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The Comparative Pathology of Primary Endocardial Fibroelastosis in Burmese Cats

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Summary. A recently discovered, naturally occurring, familial, cardiac disorder of purebred Burmese cats resembling primary endocardial fibroelastosis (EFE) was compared to EFE in man. Study of 22 kittens and 20 human infants with EFE (with appropriate controls), revealed striking clinical, gross anatomic, histopathological and ultrastructural similarities between the human and feline conditions. Clinically, the disease was manifested in both species by signs of congestive heart failure.

At autopsy, anatomic heart or great vessel defects other than EFE were not detected. Cardiac lesions were not observed in kittens less than 2 days old. In kittens 5 to 19 days old, lesions were generally limited to endocardial edema with subendothelial proliferation of fibroblasts, which caused no grossly recognizable endocardial thickening. Left ventricular dilation and endocardial thickening were observed in essentially all affected kittens which survived 20 or more days after birth, and in all human infant hearts. Dilated lymphatic capillaries were observed at the endomyocardial junction in many of the feline and human hearts. Rapidly maturing collagen fibrils, and later elastic fibers, were formed by fibroblasts near the endothelial surface. Collagen and elastic fibers in the deeper endocardium became 3 to 5 times thicker than those in age-matched controls. Purkinje fibers of the left bundle branch became incorporated into the fibroelastic endocardial thickening in many human and feline cases. Most of these conduction fibers underwent degeneration and atrophy.

The similarity of findings in feline and human EFE indicate that affected Burmese cats may be a valuable model of human EFE. The concurrence of early endocardial edema and dilated lymphatics suggests that lymphatic obstruction may be important in the pathogenesis. The observation that early

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cases of EFE may appear grossly normal suggests that the disease may occur more frequently than is commonly diagnosed. Isolation and degeneration of Purkinje fibers may be responsible for serious conduction disturbances. Finally, the heredity nature of primary EFE in Burmese cats should promote further investigation into this cause of the human counterpart.

Key words: Endocardium – Feline – Congenital heart disease – Hereditary – Fetal endocarditis

Introduction

Endocardial fibroelastosis (EFE) is a pathological disorder characterized by a diffuse fibrous and elastic thickening of the endocardium. The condition is often thought to be congenital as most victims are infants which die of congestive heart failure before reaching one year of age. The left side of the heart is usually dilated and moderately hypertrophied, as well as having a diffusely thickened endocardium; the right side of the heart is seldom involved.

There are undoubtedly many causes and probably several mechanisms by which endocardial fibrous and elastic thickening develops (Mitchell et al. 1966). The condition is secondary to or associated with certain congenital cardiac or vascular anomalies (Anderson and Kelly 1956; Fontana and Edwards 1962; Perez Diaz et al. 1977); myocarditis, especially virus-induced (Factor 1978; Hutchins and Vie 1972; Schryer and Karnauchow 1974; St. Geme et al. 1974; Mehrizi et al. 1965); myocardial necrosis (Muraki et al. 1974) and myocardiosis as with certain glycogen storage diseases (Hers 1965). Localized endocardial thickening is associated with endomyocardial diseases such as endomyocardial fibrosis (Davies and Ball 1955), Becker's disease (Becker et al. 1953) and Löffler's disease (Gould 1968) and myocardial infarction, radiation injury, carcinoid syndrome and jet impact lesions.

Many cases of EFE are not associated with other cardiovascular anomalies, myocardial lesions or any other of the above conditions and are of unknown etiology and pathogenesis. It is this group of cases, which we refer to as primary EFE, that is the subject of this report. This form of EFE has been reported to occur in several families and different modes of genetic transmission have been proposed (Nielsen 1965; Chen et al. 1971; Hunter and Keay 1973; Lindenbaum et al. 1973; Westwood et al. 1975; Kelly and Anderson 1956). Pathogenetic theories of primary EFE include: anoxia (Johnson 1952), endocardial polymerization of fibrinogen derived from blood (Still and Boult 1956 and 1957), mechanical stress as in prolonged cardiac dilation (Black-Schaffer 1957) and obstruction of cardiac lymphatic drainage (Miller et al. 1963; Miller 1963; McKinney 1976; Symbas et al. 1963; Doerr 1967).

A limiting factor in the discovery of the cause and pathogenesis of primary EFE has been the lack of a naturally occurring animal model. Recently, a pair of adult purebred Burmese cats were discovered to produce offspring consistently affected with EFE (Zook 1978). The adults and several surviving kittens appear normal, but all have electrocardiographic, phonocardiographic and radiographic abnormalities of the heart suggesting that they are affected with

the same disease. All other offspring of the affected pair developed signs of congestive heart failure and died or they were sacrificed. Postmortem examinations on all kittens over 2 days of age confirmed the diagnosis of primary EFE (Paasch 1979; Paasch and Zook 1980).

The present study, the comparison of primary EFE in Burmese kittens with EFE in man, was undertaken in order to determine if the feline entity could provide a useful animal model of the human disease and in hopes of revealing insight into the cause and pathogenetic mechanisms of primary EFE in man.

Materials and Methods

Human Case Material. Case material was obtained from Children's hospital National Medical Center and from the Armed Forces Institute of Pathology, both of Washington, D.C. Hearts from 20 infants, 1 to 6 months and one 20 months old, were selected on the following basis: a. absence of anatomic defects other than EFE, b. absence of microscopic myocardial lesions, and c. well preserved specimens with the presence of a central portion of the interventricular (IV) septum. The history, clinical and autopsy findings were available in nearly every case, and the entire heart was present for study in most. Although not included in this report, cases of secondary EFE associated with myocardial lesions were studied for comparison. Control hearts were obtained from 7 infants, 1 to 6 months old, who had no history of heart disease.

Feline Case Material. Hearts affected with EFE were obtained from 22 kittens that were the offspring of the pair of purebred Burmese cats described earlier. The hearts were examined for evidences of congenital anatomic heart and great vessel defects. Estimates of the degree of chamber dilatation and endocardial thickness were made and photographs were taken after hearts had been immersed in formalin for at least 48 h and could be directly compared to each other and to controls. Control hearts were obtained from 14 kittens, 1 to 60 days old, that were the offspring of apparently unrelated healthy mongrel cats bred, born, and raised in the same environs as the test cats.

