry system.

The percentage of the tissue section occupied by disorganized cardiac muscle cells was calculated by the use of methods previously described.[19] Values for Types I and II disorganization could not be combined in cats that had both types, because this calculation often resulted in a marked underestimation of the overall extent of disorganization in a tissue section. Hence, the percentage of disorganization plotted for each cat was the value for Type I or Type II, whichever value was greater. For the purposes of certain analyses, quantitative data of cellular arrangement in the anterior and posterior left ventricular free wall sections were combined and the sum expressed as representing the "left ventricular free wall."

Statistical Analysis

Where appropriate, the Student *t* test was employed to assess statistical significance.

Results

Clinical Findings

The 51 cats with hypertrophic cardiomyopathy ranged in age from 6 months to 16 years (mean, 7

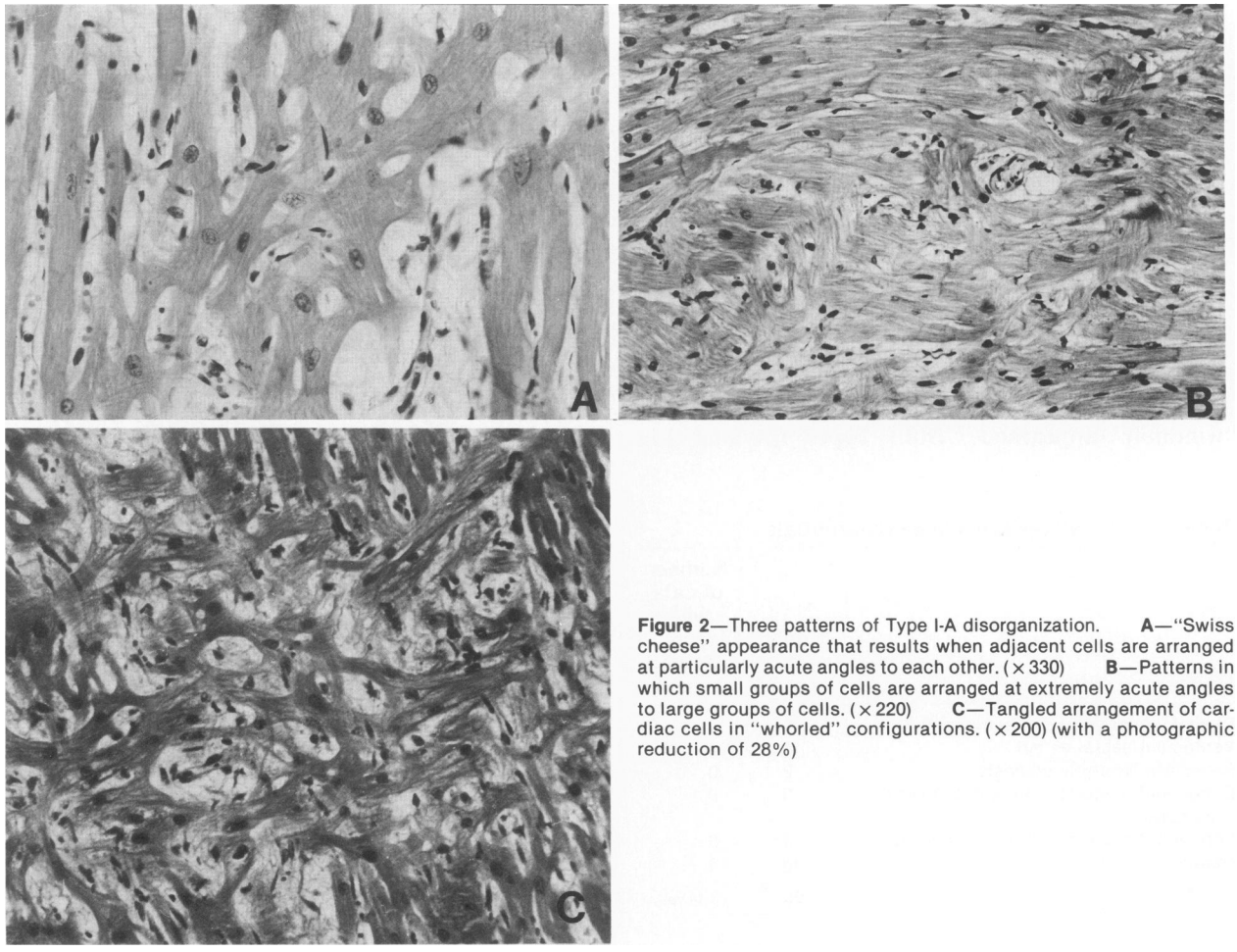

Figure 2—Three patterns of Type I-A disorganization. **A**—"Swiss cheese" appearance that results when adjacent cells are arranged at particularly acute angles to each other. (× 330) **B**—Patterns in which small groups of cells are arranged at extremely acute angles to large groups of cells. (× 220) **C**—Tangled arrangement of cardiac cells in "whorled" configurations. (× 200) (with a photographic reduction of 28%)

