The Progression of Interstitial Myocarditis to Idiopathic Endocardial Fibroelastosis

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Diffuse interstitial mononuclear cell myocarditis of unidentified but probable viral etiology in patients with endocardial fibroelastosis (EFE) suggested a possible pathogenetic relationship. Clinical and autopsy findings were reviewed in 64 children with one or both conditions. Five had myocarditis only and 18 had idiopathic EFE only, but in 41, both lesions coexisted and demonstrated the progression of myocarditis into idiopathic EFE. Patients with myocarditis but without EFE all died within 2 weeks of the onset of symptoms. With longer survival, myocarditis subsided but EFE and myocardial hypertrophy increased progressively. Marked EFE and hypertrophy, with trivial or no residual myocarditis, occurred with survival times over 4 months. Mitral insufficiency due to ventricular dilatation and a papillary muscle displacement commonly developed with prolonged survival. The results of the study are consistent with the hypothesis that in some patients interstitial myocarditis may produce left ventricular dilatation of a duration sufficient for the development of myocardial hypertrophy and EFE. These nonspecific responses to increased expenditure of myocardial energy and increased mural tension produce ventricular compensation, but result in a marked loss of cardiac reserve. Relative mitral insufficiency perpetuates the cycle of congestive failure and diminishing cardiac reserve by causing further ventricular dilatation with consequent myocardial hypertrophy (Am J Pathol 66:483–496, 1972).

THE IDEA THAT A PATHOGENETIC RELATIONSHIP might exist between diffuse interstitial mononuclear cell myocarditis and idiopathic endocardial fibroelastosis was suggested at autopsy by the coexistence of both conditions in children. Diffuse interstitial mononuclear cell myocarditis of undetermined etiology, originally described by Fiedler,[1] now appears to be usually due to a viral infection, especially Coxsackie B virus.[2,3] An association between Coxsackie epidemics and a subsequent increase in the incidence of idiopathic endocardial fibroelastosis has been noted.[4]

The concept that endocardial fibroelastosis (EFE) develops as a nonspecific reaction to increased mural tension of whatever cause has been supported by pathologic studies.[5,6] The etiology of the idiopathic form

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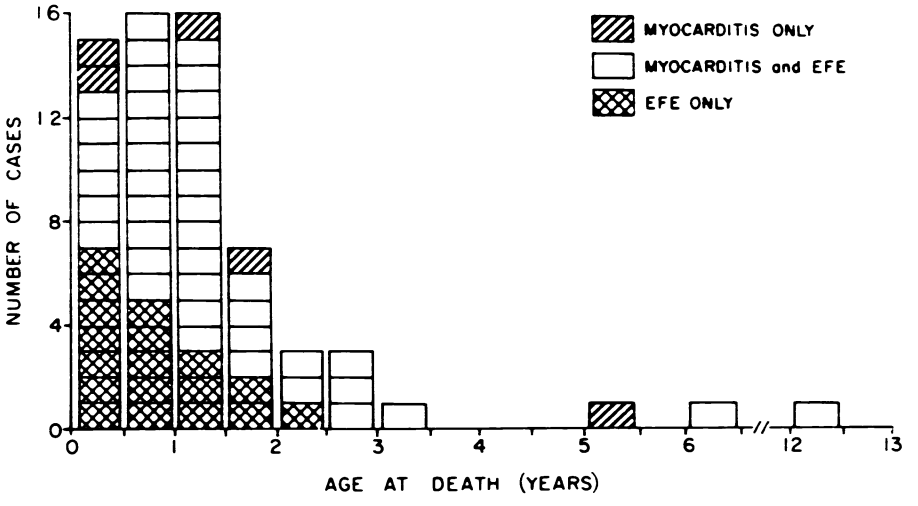
of EFE has been variously ascribed to myocardial hyperplasia,[7] mitral insufficiency,[8] anoxia [9] and a myocardial metabolic abnormality.[10]

In this study clinical and pathologic features of 64 children with interstitial myocarditis and/or idiopathic EFE were analyzed. An attempt is made to explain the pathogenesis of idiopathic EFE as the response to increased endocardial tension produced by left ventricular dilatation, which in turn is secondary to myocarditis and relative mitral insufficiency.

