# Studies in Rheumatic Fever

## *VI. Ultrastructure of Chronic Rheumatic Heart Disease*

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**The fine structure alterations in the atrium and atrial appendage, mitral valve and papillary muscle are described in 11 matched patients with chronic rheumatic heart disease. The muscle changes consisted of loss of myofilaments and accumulation of lipid and osmiophilic dense bodies. The connective tissue stroma of the atrium and the mitral valve showed extensive deposition of collagen and elastic fibers. There were numerous foci of collagen degeneration, characterized by fraying of the collagen fibers and accumulation of homogeneous granular material at these sites. Although the muscle changes were more striking, the connective tissue alterations appear important in the evolution of the chronic disease. The extent of collagen degeneration appeared to parallel the degree of collagen formation. The muscle fiber degeneration and connective tissue alterations did not correlate with the clinical findings. At the resolution of the electron microscope, the continuing process in the rheumatic heart appears to be primarily collagen formation and degradation rather than primary degeneration of the muscle fibers. It is the balance of these processes which determine the clinical state of the patient. Acute muscle damage along with evidence of inflammation do not seem to be associated with progressive, chronic rheumatic heart disease (Am J Pathol 73:623–640, 1973).**

RHEUMATIC CARDITIS characterized by the Aschoff body is a presumed disease of the cardiac connective tissue in which the chronic changes are frequently valvular fibrosis and myocardial scarring. The fine structure of the tissue changes in subclinical chronic rheumatic heart disease has not been characterized in detail, in spite of the obvious relevance of these changes to the presumed pathogenesis. The most extensive electron microscopic observations of rheumatic heart disease were published by Lannigan and Zaki.[1] Their study, however, was primarily concerned with the ultrastructure of the Aschoff body in the surgically removed atrial appendage. Although they carefully noted the fine structural changes of the stroma, myocardium and endocardium surrounding the Aschoff bodies, no attempt was made to describe these alterations throughout the atrial appendage. Hartman *et al*[2] noted an increase

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of collagen and packing of the collagen fibers in their electron microscopic study of the rheumatic mitral valve. However, because of technical difficulties encountered in sectioning the material, they were unable to further characterize these changes. More recently, Malinovsky *et al*[3] have described the ultrastructural changes of the ventricular myocardium of patients with rheumatic heart disease.

Laufer *et al*[4] studied biopsies obtained from the atrium, papillary muscle, left ventricule and mitral valve of patients with and without rheumatic disease. Using light and electron microscopy and immunofluorescence, they attempted to correlate morphologic findings with the clinical and functional state of the myocardium and valves. A total of 25 cases, clinically diagnosed as mitral valvular disease, presumably of rheumatic origin, were studied. These workers concluded that no histologic signs of rheumatic activity were observed, but no mention is made of Anitschkow cell activity. In addition, they state that no specific diagnostic electron microscopic findings in the myofibers were present, although they noted increased fat droplets, focal increase in glycogen, and focal muscle disruption and necrosis. Laufer *et al*[4] regard the presence of small myocardial scars and increased interstitial collagen as the major factors in determining myocardium function.

Because of the difficulties encountered in studying random clinical cases of mitral valve disease where antecedant rheumatic carditis is presumed, we deliberately selected our case material. Hopefully, a significant number of variables would be controlled and thus render the structural findings more significant. The purpose of this paper is to present the ultrastructural aspects of established chronic rheumatic mitral stenosis in cases closely matched for history, age, sex and major clinical findings. Attention is also directed to the presence and activity of Anitschkow cells and the nature of the stromal collagen.

## Materials and Methods

Patients were selected from a large group with surgically treated rheumatic mitral valvular disease. A total of 11 patients were matched on the following basis: age, sex, proven or known attacks of rheumatic fever, 30- to 40-year "duration" prior to surgery, development of mild to moderate congestive failure treated successfully by a medical regimen, atrial fibrillation of mild to moderate degree controlled by drugs and moderate to severe mitral stenosis with mild to moderate left atrial enlargement (Table 1).

All patients were considered surgical successes and are still alive 5 or more years following mitral valve replacement. None of the patients developed postoperative problems that could be considered as "rheumatic" activity.

Table 1—Clinical Findings

| Patient | Age/sex | Rheumatic attacks* (age in yrs) | Congestive failure† | Response to treatment‡ | Atrial fibrillation§ | Est total Duration (yrs)‖ | Mitral stenosis¶ | Left atrial enlargement** |
|---|---|---|---|---|---|---|---|---|
| DB | 45 M | 6, 14 | + | Good | Mild | 39 | +++ | Mod |
| AC | 48 M | 6, 12 | ++ | Good | Mild | 36 | ++ | Mild |
| JF | 46 M | 8, 11, 18 (?) | + | Good | Mod | 38 | +++ | Mod |
| RG | 49 M | 6 (?), 10, 14 | ++ | Exc | Mild | 43 | +++ | Mod |
| FM | 44 M | 10, 11, 16 | + | Good | Mild | 34 | ++ | Mod |
| RT | 46 M | 6, 9, 10 | + | Exc | Mild | 40 | +++ | Mild |
| HR | 42 M | 8, 12 (?), 17 | ++ | Exc | Mod | 34 | ++ | Mod |
| LT | 48 M | 7, 12, 20 (?) | ++ | Good | Mild | 41 | ++ | Mod |
| LW | 47 M | 11, 14 | + | Exc | Mild | 36 | ++ | Mod |
| RY | 44 M | 7, 15 | + | Good | Mild | 37 | ++ | Mild |
| MZ | 49 M | 9, 14 | ++ | Good | Mild | 40 | +++ | Mod |