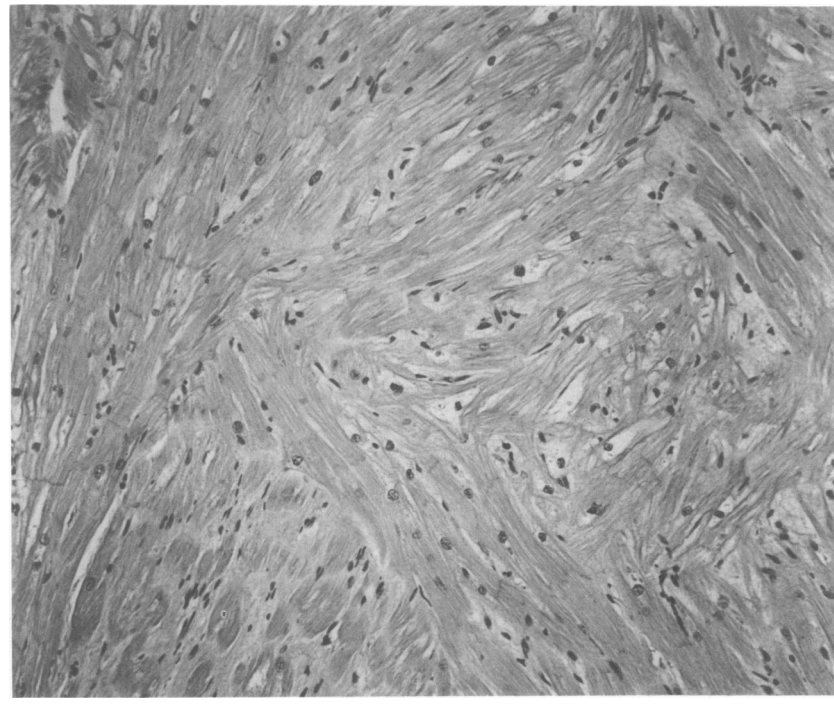

Figure 3—Type I-B disorganization. Broad bundles of muscle cells are arranged at oblique or perpendicular angles to each other. (×130)

years); 39 were male and 12 were female. Cardiac failure was manifested by 22 (43%) of the cats, and aortic thromboembolism[2-8] was present in 21 (41%) of the animals. Eight (15%) cats died suddenly, although each had manifested heart failure previously. The remaining 43 cats were euthanatized, 36 because of intractable heart failure and 7 for reasons not related to cardiac disease, such as pneumonia, anemia, osteosarcoma, urinary tract calculi, or traumatic injury.

Gross Anatomic Findings

Heart weights in the 51 cats with hypertrophic cardiomyopathy (6.4 ± 0.1 SEM g/kg were significantly greater than in 36 cats without cardiac disease (4.8 ± 0.1 mg/kg; $P < 0.001$) but did not differ from the 29 cats with heart diseases other than hypertrophic cardiomyopathy (6.1 ± .3 g/kg). Ventricular septal thicknesses in the 51 cats with hypertrophic cardiomyopathy ranged from 7 to 12 mm (mean, 8 mm); posterior