Observations

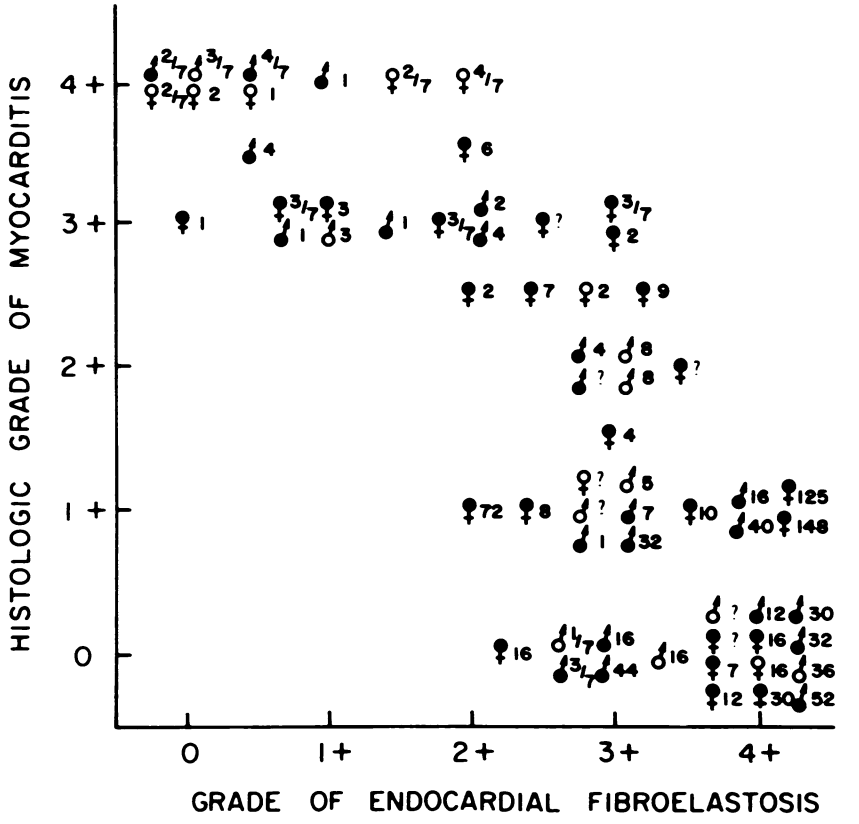
The autopsy files of the Johns Hopkins Hospital were reviewed for all patients with either interstitial myocarditis or endocardial fibroelastosis. Patients were excluded if the myocarditis appeared to be a minor component of some other disease, such as poliomyelitis, active syphilis, endocarditis, trichinosis or a collagen vascular disease. Similarly, patients with endocardial fibroelastosis were excluded if an accompanying cardiovascular abnormality of any type etiologically related to EFE was present, such as anomalous origin of the left coronary artery from the pulmonary artery, aortic valve stenosis or atresia, coarctation of the aorta or Type II glycogenosis. Sixty-four patients remained and of these, 5 had interstitial myocarditis only, 41 had interstitial myocarditis and EFE and 18 had idiopathic EFE only. Ages ranged from 11 days to 12 years, average 1 year, and their distribution is shown in Text-fig 1. The youngest patient with EFE only was 10 weeks old.



TEXT-FIG 1—Distribution by age of the 64 patients studied.

The clinical features of each patient were reviewed to determine the duration of illness. In 7 patients, there was insufficient information. In the remainder, the clinical course ranged from a few hours to almost 3 years, as shown in Text-fig 2. In several patients, there had been no overt illness until a few days before death. The majority had clinical findings consistent with heart failure, such as tachypnea, rales, pulmonary infiltrates, enlarged liver and peripheral edema. In several patients, a history was obtained of a flu-like illness followed by progressive and eventually intractable congestive heart failure. A Coxsackie B5 virus was cultured from 1 patient at the time symptoms of congestive heart failure began.[11]

The histologic sections of the heart from each patient were reviewed



TEXT-FIG 2—Symbols representing each patient by sex and race (*open circle* indicates white, *filled circle*, black) are located according to the grade of interstitial myocarditis and of EFE found on histologic examination of the heart. A number to the right of the symbol is the duration of clinical illness in weeks; a question mark indicates that the duration of illness is unknown.

and assigned a grade on a scale of 0–4+ for degree of interstitial myocarditis and for degree of endocardial thickening in the left ventricle; the symbols representing each patient in Text-fig 2 were located accordingly. Thirty-two patients were male and 32 female. Only 18 (28%) of the patients in the study were white, in contrast to the entire comparable age group of 1853 patients in the autopsy file, which is 70% white. The greater number of blacks among the patients studied is thought to reflect a propensity for fatal myocarditis and idiopathic EFE in the socioeconomically depressed. The data do not permit a more complete analysis of this complex question.