Preparation of Tissues. Multiple sections of the heart were obtained from every case and were processed for routine histology. Sections were stained with Hematoxylin and eosin (H & E), Masson's trichrome for collagen, and Elastica Van Gieson (EVG) for elastic fibers. In addition, some were stained with phosphotungstic acid-hematoxylin (PTAH) for fibrin and Alsian blue and colloidal iron for mucopolysaccharides. Endocardial measurements were taken from the left side of the I–V septum, halfway between the aortic valve and apex in order to avoid trabeculation and site variation in endocardial thickness. Ten measurements were taken from each heart.

Tissues for transmission electron microscopy (TEM) were processed from 3 control human infants, 4 infants affected with EFE, 7 control kittens and 7 kittens affected with EFE. Slices from the left side of the I–V septum, halfway between the aortic valve and apex were diced, fixed in isotonic Sorensen's buffered 3% glutaraldehyde (pH 7.2–7.4), postfixed in osmium tetroxide (1% solution in Sorensen's buffer), dehydrated in a graded series of ethanol and embedded in araldite 502. The hearts of 7 control and 7 affected animals were first perfused in situ with isotonic saline followed by glutaraldehyde fixative injected by a perfusion pump into the left atrium with the terminal aorta severed. One micrometer (μm) thick sections were cut, stained with toluidine blue and examined under a microscope to assure proper orientation. Thin sections were cut with a diamond knife on a Porter Blum MT-2 microtome, mounted on copper grids and double stained with lead citrate-uranyl acetate for 5 min each. Some of the tissues were stained with 1% aqueous solution of phosphotungstic acid (PTA) for 1 h and counterstained with lead citrate-uranyl acetate to enhance the appearance of collagen and elastin. The sections were examined and photographed with an EM-10 Zeiss TEM.

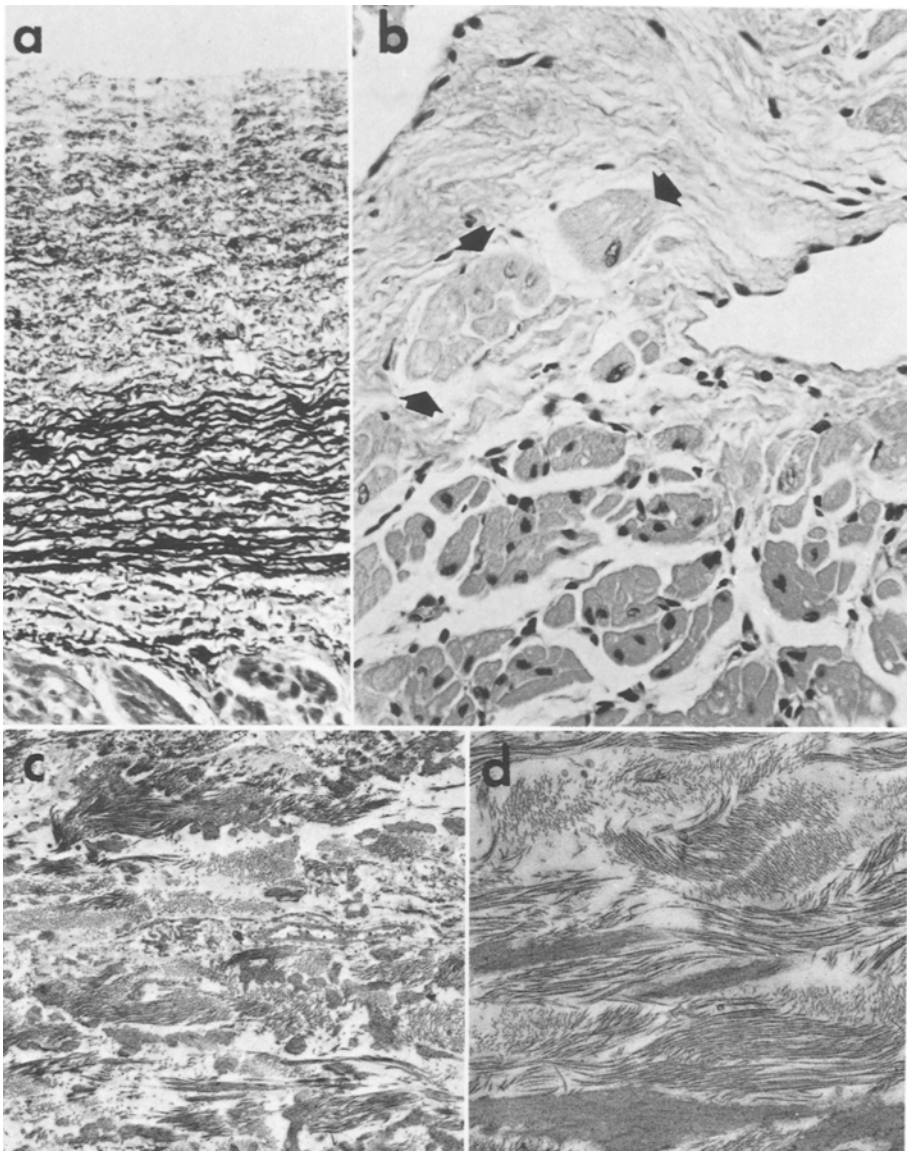

Fig. 1a–d. Endocardia from human infants with primary endocardial fibroelastosis. **a** Severely thickened endocardium of 180-day-old infant has superficial layer of thin, haphazardly arranged fibers and deeper layer of thick, well-organized fibers. Elastica Van Gieson stain, 125×. **b** Thickened endocardium contains isolated Purkinje cells (*arrows*) and dilated lymphatic (*right*). H & E, 400×. **c** The endocardium contains much collagen and elastic fibers and rare cells in this 180-day-old infant. 1,000×. **d** The deep endocardium (same case as c) contains thick, well-organized collagen and elastic fibers. 6,000×