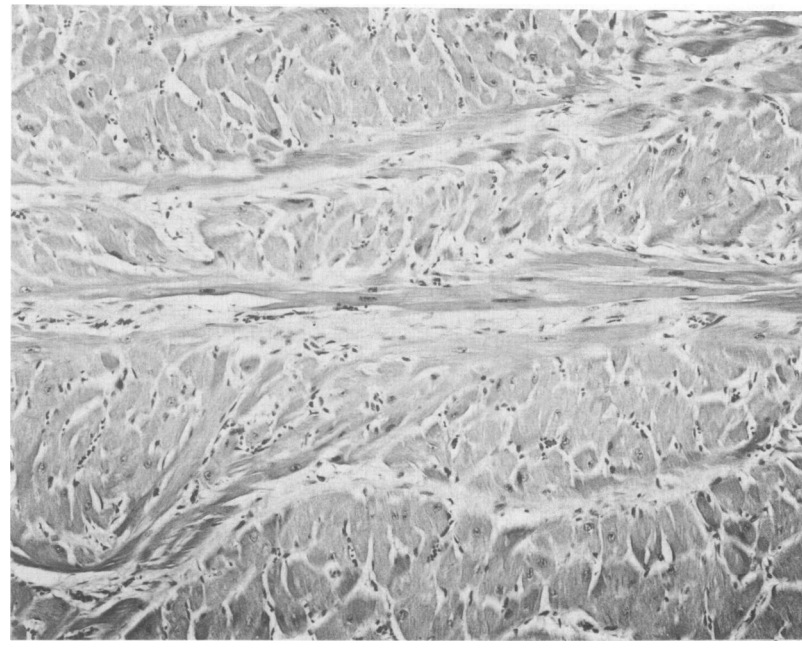

Figure 4—Type II-B disorganization. Relatively narrow longitudinally cut bundles of cells are interlaced among larger groups of transversely cut cells. (×130)

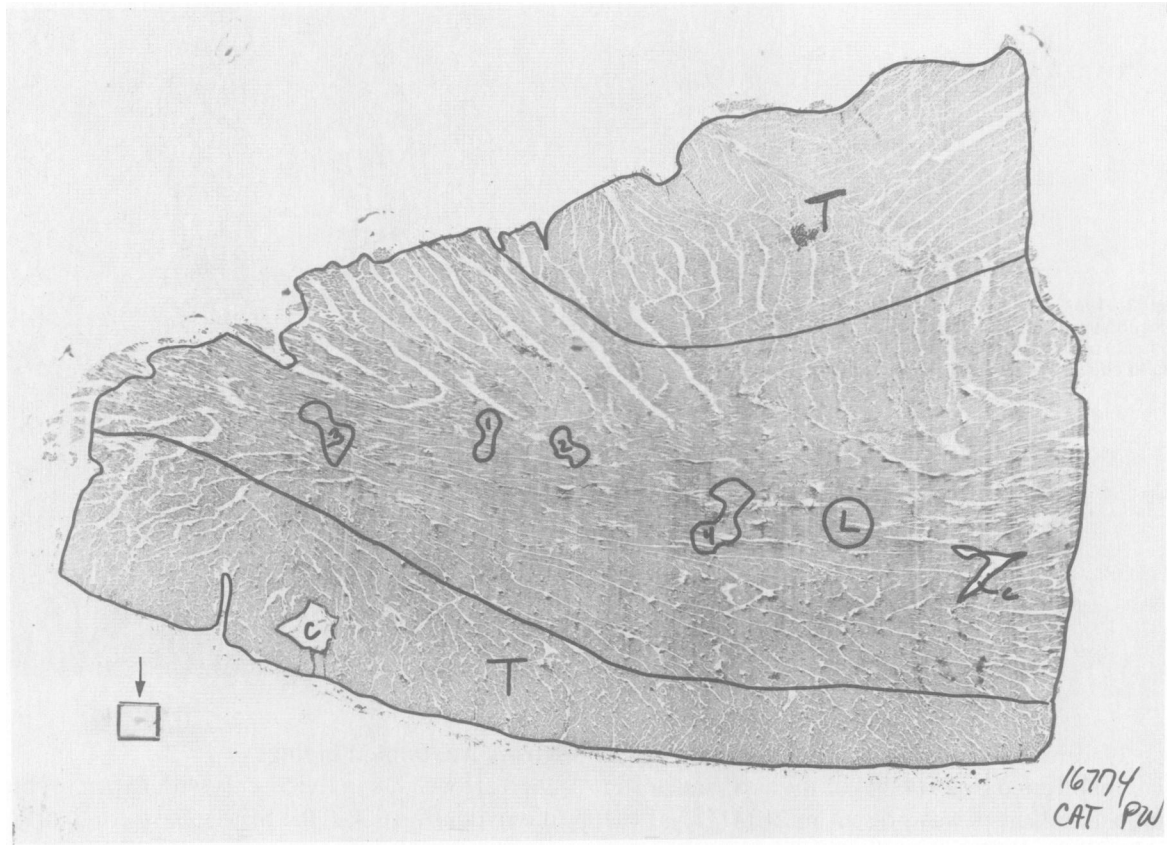

Figure 5—Photographic enlargement of a tissue section with the transparent overlay in place. Areas of myocardium containing disorganized cardiac muscle cells or normally arranged cells cut longitudinally or transversely have been demarcated on the overlay. Section of posterior left ventricular free wall taken from a cat with hypertrophic cardiomyopathy (×2000). Actual size of the tissue section is shown in lower left (*arrow*) for comparison.

free wall thicknesses ranged from 6 to 11 mm (mean, 8 mm).