The patients were divided into 5 groups according to duration of clinical illness. The average and range of the grade of interstitial myocarditis and of EFE was determined for each group (Table 1). Using the same 5 groupings, average heart weight relative to body surface area was determined for the 46 patients with required measurements of heart and body weight and body length. In 64 control patients matched for age, race and sex from the autopsy files, there was a range of 48–186 and an average of 117 g of heart/sq m of body surface area. No significant variation of relative heart weight with age was found in the control patients. The table shows an increase in myocardial hypertrophy and EFE and a decrease in myocarditis with greater duration of illness.

The pathologic features of patients revealed a consistent sequence of

Table 1—Average Grades of Myocarditis and EFE, and Relative Heart Size of Patients Grouped by Length of Clinical Illness

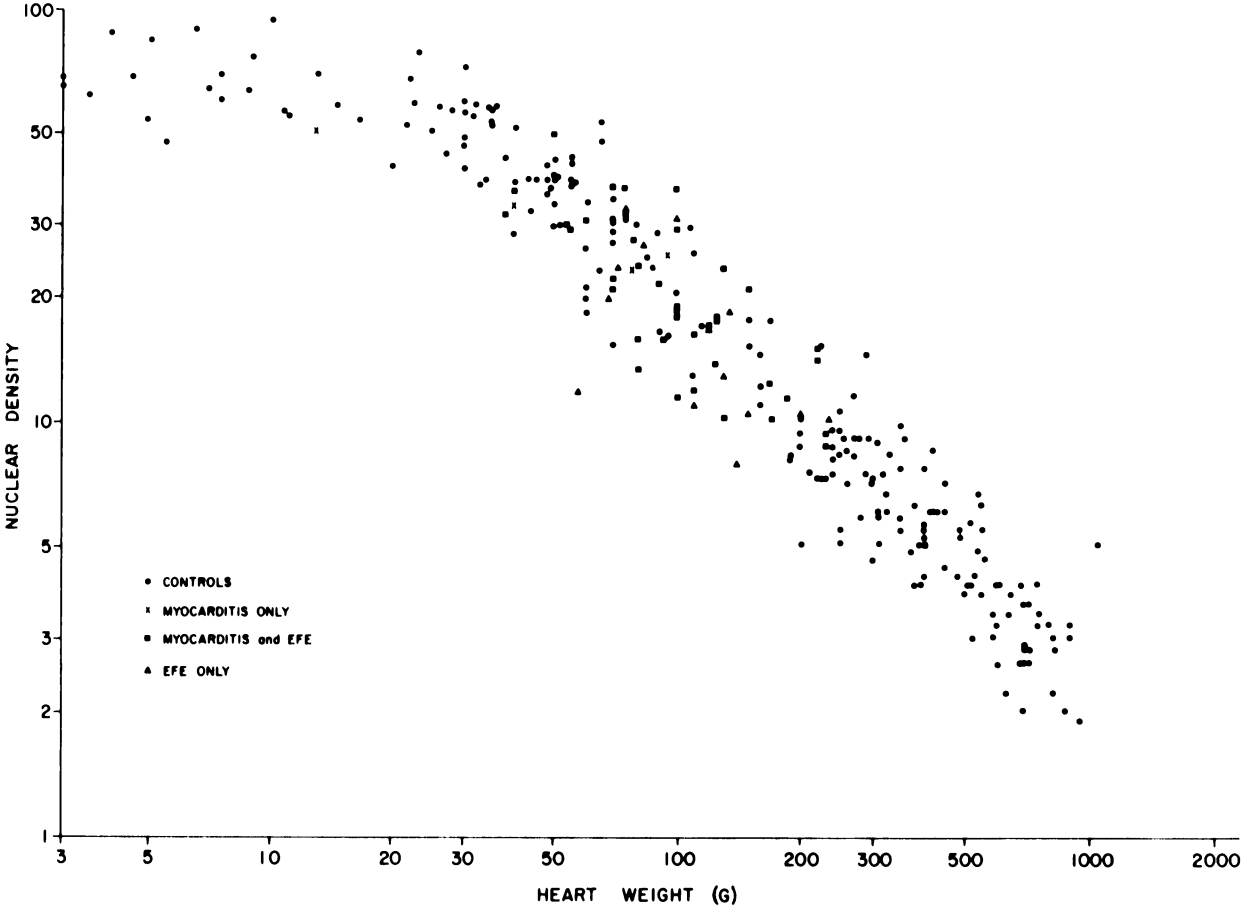
	Duration of clinical illness (weeks)				
	0–2	2–4	4–8	8–12	over 12
Histologic grade of myocarditis					
Average	3.0	2.7	1.6	1.2	0.3
Range	0–4	1.5–3.5	0–3.5	0–2.5	0–1
No. patients	22	6	8	3	18
Histologic grade of EFE					
Average	1.5	1.9	2.8	3.5	3.6
Range	0–3	0.5–3	2–4	3–4	2–4
No. patients	22	6	8	3	18
Grams heart/sq m body surface					
Average	210	234	302	339	322
Range	81–316	212–282	202–395	119–537	200–500
No. patients	17	5	6	3	15