Table 1. Light microscopic observations of human hearts with primary endocardial fibroelastosis

Case	Sex	Age (Mo.)	Endocardial thickness (μm)	Dilated lymphatics	Isolation of Purkinje cells
528457	F	1	52.6± 15.6	Yes	Yes
1480309	F	1	95.6± 34.6	Yes	Yes
535166	F	1	126.7± 24.5	Yes	Yes
682962	F	1	244.4±120.0	No[b]	Yes
A 11–60[a]	M	1	411.7± 58.4	No	No
804310	M	2	366.7± 70.7	No	No
A 12–60[a]	F	3	82.0± 32.3	No	Yes
A 94–56	F	4	338.3± 64.0	Yes	Yes
540163	F	5	40.6± 12.9	No	Yes
324840	F	5	213.1± 34.1	Yes	No
1389434	M	5	117.8± 42.7	No	No
1359670	M	5	48.9± 26.7	No	Yes
A 76-58[a]	F	5	142.2± 30.3	Yes	Yes
781710[a]	M	6	105.0± 55.5	No	No
1379993	M	6	107.2± 31.1	No	No
1430943	F	6	466.7±102.4	No	No
1456779	F	6	134.4± 39.1	No	No
A 75-57	F	20	123.3± 44.7	Yes	No
A 15-52	F	?	60.6± 22.1	Yes	Yes
A 81-52	M	?	67.2± 35.6	Yes	Yes

[a] Also studied by transmission electron microscopy
[b] No=not observed

Results

Human Endocardial Fibroelastosis Cases and Controls

Clinical Findings. Signs of chronic congestive heart failure were reported in 16 of 20 cases. The infants died between 1 and 6 months of age; four died suddenly and unexpectedly.

Gross and Light Microscopic Observations. Hydropericardium, hydrothorax, pulmonary edema and acute pneumonitis were reported in most affected children. Cardiac lesions included left atrial and ventricular dilation with severe, diffuse endocardial thickening which did not extend into the myocardium. The endocardium below the undisturbed endothelium consists of dense, hypocellular connective tissue containing two distinct layers of elastic fibers; delicate fibers in the superficial layer and thick, well oriented fibers deep (Fig. 1a). Fibrocytes are few and no inflammatory cells are seen. The endocardium measures at least 37 μm thick (Table 1) and reaches a maximum of 569 μm in the end stage cases. The degree of endocardial thickness does not increase proportionally with age ($r=0.145$).

Dilated lymphatic vessels are observed at the endomyocardial junction in 9/20 (45%) cases. The empty channels average approximately 40 μm in diameter and have walls formed exclusively by endothelial cells (Fig. 1b). In 11 cases

(55%), modified myocardial cells typical of Purkinje fibers are isolated from the myocardium and surrounded by the endocardial fibrous and elastic proliferation (Fig. 1 b). No lesions are observed in other myocardial cells.

Control infant hearts have no recognizable gross or microscopic lesions and dilated endocardial lymphatics are not recognized. The left ventricular septal endocardium of control infants increases in thickness with age from 3.9 ± 0.3 μm at one month to 19.1 ± 3.4 μm at 6 months of age.

Transmission Electron Microscopic Findings. The thickened endocardia of infants with primary EFE are composed of dense, thick and well organized collagen bundles, elastic fibers and fibroblasts below the intact endothelia. The elastic and collagen fibers in the superficial endocardium have diameters of approximately 750 nm, and 1,000 nm respectively. In the deeper endocardial strata, both elastic fibers and collagen are thicker, averaging 2,000 nm and 3,000 nm respectively (Fig. 1 c, d). Quality of preservation does not permit study of minute detail, however, the identity of dilated lymphatics and isolation of Purkinje fibers observed by light microscopy are readily confirmed.

The endocardia of control hearts contains occasional fibroblasts and connective tissue fibers. Collagen fibrils and bundles are delicate close to the endothelial surface, becoming 1,000–2,000 nm thick in the deeper endocardial layers. Elastic fibers are scarce. The conduction fibers and the vascular system are as expected.

Feline Cases of Endocardial Fibroelastosis and Age-Matched Controls

Clinical Findings. Clinical signs were observed in 12 of the 22 kittens affected with EFE. The signs included dysnea, tachypnea, pulmonary rales, tachycardia, gallop rhythm and roentgenographic evidence of cardiomegaly. Three kittens died after a clinical course of congestive heart failure. Nine were euthanized after exhibiting one or more of the above clinical signs. The remaining 10 kittens appeared clinically healthy although 4 died suddenly and unexpectedly; the others were sacrificed, some at quite early ages.

Necropsy Findings. No gross evidence of heart disease was observed in three 1- to 5-day-old kittens (Table 2) with EFE. Left ventricular dilation, the principal cause of cardiomegally (Fig. 2 a, b) was recorded in 18 kittens. Fluid retension in body cavities occurred in 17. Gross evidence of left ventricular endocardial thickening was present in 16 cases. All cats with grossly thickened endocardia survived 20 or more days, and all but one had dilated hearts. No lesions were observed in controls.

Light Microscopic Observations. The endocardium is edematous and cellular in the 3-, 5-, and 10-day-old kittens. The fine, loosely separated connective tissue fibers and the fibroblasts in the newborns gradually becomes the thicker, more compact connective tissue fibers and less cellular endocardium of older kittens. Thick and well oriented elastic fibers are readily identified in the 22-day-

Table 2. Gross and microscopic observations of Burmese kittens with primary endocardial fibroelastosis