* Age at time diagnosis of acute rheumatic fever and/or carditis established by clinical and laboratory tests; (?) indicates clinical data only

† Rated from + to ++++ on the basis of venous pressure, clinical and laboratory data, before treatment

‡ Rated as poor, fair, good and excellent

§ Mild (ventricular rate 60–100), moderate (ventricular rate 100–120)

‖ Time period between first attack and surgery

¶ Range from + (mild stenosis, fibrotic valve) to ++++ (severe stenosis, calcific valve)

** Determined at time of surgery, mild or moderate

At the time of surgery, biopsies were taken from the left auricular appendage, left atrium at its junction with the appendage, the anterior leaflet of the mitral valve and the anterior papillary muscle.

Control tissues from nonrheumatic patients also undergoing cardiac surgery were difficult to obtain. Therefore, we limited our study to an intragroup analysis. The biopsies were immediately cut into small blocks and fixed in 3% phosphate-buffered glutaraldehyde (pH 7.4). After fixation for 3 hours the blocks were oriented under a dissecting microscope, retrimmed, postfixed in 1.5% phosphate-buffered osmium tetroxide, dehydrated in graded alcohols and embedded Epon 812. Sections were cut with a diamond knife on a Reichert automatic microtome, stained with 2% uranyl acetate in 95% ethanol and lead citrate [5] and examined under an Hitachi 11A electron microscope at 75kV.

## Results

The fine structure of normal human atrial muscle has been reported;[6] however, no detailed studies similar to that of cat atrial muscle [7] are available. It is the consensus of most authors that the fine structure of atrial muscle is comparable between larger mammals including man.[8–10] In contrast, the fine structure of normal human ventricular myocardium has been studied in detail.[11,12]

### Left Atrial Appendage and Atrium

The most striking changes were in the atrial muscle fibers. In fibers from both the atrial appendage and the atrium, varying degrees of loss of myofilaments (Figure 1), as compared to normal atrial muscle, were noted. The apparent loss of myofilaments was more extensive than the normal sectioning artifacts seen in atrial muscle (myofibrils often appear to run in and out of the plane of section). Although some edema fluid was present, this was not secondary to congestive heart failure, since none of these patients were in congestive failure at the time of surgery; nor was it secondary to cardiac bypass, since acute cardiac edema is characterized by the accumulation of fluid between myofibrils.[13] Here, in areas of myofilament loss there was an increase in glycogen and an aggregation or apparent increase in the number of mitochondria. The mitochondria were smaller than normal but were otherwise unremarkable. Scattered lipid droplets as well as osmiophilic dense bodies, lipochrome granules and occasional myelin figures were noted in the sarcoplasm and occasionally in mitochrondria. The number of these structures was directly related to the degree of myofilament loss. In approximately one-third of the specimens there was either generalized or focal extensive myofilament loss. In these areas, aggregates of remaining filaments were occasionally arranged in a pattern reminiscent of smooth muscle myofibrils (Figure 2), and structures re-

sembling spindle-shaped densities were seen. At higher magnification, however, these supposed spindle-shaped densities have a periodicity and lattice-work arrangement suggestive of Z band material. The arrangement of this Z-band-like material and its frequent association with lipid droplets and myelin figures suggest that it is residual tropomyosin from degenerate Z bands. In 2 of the patients, focal areas of true Z band thickening were noted in the muscle of both the atrium and the atrial appendage (Figure 3).

The nuclei of many of the muscle fibers were irregular, with deep invaginations of the nuclear membrane; the chromatin was often clumped against this folded membrane. The sarcotubular system, as well as the sarcoplasmic reticulum, was generally dilated. This was most prominent in areas of extensive myofilament loss where aggregation of both sarcotubular system and sarcoplasmic reticulum was prominent. Nuclear membrane invaginations, chromatin clumping, sarcotubular dilatation and dilatation of the sarcoplasmic reticulum are normal in contracted cardiac muscle. All of our material was fixed in the contracted state. However, these features were more prominent in areas of extensive myofilament damage than is noted in contracted normal atrial muscle. The sarcolemma and intercalated discs were normal appearing in all specimens.