changes when taken in terms of duration of clinical illness. A diffuse, interstitial, predominantly mononuclear cell myocarditis with variable but usually slight focal myocardial necrosis (Fig 1) was associated with a short illness. Subsiding myocarditis, a moderate degree of myocardial hypertrophy and progressive formation of elastic fibers in the thickened endocardium (Fig 2) is seen with illness of several weeks' duration. With prolonged illness of many months duration, the myocarditis is trivial or absent, myocardial hypertrophy is marked and the endocardium is greatly thickened and contains many elastic lamellae (Fig 3) arranged like the elastic tissue of the aorta. Gross examination shows ventricular dilatation at all stages. The gross appearance of the heart in patients with a long clinical illness is quite characteristic (Fig 4). The left ventricle is enormously dilated and hypertrophied. The endocardium is thick and pearly white, especially over the outflow tract. The papillary muscle insertions show a relative displacement toward the base due to proportionately greater dilatation of the apex. The thickened, rolled, free edge of mitral leaflets and the plaque-like thickenings on the atrial endocardium are characteristic changes secondary to mitral regurgitation.

In order to evaluate myocardial hyperplasia as a possible cause of EFE, nuclear density was determined by taking the average count of the number of myocardial nuclei falling within a grid superimposed on five randomly selected representative areas of histologic sections of left ventricular myocardium. The slides were examined and the counts performed at 1200× magnification. When values obtained from 57 patients in the study in whom heart weight was known were compared with values from 204 controls, no significant difference in nuclear densities relative to heart size was observed (Text-fig 3).

Discussion

The study suggests that interstitial myocarditis may be a precursor of idiopathic EFE. Diffuse interstitial myocarditis produces a marked ventricular dilatation. Continuation of the myocarditis and development of relative mitral insufficiency due to the dilatation increases the functional burden on the ventricle. After the myocarditis has largely subsided, marked dilatation persists and produces myocardial hypertrophy, endocardial thickening and alterations secondary to mitral regurgitation (Fig 5). The dilated heart is subject to decompensation. The Starling mechanism is not effective, since the ventricle is already dilated and the myocardium is required to put forth a much greater than normal effort even at rest. The compensatory hypertrophy that develops



TEXT-FIG 3—A log-log graph of myocardial nuclear density and heart weight of 57 patients in the study and 204 controls. The heart grows to about 30 g by increasing the number of cells. Further cardiac growth is accomplished by increasing the size of individual cells but not their number. There are no significant differences in nuclear density as compared to heart weight between patients and controls.

does not correct the loss of cardiac reserve since enlarged myocardial fibers function less efficiently and ventricular dilatation, which is the major abnormality, persists. Further dilatation occurs with increased demands on the heart and leads to more hypertrophy. Eventually all ability to compensate is lost and congestive heart failure becomes continuous and intractable.

The myocarditis observed in these patients corresponds to that described by Fiedler [1] and to the myocarditis seen in demonstrated viral infections. While many viruses may produce a myocarditis as a component of systemic infection, "isolated" myocarditis with little or no findings in other organs is characteristic of Coxsackie B infection.[2,3] Although the clinical and morphologic features of the patients studied are strongly indicative of Coxsackie infection, postmortem viral cultures in 5 patients were negative.