Cat	Sex	Age (days)	Gross observations			Microscopic observations		
			Endocardial thickening (μm)	Left ventricular dilation	Heart failure[a]	Endocardial thickness	Dilated lymphatics	Isolation of Purkinje fibers
79-33[d]	M	1	0[b]	0	0	1.3± 0.5	No[e]	No
78-115	F	3	0	0	0	9.9± 6.7	No	No
79-32[d]	F	5	0	0	0	3.7± 0.4	No	No
78-100	F	8	0	+++	+++	52.5±20.5	No	Yes
78-147[d]	M	10	0	+	++	44.5±30.5	Yes	No
78-167	M	19	0	0	0	28.0± 2.6	No	No
78-136[d]	M	20	+	++	++	55.0± 3.3	No	No
76-40	?[c]	22	++	+++	+++	93.0± 6.3	No	Yes
78-173	M	22	+	+	++	71.0± 7.8	No	Yes
78-171[d]	F	22	++	++	+++	71.0± 5.2	No	Yes
78-174	F	24	++	+	0	56.0±40.1	Yes	No
77-13	?	25	++	++	++	118.5± 8.8	Yes	Yes
79-3	F	28	++	++	++	49.0± 7.4	Yes	Yes
77-6	M	30	+++	+++	+++	62.0±25.3	Yes	Yes
77-84	M	30	++	0	++	28.0± 2.6	No	No
77-14	M	46	+++	+++	++	69.0±26.4	Yes	Yes
79-5[d]	M	46	++	+++	+++	50.0±19.7	Yes	Yes
77-48	M	52	+++	+++	+++	50.0±17.2	No	No
78-143[d]	M	60	+++	+++	+++	138.0±29.4	No	No
77-51	F	60	+++	+++	++	27.2± 9.0	No	Yes
77-60	F	63	+++	+++	++	42.0±11.4	No	Yes
77-61	M	63	+++	+++	++	28.5± 6.3	No	No

[a] Congestive heart failure as evidenced by fluid retention in body cavities
[b] Lesions are graded 0=absent, +=mild, ++=moderate, +++=marked
[c] Unrecorded sex
[d] Also studied by transmission electron microscopy
[e] No=not observed

old (Fig. 2c, d). In one 60-day-old kitten the endocardium reaches a maximum thickness of 180 μm with an exhuberant proliferation of fibroelastic elements. The elastic fibers have the same distribution observed in the human EFE cases. Near the endothelium, delicate and randomly oriented fibers predominate; in the deeper endocardial layers, elastic fibers are large and oriented parallel to the surface. The endocardium is uniformly thickened in 20 cases; some variation in endocardial thickness is found in 2. Distended lymphatics are found at the endomyocardial junction in 7 cases (Fig. 2e). The proliferated endocardial fibroelastic components are seen to isolate and engulf nests of myocardial cells typical of Purkinje fibers (Fig. 3) in 11 of the 22 cases (Table 2).

The endocardium of control kittens tends to increase in thickness with age ($r=0.91$) ranging from 1.5 ± 0.5 μm at one day old to 5.3 ± 0.5 μm at 60 days old. The endocardium does not appear edematous nor cellular and there are no altered vessels nor changes in Purkinje cells.