Ventricular septal to posterior left ventricular free wall thickness ratios were significantly greater in the 51 cats with hypertrophic cardiomyopathy (1.02 ± 0.02) than in the 65 control cats (0.85 ± .01; $P <$ 0.001) (Figure 6). Asymmetric septal hypertrophy (defined as a ventricular septal to free wall thickness ratio of ⩾ 1.1; range, 1.1.–1.6; mean, 1.3 ± 0.04) (Figure 7) was present in 16 (31%) of the 51 cats with hypertrophic cardiomyopathy (but only 3 [4%] of the 65 control cats). The mean septal to free wall ratio was 0.9 ± 0.1 (range, 0.8–1.0) in the cats with symmetric left ventricular hypertrophy.

Quantitative Histologic Findings

Disorganized cardiac muscle cells were present in the ventricular septum of 15 (30%) of the 51 cats with hypertrophic cardiomyopathy and absent in the remaining 36 cats. In 14 of these 15 cats the disorganization was marked (involving 5% or more of the relevant areas of the tissue section; range, 5.5–46.0%), including 7 cats in which >30% of the tissue section was involved. The remaining cat had septal disorganization involving 4.3% of the section. Septal disorganization was significantly more common in the cats with hypertrophic cardiomyopathy (15 of 51, or 30%) than in the controls (3 of 65, or 4%; $P<0.01$); similarly, the extent of septal disorganization in the cats with hypertrophic cardiomyopathy (mean percentage of section disorganized, 6.9 ± 1.8%) was significantly greater than in the controls (mean percentage, 0.3 ± 0.2%) (Figure 8).

Each of the 15 cats with septal disorganization had septal to free wall thickness ratios of ⩾1.1, although one other cat with an abnormal thickness ratio had no disorganization. Septal disorganization was absent in each of the remaining 35 cats with septal to free wall ratios of <1.1.

Type I disorganization, particularly I-A, was most commonly the predominant form of disorganization

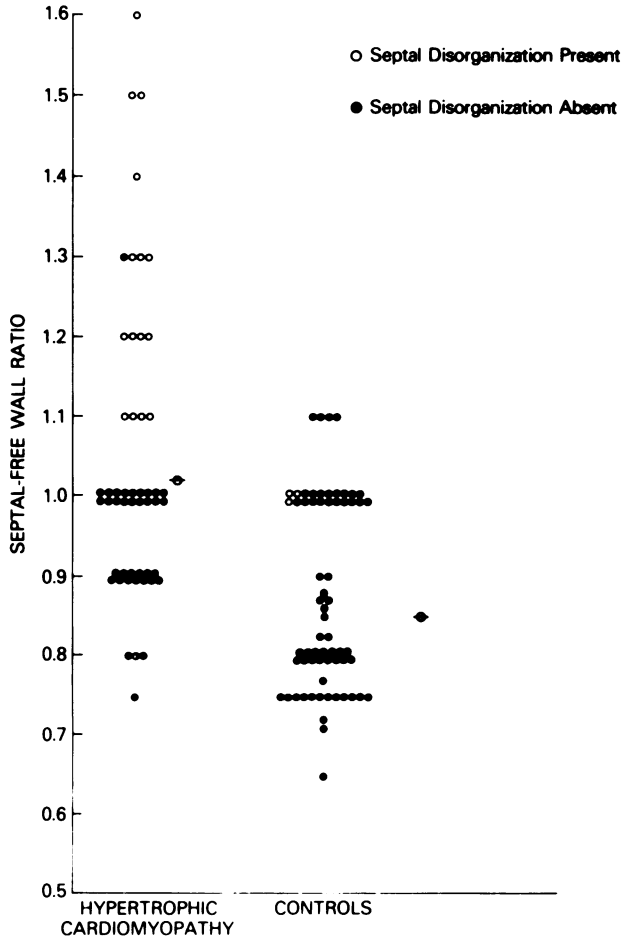

Figure 6—Ventricular septal-posterior left ventricular free wall ratios in 51 cats with hypertrophic cardiomyopathy and 65 control cats. Mean values are indicated by *short horizontal lines.*

observed, occurring in 14 of the 15 cats with hypertrophic cardiomyopathy and septal disorganization; Type II disorganization predominated in the other cat (Table 2).