Mitral insufficiency in idiopathic EFE has been demonstrated angiographically and occurred in most of the patients studied.[12] Changes secondary to mitral regurgitation were found in 14 of 22 of the patients in the present series in whom the clinical course was greater than 2 months. Lesions related to mitral insufficiency have been described in idiopathic EFE and have been accorded a role in producing endocardial thickening.[8]

The means by which ventricular dilatation, produced initially by myocarditis and subsequently perpetuated by mitral insufficiency, gives rise to hypertrophy and EFE can be understood in physical terms (Text-fig 4). Hypertrophy is the response to a chronic increase in myocardial effort or "load". The true work of propelling blood, one component of energy expenditure, remains essentially unchanged in EFE.[12] The tension-time integral represents the effort expended to keep the myocardium in a state capable of functioning [13] and is largely dependent on mural tension. Tension in any section of the wall of the ventricle will be approximately proportional to the square of the radius. Dilatation of the ventricular cavity increases tension and, thereby, the load on the myocardium, the major portion of which consists of the tension-time integral even under normal conditions.

EFE has been show to occur in situations in which mural tension is increased.[5,6] In idiopathic EFE, the tension increase is secondary to ventricular dilatation. The apparent time-course of the development of EFE in patients with myocarditis in this series is similar to that occurring in patients with large myocardial infarcts, in whom the exact duration of increased tension could be determined.[6]

A variety of etiologic explanations of idiopathic EFE have been ad-

HYPERTROPHY DEVELOPS WHEN MYOCARDIAL ENERGY EXPENDITURE IS INCREASED

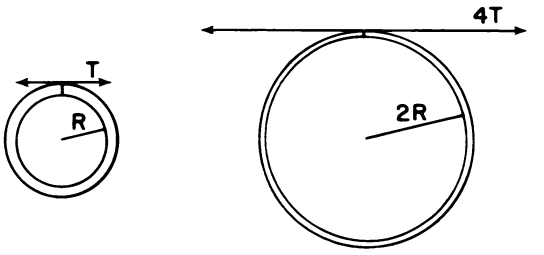
"Load" = Mechanical Work + Tension-time Integral

$$E = \int P_V \, dV + a \int T \, dt$$

FIBROELASTOSIS DEVELOPS WHEN ENDOCARDIAL TENSION IS INCREASED

Tension = Pressure × Area

$$T = P \times \pi R^2$$



TEXT-FIG 4—Physical relationships showing the importance of mural tension (T) in producing myocardial hypertrophy and EFE.

vanced; but consideration need only be given to those that would cause persistent dilatation of the left ventricle. Myocardial hyperplasia, with an excess number of muscle cells per unit of heart, has been held to be the cause of the dilatation.[7] The patients in this study, however, have myocardial nuclear densities characteristic of hypertrophy, not hyperplasia (Text-fig 4). Anoxia is a well-known cause of ventricular dilatation. However, pointed study of patients with idiopathic EFE has shown an increase in myocardial vasculature [14]; as indeed might be expected with the extra energy expenditure required of the myocardium. A metabolic defect in the myocardium, leading to improper function and chamber dilatation, is a possible, but as yet undemonstrated, cause of idiopathic EFE. Two previously described patients [15] included in the present series are siblings, both show idiopathic EFE without myocarditis, and could possibly have a hereditary myocardiopathy. Considerable misunderstanding stems from a failure to separate patients with idiopathic EFE from those with EFE due to aortic valve obstruction or coarctation of the aorta. Both malformations are capable of producing chronic ventricular dilatation and initiating nonspecific reactive changes of myocardial hypertrophy and EFE by the mechanism described.

Round heart disease of turkeys [16] shows a striking parallel to the

natural history of idiopathic EFE proposed in this study. Affected birds have a myocarditis, with demonstrable viral particles, in early life. Surviving turkeys develop marked cardiac dilatation, hypertrophy and EFE.

In conclusion, the findings of this study are consistent with the hypothesis that some cases of idiopathic EFE may be the end stage of a myocarditis. Presumably, treatment of the condition should be directed toward correcting ventricular dilatation during the stages of active myocarditis and to correcting mitral insufficiency, if present, in the later stages. Further studies are needed to determine the frequency with which viral myocarditis ends as idiopathic EFE, the exact etiologic agents involved and whether or not some inherited abnormality of myocardial metabolism may lead to the clinical and pathologic features of idiopathic endocardial fibroelastosis.