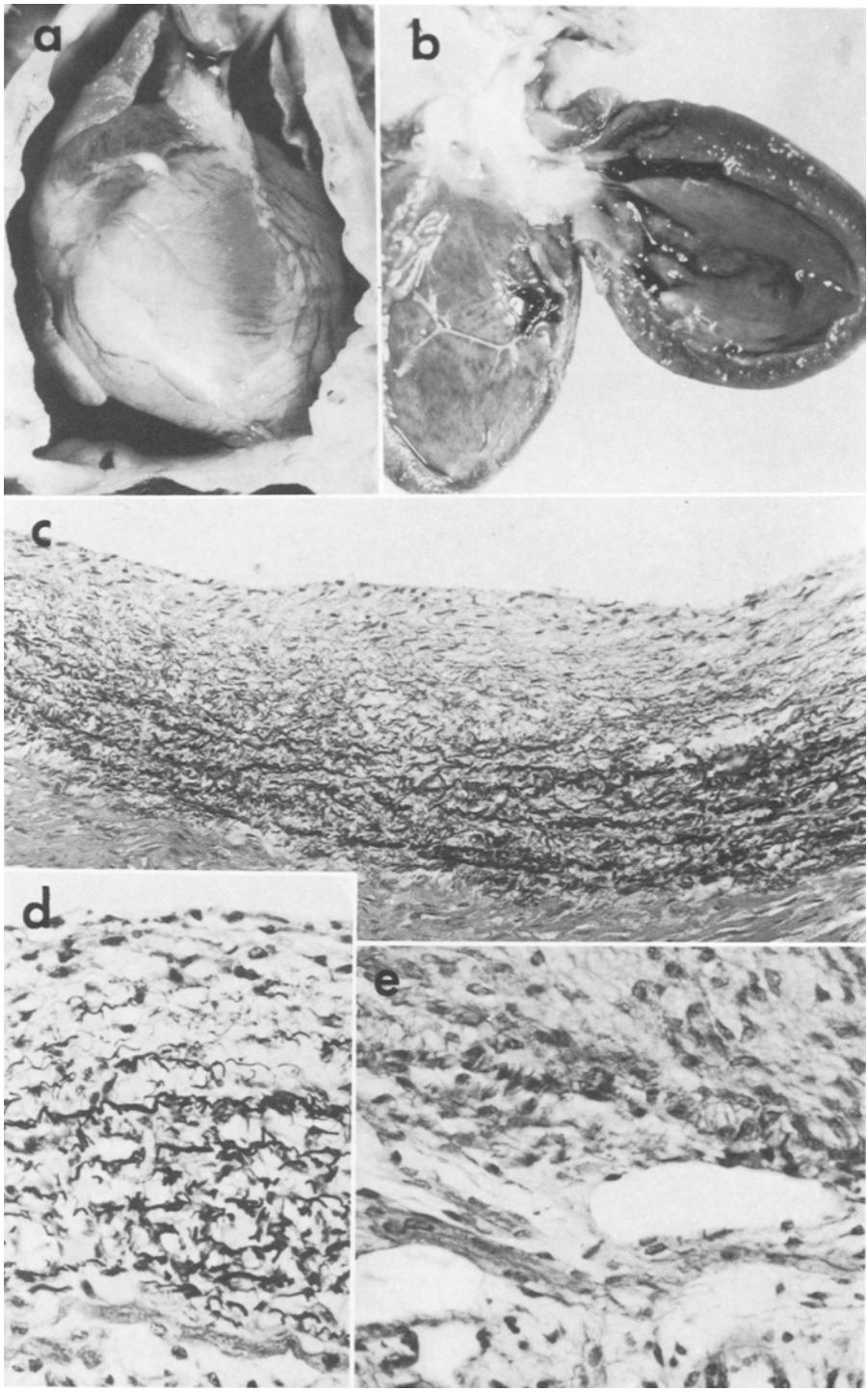

Fig. 2a–e. Hearts from Burmese cats with primary endocardial fibroelastosis. **a** Severely enlarged heart of Burmese kitten in situ with ventral thorax removed. **b** Severely dilated (and hypertrophied) heart of 60-day-old feline with moderate endocardial thickening. Note elongate papillary muscles. **c** Thick, well-organized connective tissue fibers in deep endocardium of 22-day-old form sharp junction with myocardium: Newly formed fibers are laid down by cells just under endothelium. Elastica Van Gieson stain, 125×. **d** Endocardium from 60-day-old kitten demonstrates thin, newly synthesized subendothelial fibers and older and thicker fibers deep. Elastica Van Gieson, 330×. **e** Two distended and empty lymphatic vessels are located at endomyocardial junction in 24-day-old. H & E, 500×

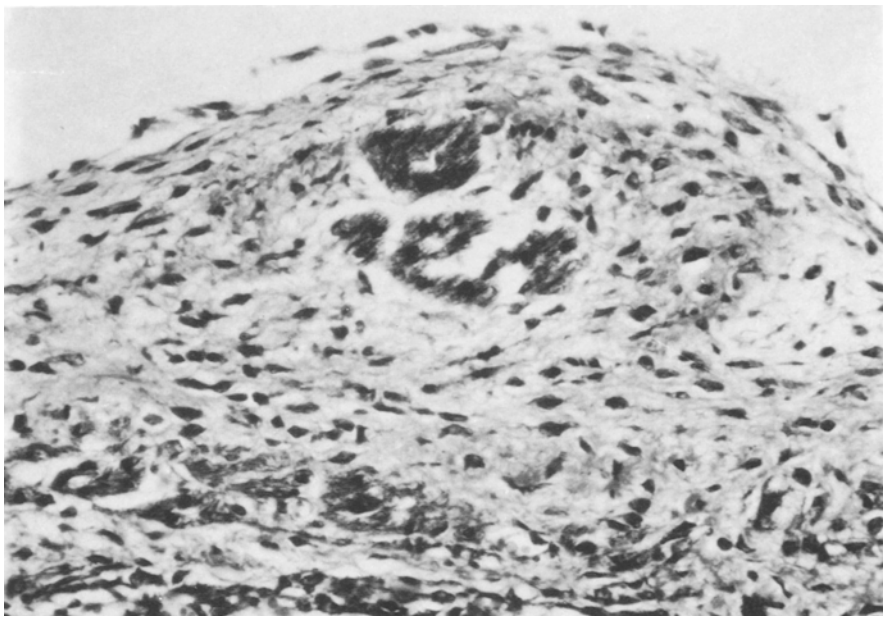

Fig. 3. Purkinje fibers are isolated by fibrous and elastic fibers in 22-day-old. H & E, 500×

Transmission Electron Microscopic Findings. The endocardium of the 1-day-old kitten with EFE is similar to that of the 1-day-old control; no differences are found. The 5- and 10-day-old affected kittens have endocardia several times thicker than those in age-matched controls. The thickening is caused principally by the accumulation of flocculent material representing edema fluid (Fig. 4a). Fibroblasts are abundant and active, endowed with conspicuously dilated cisternae of rough endoplasmic reticulum. Cellular and fibrilar elements are loosely arranged in the edematous endocardium. Collagen bundles have an average diameter of 1,300 nm. At the endomyocardial junction of the 10-day-old kitten, several dilated lymphatic capillaries are observed. Lymphatic vessels are readily identified: they are distended with proteinaceous material, but contain no erythrocytes; they are lined by endothelial cells only, which have no basal lamina; and valves are present in some sections. Fibroblasts are abundant in the 20-day-old and most contain many profiles of granular endoplasmic reticulum. Mature collagen fibrils are grouped forming 3,000 nm thick bundles oriented in transverse and longitudinal directions. Only a few elastic fibers are observed at that stage, but dilated lymphatic vessels are present at the endomyocardial junction. The 22-day-old cat has many fibroblasts in the endocardium. The superficial subendothelial layer contains loosely arranged fibrils and immature elastic fibers, whereas in the deeper endocardium collagen fibrils are grouped forming 3,000 nm thick bundles. At the endomyocardial junction, isolation of modified myocardial (Purkinje) fibers is repeatedly observed. The isolated fibers have sarcoplasms containing poorly organized and rudimentary myofilamentous material, abundant mitochondria and glycogen characteristic of Purkinje fibers.