Seven of the 15 cats with hypertrophic cardiomyopathy and septal disorganization also had abnormally arranged cardiac muscle cells in the left ventricular free wall. Each of these 7 cats had septal to free wall thickness ratios of ⩾1.1, and 4 had particularly marked ventricular septal thickening (10 to 12 mm). Free wall disorganization ranged from 0.5% to 19.7% and involved >5% of the tissue section in 4 of the 7 animals. In the 7 cats the extent of ventricular septal disorganization (mean, 21 ± 5.0%) was significantly greater than that present in the left ventricular free wall (mean, 7 ± 3.1%; $P < 0.05$) (Figure 9). Left ventricular free wall disorganization was absent in the other 8 cats with septal disorganization, the 36 cats with hypertrophic cardiomyopathy and no septal disorganization, and the 65 control cats.

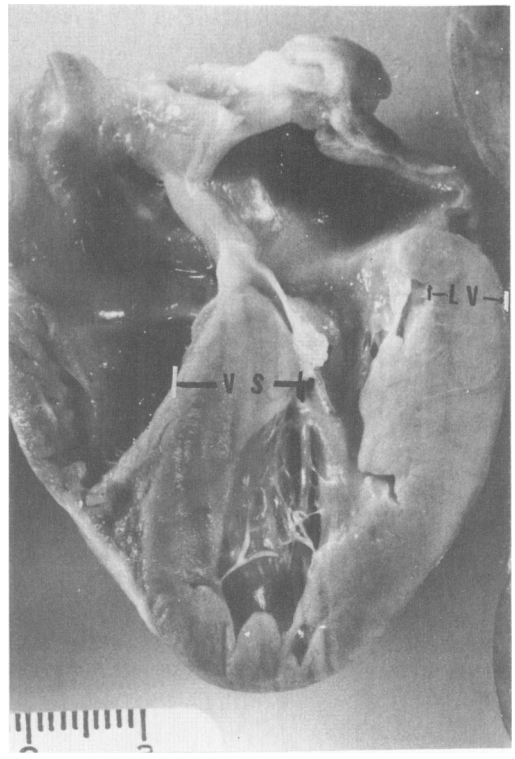

Figure 7—Heart from a 2½-year-old male domestic cat showing disproportionate thickening of the cephalad portion of the ventricular septum (*VS*) with respect to the left ventricular free wall (*LV*); septal to free wall thickness ratio is 1.3. At the point of maximum thickening, the septum bulges prominently into the left ventricular outflow tract.

Discussion

The findings of this gross anatomic and quantitative histologic study indicate that about one fourth of the cats with hypertrophic cardiomyopathy showed disorganization of cardiac muscle cells in the ventricular septum, similar in extent and appearance to the characteristic histologic hallmark in human patients with hypertrophic cardiomyopathy.[19,21] Of note, each of the 15 cats with marked septal disorganization also had asymmetric thickening of the ventricular septum with respect to the left ventricular free wall (defined as a septal to free wall thickness ratio of ⩾1.1 in cats. Hence, this study identified a subgroup of cats with hypertrophic cardiomyopathy that resembled morphologically the form of the disease that occurs in man, ie, with asymmetric ventricular hypertrophy and marked disorganization of cardiac muscle cells in the septum. However, the majority of cats studied (70%) showed a structural form of hypertrophic cardiomyopathy uncommonly observed in man, characterized by symmetric, concentric ventricular hypertrophy,[22] as well as normally arranged cardiac muscle cells in the septum. It is not clear from available information

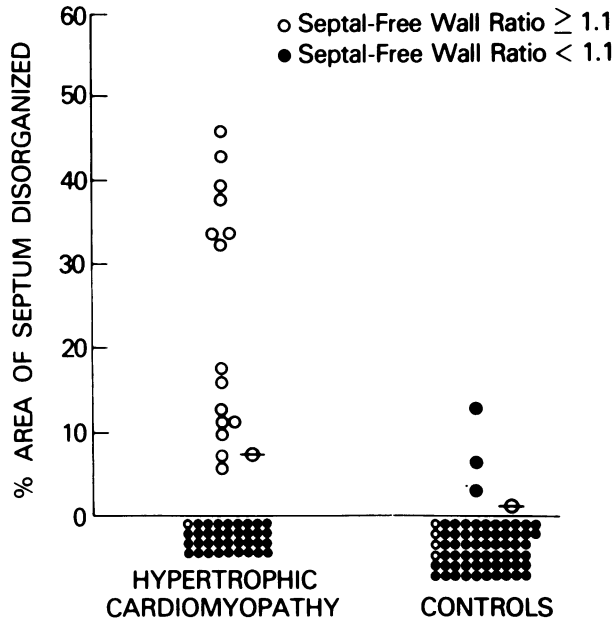

Figure 8—Percentage of the area of ventricular septum occupied by disorganized cardiac muscle cells in 51 cats with hypertrophic cardiomyopathy and 65 control cats. Mean values are indicated by *short horizontal lines.*