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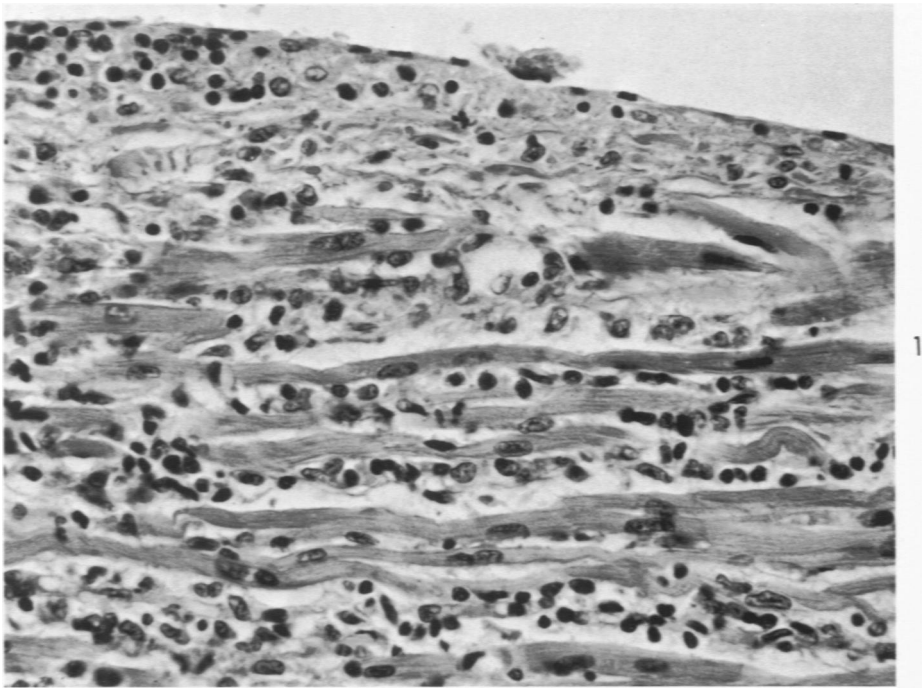


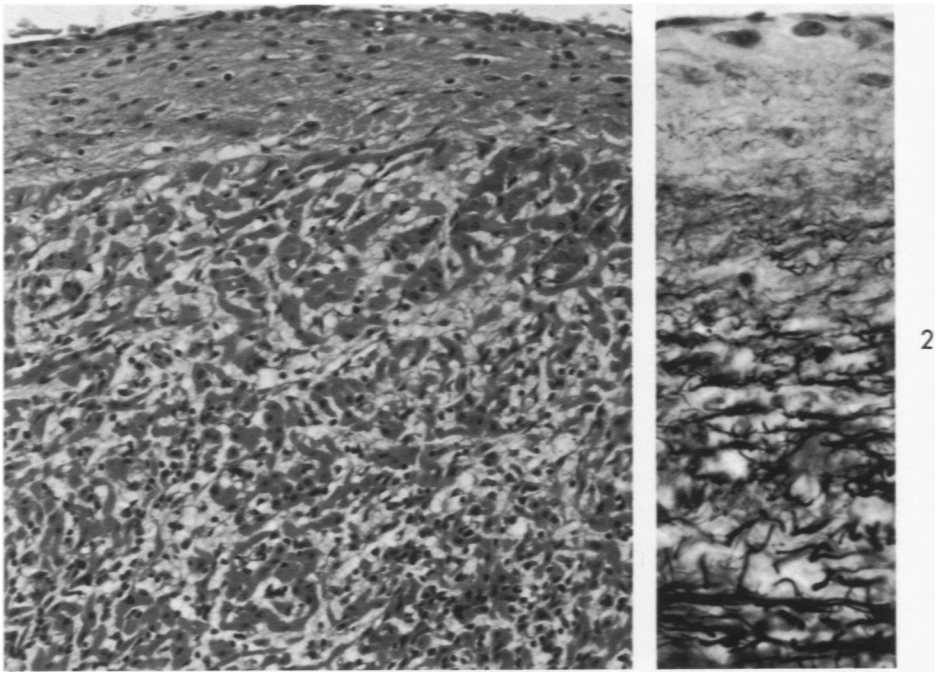
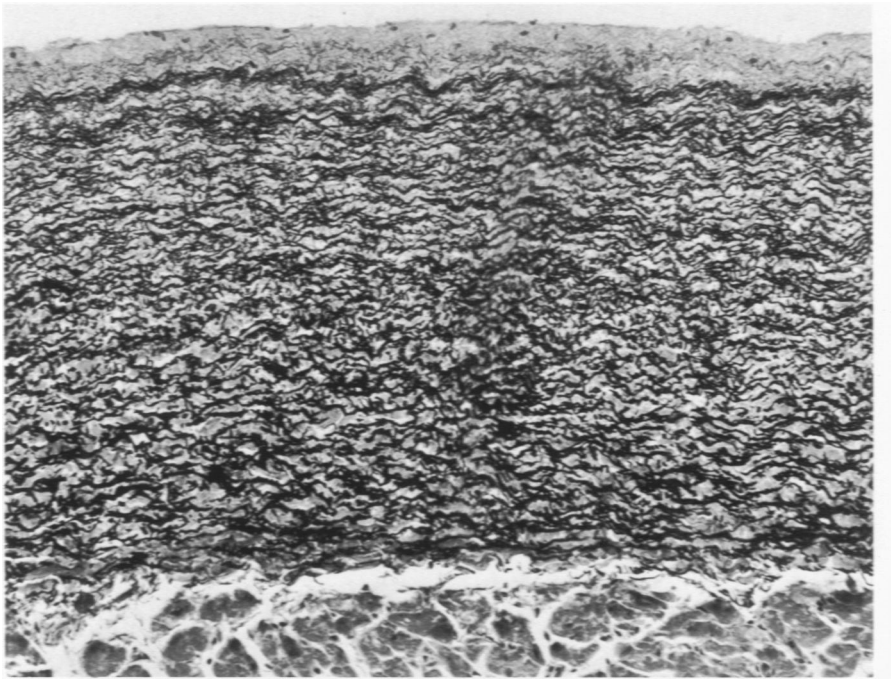