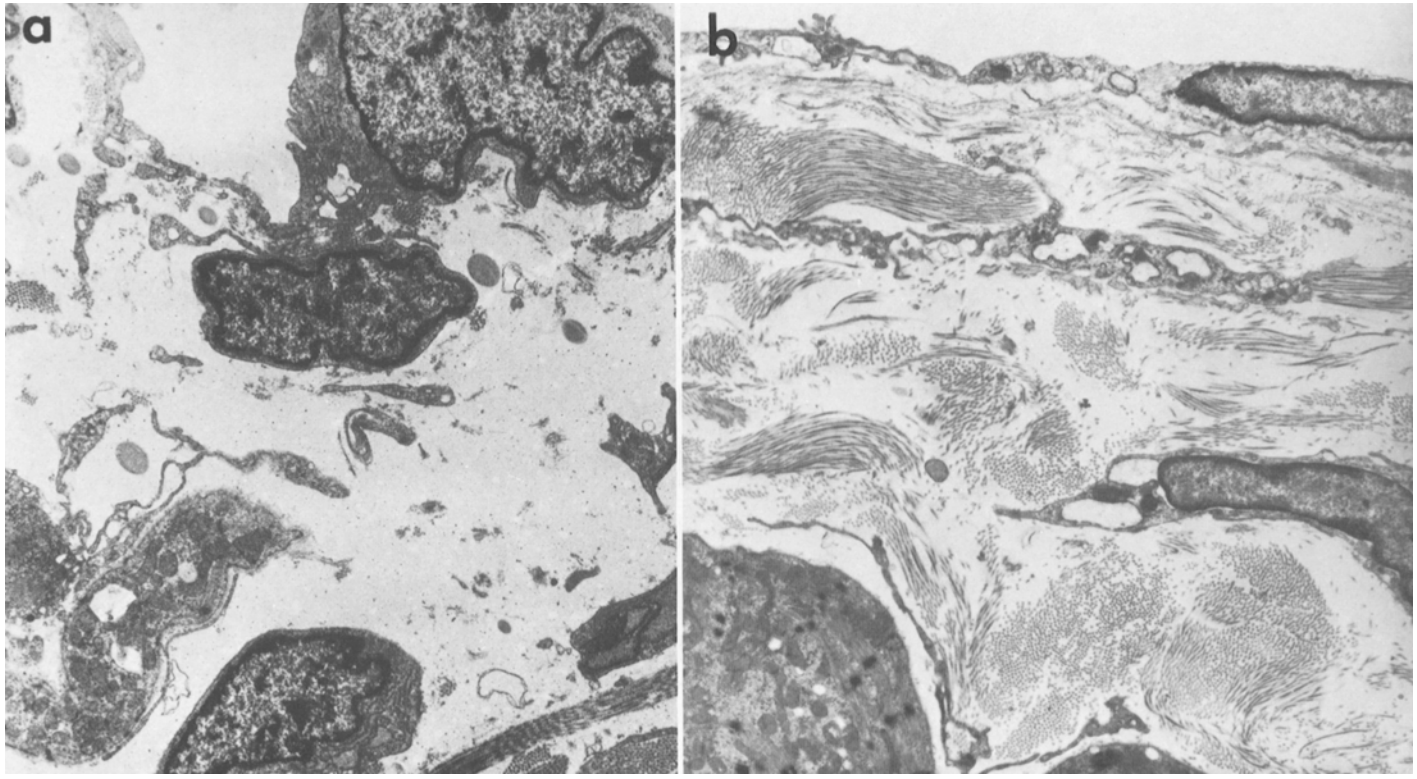

Fig. 4a and b. Transmission electron microscopic appearance of feline endocardial fibroelastosis. **a** The superficial endocardial components (active fibroblasts and connective tissue fibers) from 10-day-old kitten are separated by edema. The endothelium is not remarkable. 8,200×. **b** Fibrotic endocardium from 46-day-old Burmese contains fibroblasts, immature collogen fibers superficially and collagen bundles in the deeper layers. 6,000×