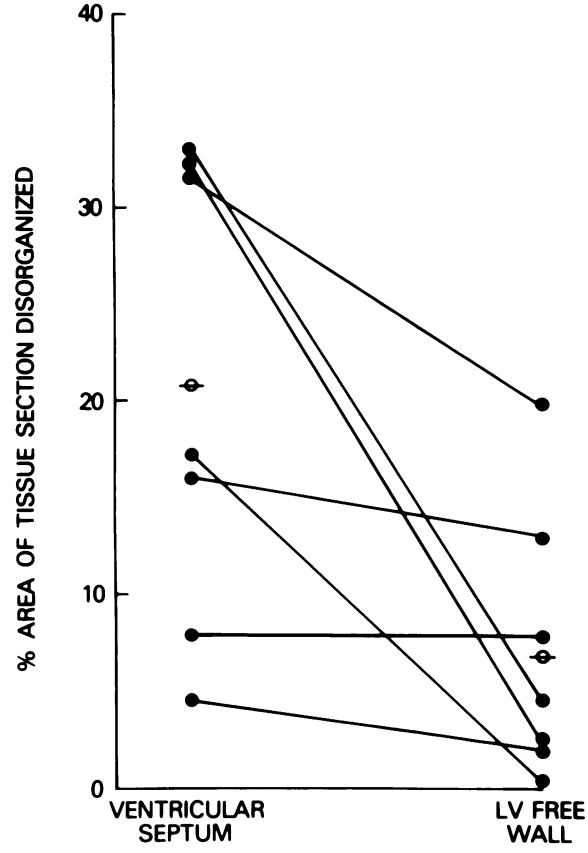

Figure 9—Comparison of the extent of ventricular septal and left ventricular (*LV*) free wall disorganization in 7 cats with hypertrophic cardiomyopathy. Values for each cat are connected by a *solid line.* Mean values are indicated by *short horizontal lines.*

whether these two morphologic forms of feline hypertrophic cardiomyopathy represent etiologically distinct diseases or are different phenotypic expressions of a single disease entity.

Septal disorganization was relatively uncommon (30%) in the overall population of 51 cats; hence, this histologic abnormality must be considered an insensitive marker of feline hypertrophic cardiomyopathy. Nevertheless, when septal disorganization was present, it was usually marked; in 14 of the 15 cats with disorganization, abnormally arranged cardiac muscle cells occupied >5% of the tissue section, and in the remaining cat 4% of the section was involved. On the other hand, marked septal disorganization was uncommon in cats with cardiac diseases other than hypertrophic cardiomyopathy (only 3% of the 65 controls); therefore, septal disorganization was a relatively specific finding (specificity = 97%) for feline hypertrophic cardiomyopathy.

Table 2—Predominant Types of Cardiac Muscle Cell Disorganization Identified in Cats With Hypertrophic Cardiomyopathy and in Control Animals

Predominant type of disorganization	Hypertrophic cardiomyopathy		Controls
	Ventricular septum	LV free wall	Ventricular septum
I-A	14	7	1
I-B	0	0	1
II-A	1	0	0
II-B	0	0	1
TOTALS	15	7	3

Disorganized architecture of the left ventricular free wall was uncommonly observed in our population of cats. Cardiac muscle cell disorganization was present in the free wall of only 7 of the 51 cats and was marked (>5%) in only 3 cats. Of note, each of the cats with left ventricular free wall disorganization also had marked disorganization of cardiac muscle cells in the ventricular septum, as well as asymmetric septal hypertrophy. Also, 4 of these 7 animals died suddenly and unexpectedly. Although we cannot be definitive at this time, these findings do suggest that such cats may have a more severe morphologic form of feline hypertrophic cardiomyopathy.

In conclusion, it is evident that a primary myocardial disease, often with pathologic features similar to those of hypertrophic cardiomyopathy in man, occurs in cats. This spontaneously occurring feline disease may prove to be a valuable aid in the investigation of human cardiomyopathies.

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