Fig 1—Severe diffuse interstitial predominantly mononuclear cell myocarditis (grade 4+). The endocardium has a focal infiltrate but is of normal thickness. Occasional single muscle fibers are necrotic (H&E, × 420). **Fig 2**—*Left:* Residual interstitial myocarditis (grade 3+) and endocardial thickening (grade 3+) (H&E, × 195). *Right:* Newly formed elastic fibers in the thickened endocardium (VvG, × 500).

Fig 3—Mature stage of EFE (grade 4+) with a markedly thickened endocardium containing elastic lamellae in a pattern similar to the aorta. The myocardium is markedly hypertrophied (H&E, × 420). **Fig 4**—Typical idiopathic EFE (grade 4+) with marked ventricular dilatation and hypertrophy, diffuse EFE, thickening and rolling of the free edge of the anterior mitral leaflet, and endocardial plaques on the left atrium and the posterior mitral leaflet. The two latter changes are secondary to mitral regurgitation.



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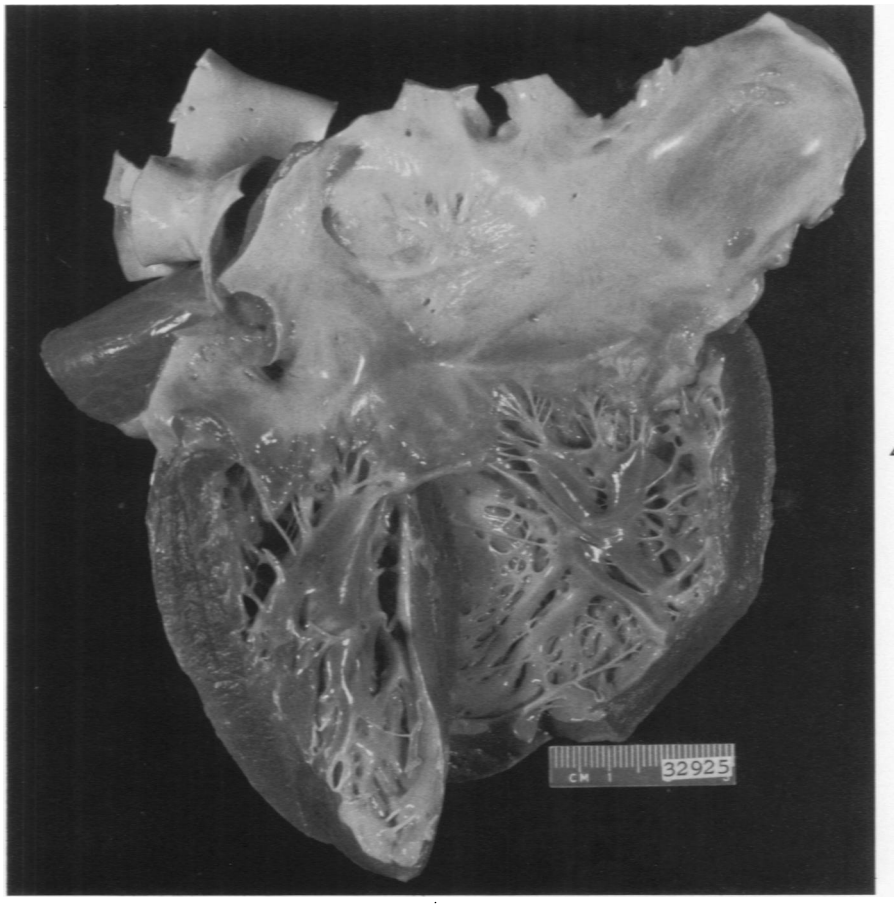