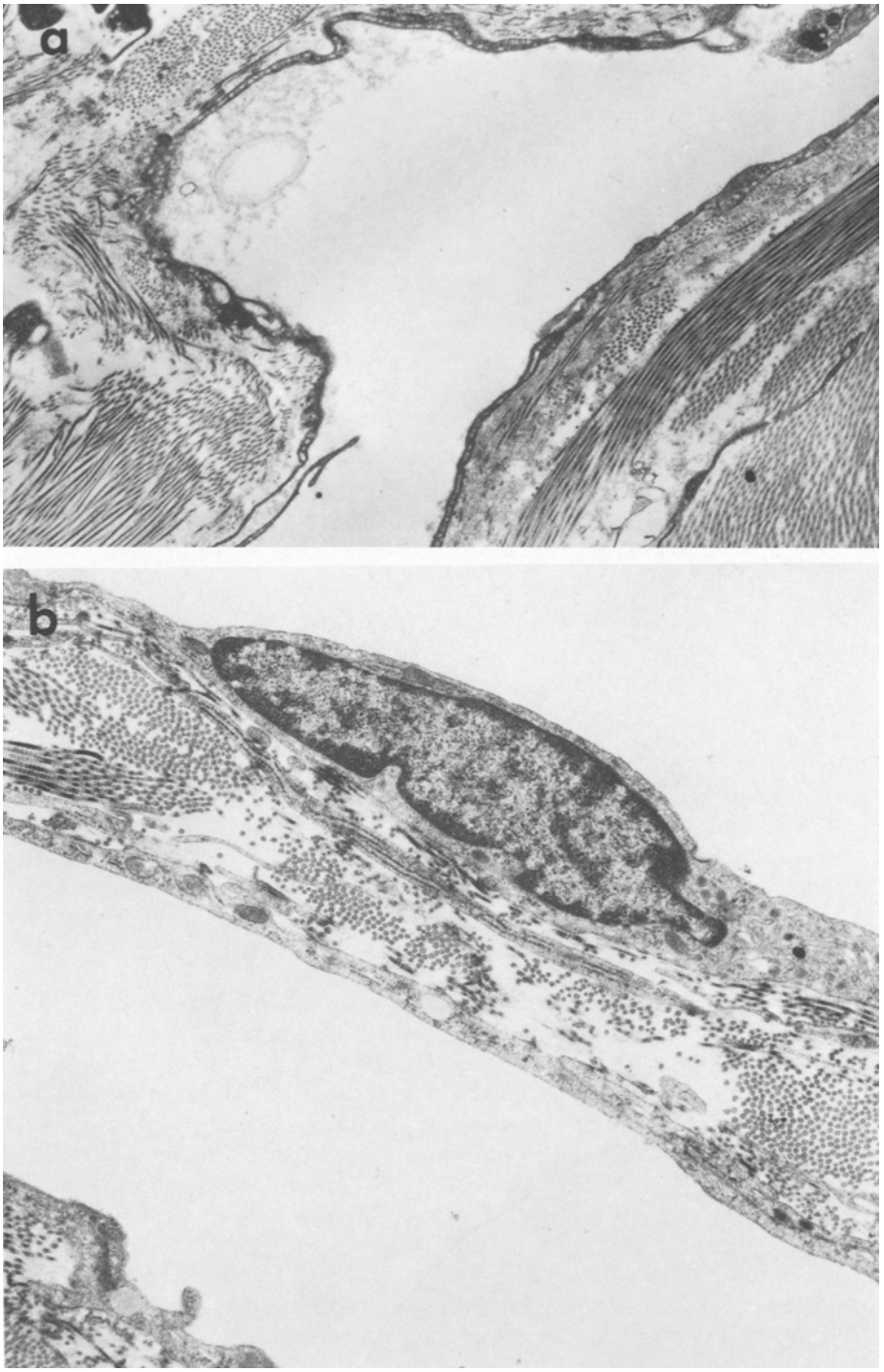

Fig. 5a and b. Dilated lymphatic vessels from Burmese cats with endocardial fibroelastosis. **a** Distended lymphatic at endomyocardial junction from same cat as in Fig. 4b, contains flocculant material. 12,500×. **b** Thin shelf of mature collogen fibers separate two lymphatics lined by thin endothelium without basement membrane in 20-day-old kitten. 15,000×

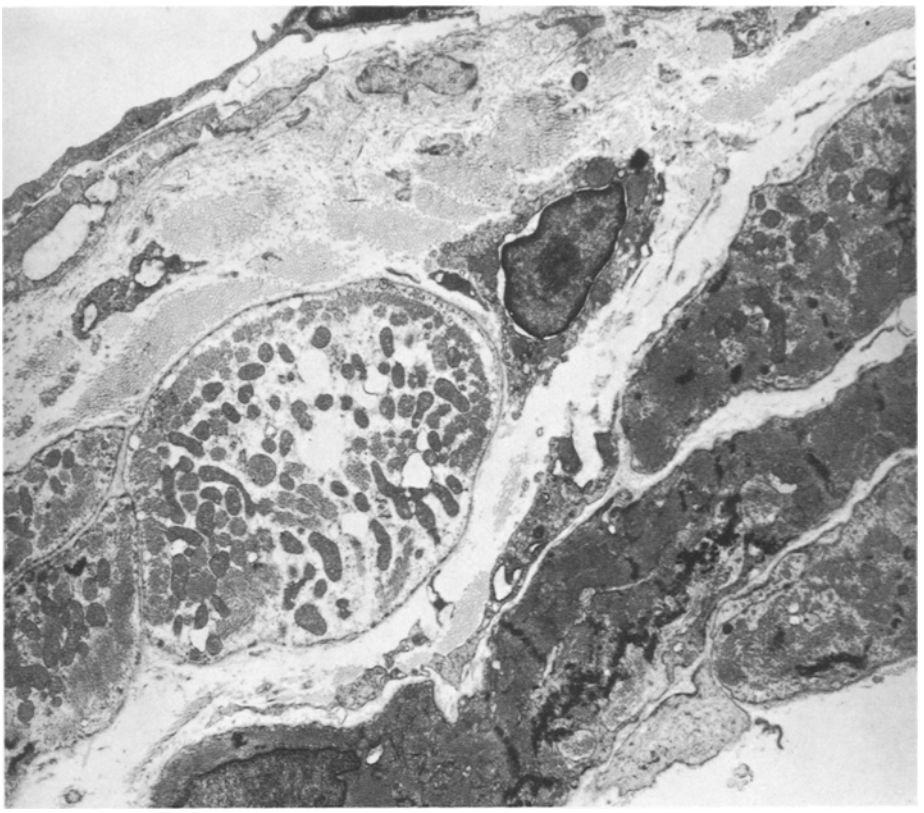

Fig. 6. Atrophic Purkinje cells, mid to lower left, depleted of glycogen and containing vacuoles, are isolated from myocardium below by fibroblasts and their fibers (same cat as in Fig. 4b). 6,000×

These cells are surrounded by cytoplasmic processes of fibroblasts and by collagen and elastic fibers that completely separated them from the adjoining myocardium.

Active fibroblasts are plentiful in the endocardium of the 46-day-old cat. In the superficial endocardial strata, loosely arranged collagen fibrils and delicate inconspicuous masses of elastic amorphous substance with peripheral microfibrils predominate (Fig. 4b). In the deeper endocardial layers, collagen bundles 5,000 nm thick are oriented in several directions. At the endomyocardial junction prominent lymphatic capillaries are present (Fig. 5a). The lymphatic capillaries are lined by attenuated (200 nm thick) endothelia (Fig. 5b). At the same location are isolated Purkinje cells; atrophic Purkinje cells contain vacuoles and swollen mitochondria (Fig. 6). The typical end-stage distribution of elastic and collagen fibers are present in the 60-day-old affected kitten. Close to the endothelial lining elastic and collagen fibers have diameters of less than 1,000 nm. Elastic fibers near the endomyocardial junction have diameters of 3,250 nm. Collagen fibers there are also thick having diameters between 3,000 and 5,000 nm. No

isolated Purkinje fibers nor dilated lymphatic capillaries are observed in this case.

The subendothelial endocardial components in newborn control kittens consist of fibroblasts with multiple individual collagen fibrils. A few collagen fibrils are grouped forming delicate bundles with average diameters of 180 nm. In the 20-day-old control collagen bundles are around 500 nm in diameter. In the 40- to 60-day-old control kittens, only individual collagen fibrils are observed in the superficial endocardial strata, whereas collagen bundles with thicknesses of 1,000 nm are observed near the endomyocardial junction. A similar distribution occurred among elastic fibers. Delicate aggregates of amorphous substance with peripheral microfibrils are found subendothelially. Deeper endocardial layers contain masses of elastic amorphous substance 600 nm in diameter, nearly devoid of peripheral microfibrils and tending to form a dense elastic lamina. No endocardial smooth muscle cells were observed in test or control kittens.

Discussion

Comparison of the clinical and pathological findings in human infants and kittens affected with primary EFE revealed many similarities and no remarkable differences. The clinical signs, gross, light and electron microscopic appearances were comparable, even to rarely described features – the distension of lymphatics and degeneration of Purkinje cells. All human infants in this (and most) studies died as a result of their disease, thus cardiac lesions were relatively well advanced and were grossly obvious. Kittens were sacrificed at various intervals after birth allowing study of the development of lesions.

Six Burmese kittens died or were euthanized prior to developing gross endocardial changes. The transparent endocardium of these feline neonates consisted mostly of fibroblasts, and a few fine collagen bundles separated by edema fluid and ground substance. In those cases where the endocardium was grossly opaque, many highly organized, thicker than normal and closely packed collagen bundles were present. It is not simply the thickness of the endocardium which causes its opacity, but rather the density and organization of the endocardial connective tissue. These findings are thought to be significant. It may be that mild or developing cases of EFE are overlooked in man and animals because this disease, generally considered to have a pathognomonic gross appearance, may not be a diagnostic consideration if the endocardium appears grossly normal. A recent report supports this contention (Williams and Emery 1978). In that study, a sampling of grossly normal human infant hearts, many dying with the sudden infant death syndrome, revealed a number with fibrous endocardial thickening; some were thought to be morphologically compatible with EFE.

The thickness of the endocardium varied considerably between subjects. It is generally accepted that endocardial lesions in humans with EFE increase in thickness with time (Gould 1968; Kelly and Anderson 1956). In this study a correlation between age and endocardial thickness, although evident in controls, was not seen in either humans or cats with EFE.

Fibroblasts and fibrocytes were the principal cells found in the human and feline endocardium affected with EFE. No inflammatory cells were identified by TEM by us or by others (Fishbein et al. 1977). Smooth muscle cells were not found in the feline endocardium, but are seen in human endocardium and have been implicated as the source of elastic fiber synthesis (Martinez-Hernandez and Starcher 1972; Sekiguchi and Hirosawa 1973; Zoltowska 1971; Neustein et al. 1979). Fibroblasts are known to synthesize and assemble amino acids and polypeptides that form the elastic fibers, as well as collagen (Haust and Moore 1967) and it is this cell type which synthesizes the collagen and later the elastic fibers in feline EFE. All of the endocardial fibers identified in kittens and humans by us, and in humans by others Fishbein et al. 1977) were anatomically normal, but overly thick and numerous. Others have reported chemical evidence of increased cross linking of elastic fibers (Martinez-Hernandez and Starcher 1972). Evidence of fibrin deposits reported by others (Still and Boult 1956 and 1957) were not detected.

Collagen and later elastic fibers were formed just under the normal appearing endothelial surface. Older more mature and compact bundles were left in the deeper layers as new fibers were formed above. The collagen and elastic fibers near the myocardial junction were considerably thicker than those in age-matched controls. Fibroblasts remaining in the deep endocardium tended to encircle Purkinje cells. These modified myocardial cells became entrapped in the connective tissue fibers and underwent degeneration.

The incorporation of Purkinje fibers of the left bundle branch into the endocardial fibroelastic thickening and their subsequent degeneration observed in both cats and humans (Factor 1978) may be an important event. Conduction disturbances, including left bundle branch block are reported in humans with EFE (Pavlowich 1962; Moller et al. 1964; Kelly and Anderson 1956; Moss and Adams 1968; Sugiura et al. 1979) and gradual or even sudden heart failure are possible sequelae. The isolated Purkinje fibers may no longer be seen in advanced stages of EFE, perhaps because they have already undergone atrophy or necrosis due to compression, disuse or anoxia. The fact that the conduction system of the human heart is not as conspicuous microscopically as in the cat, and that the majority of cases of EFE available for examination in man are advanced, may explain why Purkinje cell changes is not more often reported in humans. Since both cats and humans develop anatomic changes of the conduction system, study of electrophysiological changes in the heart with the development of EFE may be rewarding.

The presence of dilated endocardial lymphatic capillaries in both human and feline cases, and the endocardial edema seen in early feline cases, may be a result of complete, partial or temporary obstruction of lymphatic outflow. There was no other obvious cause of edema since no alterations were observed in the endocardial endothelium or local blood vessels. Since distended lymphatics were observed only in cats less than 50 days of age, it may be that the lymph vessels collapse because of relative disuse, relief of obstructing pressure, or compression by the increasing endocardial fibrosis. Subendocardial edema and dilated lymphatics have been observed in human EFE by others (Kline et al. 1964; Zoltowska 1971). The fact that the dilated channels are only observed

in early cases and that nearly all human cases are well advanced when autopsied, may partially explain why they have not been more often observed. Long standing lymphedema associated with incompetent lymphatic drainage is known to promote proliferation of dense connective tissue, e.g., lymphedema praecox and Milroy's disease (Robbins and Cotran 1979). Cardiac lymphatic obstruction is a known cause of lesions similar or identical to EFE in experimental monkeys (McKinney 1976), dogs (Miller et al. 1963; Symbas et al. 1963) and cats (Paasch 1979). The fact that dilated lymphatics were present in both cats and humans suggest a common pathogenetic mechanism.

It has been suspected that altered lymphatic drainage of the heart is the key to the pathogenesis of EFE (Doerr 1967; Doerr 1970). In man a rich network of lymphatics anastomose to rapidly drain lymph from the heart to lymph nodes between the aortic arch and right pulmonary artery (Miller 1963). A similar pattern of lymphatics drains the cats heart to a mediastinal lymph node just dorsal to the third sternebrae (Paasch 1979). It has been suggested that certain viruses may induce EFE by infecting lymphatics causing stagnation of the lymph (Doerr 1967). Recently, viral-like particles have been observed in altered cardiac endothelial cells, some possibly lymphatic, in a case of human EFE (Factor 1978). It may be that several environmental factors as well as genetic factors alter cardiac lymph flow inducing endocardial lesions.

The hereditary nature of primary EFE in the Burmese cat is obvious. All offspring over two days old of a particular pair have developed the disease. In humans genetic transmission is suspected, but poorly understood. Future test matings should establish the mode of inheritance of feline EFE. This animal model should then provide a sound basis for a search for the mode of transmission of the human counterpart.

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