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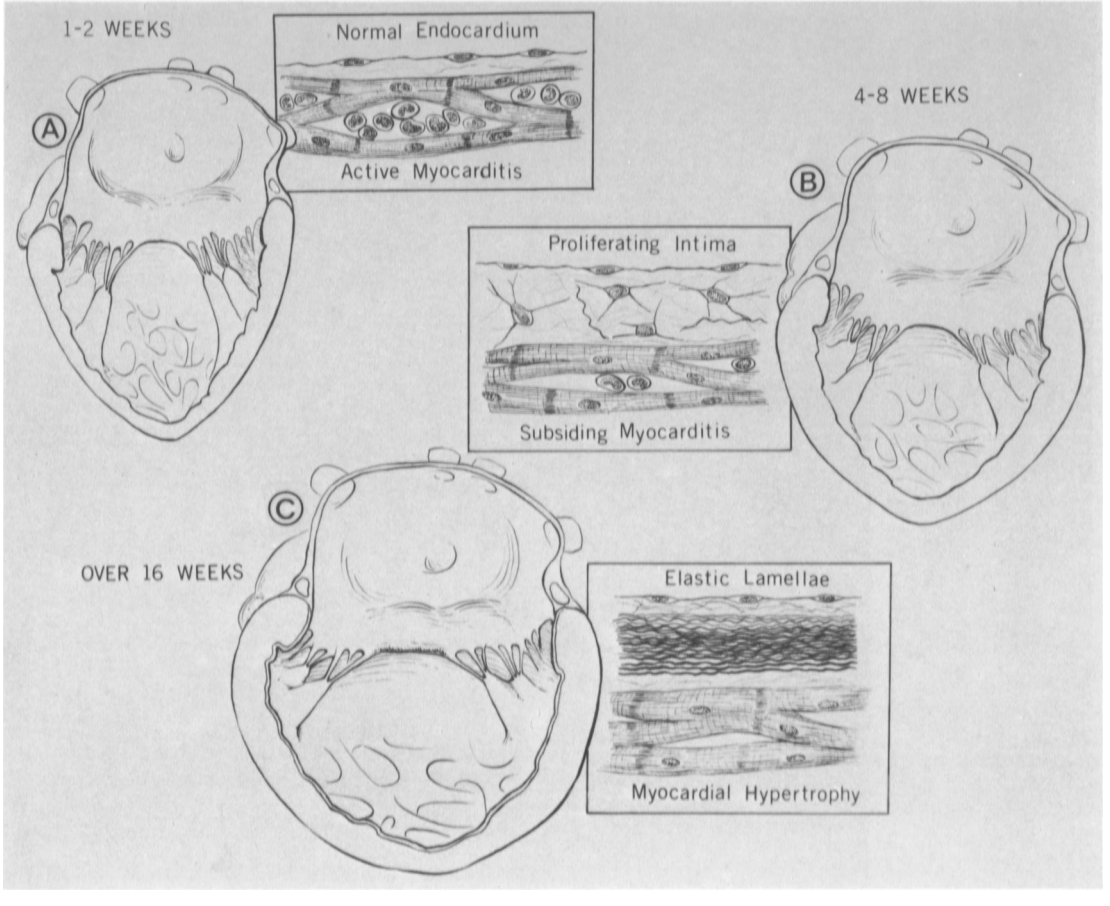

Fig 5—The progression of (**A**) active myocarditis with ventricular dilatation to (**B**) subsiding myocarditis and beginning EFE to (**C**) marked dilatation, hypertrophy, EFE and mitral insufficiency secondary to displacement of papillary muscle and dilatation of valve rings.