Throughout the interstitium there was a moderate to marked increase of collagen and elastic fibers (Figure 4). Focal areas of collagen fraying and fragmentation, and granular degeneration of collagen were noted. Neither of these changes, however, appeared to correlate with the degree of myofilament loss. The fibroblasts contained vacuoles, phagosomes, osmiophilic dense bodies and scattered myelin figures. These degenerative fibroblast changes were most prominent in cases of extensive collagen fraying. In other fibroblasts there was an increase of rough endoplasmic reticulum and collections of nonbanded fibrils (50 to 70 Å) in the extracellular space around the fibroblasts. Anitschkow cells [14,15] were prominent throughout the interstitium in all cases. Only scattered Anitschkow cells, however had the characteristic serrated (owl's-eye) nucleus. Within their cytoplasm were scattered vacuoles and osmiophilic dense bodies which were again more prominent in cases with extensive collagen fraying. The Anitschkow cells were most prominent around small blood vessels. The capillaries were surrounded by one or two such cells, while the larger vessels, those with a layer of smooth muscle, were often ringed by numerous Anitschkow cells. However, no Aschoff bodies were found. The endothelial cells lining

the capillaries were often vacuolated and occasional osmiophilic dense bodies and myelin figures were found in the cytoplasm. Their tight junctional complexes were intact and no thickening of the basal lamina was noted (Figure 5).

Similar changes were noted in the endocardial cells. Here, again, the tight junctional complexes were intact and no thickening of the basal lamina was noted. As in the capillary endothelium, microvilli were numerous. The smooth muscle cells of the subendocardium were numerous and prominent. These cells also contained scattered osmiophilic dense bodies and myelin figures. In addition, there was a moderate increase of collagen and elastic fibers in the subendocardium, which was most marked in cases with extensive stromal collagen increase.

#### Mitral Valve

Throughout all the specimens examined, there was a complete loss of distinction between spongiosa and fibrosa. The entire thickness of the valve leaflets was replaced by densely packed collagen fibers and elastic fibers (Figure 6). In many areas the collagen was frayed and fragmented, and the fibers were haphazardly arranged (Figure 7). Filamentous material was noted between collagen fibers, and the collagen fibers were often separated by collections of homogeneous material surrounded by electron-dense granules. Interpretation of these findings was complicated by precipitation of stain, presumably lead, in our material. We were unable to avoid this artifact in areas of extensive collagen damage. Nevertheless, in view of previous work [16,17] on experimental collagen damage, the changes described are significant, and true electron-dense beading is present along collagen fibers and surrounding collections of degenerated collagen. It should be emphasized that in areas of sustained and continuous collagen damage it is difficult to prevent artifactual precipitation of lead stain.

Areas of granular degeneration of collagen were also noted. In many areas the intact collagen fibers appear to end in this homogeneous or granular material, suggesting that it might be a collagen breakdown product. In other areas there were collections of osmiophilic dense bodies, myelin figures and fragmented mitochondria trapped between separated collagen fibers. Numerous fibroblasts and Anitschkow cells were found entrapped in the dense collagen. Many of these cells had osmiophilic dense bodies, vacuoles and even myelin figures in their cytoplasm. Again, scattered fibroblasts contained in-

creased amounts of rough endoplasmic reticulum and were surrounded by fine fibrils lacking any periodicity. The muscle in the valve resembled that of the atrium and atrial appendage. The spectrum of changes seen in the atrial muscle was reproduced in each valve in which muscle was observed. Some muscle fibers showed extensive loss of myofilaments, while adjacent fibers showed only minimal myofilament loss. Small vessels were noted between muscle fibers and in the dense collagen of the valve. As in the atrium, these vessels were ringed by Anitschkow cells (Figure 5). The cell junctions of the endocardial cells, both ventricular and atrial, were tightly closed, although numerous large vacuoles and clustered micropinocytotic vesicles were prominent. Numerous smooth muscle cells were noted beneath the endocardial cells and throughout the valve leaflet. These cells also contained scattered osmiophilic dense bodies and myelin figures.

#### Papillary Muscle

The normal perinuclear zone of accumulation of glycogen and mitochondria was exaggerated and occasionally contained degenerating myofibrils. Only scattered foci of myofilament loss and degeneration were noted throughout the remainder of the muscle fiber. In the cytoplasm there were scattered osmiophilic dense bodies and lipid droplets. Dilatation of the sarcotubular system and Z band thickening, noted in the atrial muscle, were also present, although infrequent.

Throughout the interstitium there was a slight to moderate increase in collagen and elastic fibers. No fraying or dissolution of the collagen fibers was noted. Fibroblasts and Anitschkow cells were prominent and scattered myelin figures and osmiophilic dense bodies were noted in their cytoplasm. The Anitschkow cells were arranged around scattered blood vessels but this was not as prominent nor as consistent as in the atrium or mitral valve. The capillary endothelium appeared normal and no thickening of the basal lamina was noted.

## Discussion

In this small carefully selected series of rheumatic patients, we could find no significant correlation between the ultrastructural changes and the clinical findings. The age of the patient, duration of disease, presence of atrial fibrillation all appeared unrelated to either the extent of myofilament loss or interstitial fibrosis. Similarly,

the clinical degree of cardiomegaly and pulmonary hypertension, present in varying degrees in all patients, appeared unrelated to the ultrastructural changes. Malinovsky *et al*[3] noted that the ultrastructural changes in the myocardium in patients with rheumatic heart disease appeared unrelated to the clinical findings. Laufer *et al*[4] also observed a variety of nonspecific changes.

The most dramatic changes were noted in the atrial appendage and left atrium. Here the extent of myofilament loss and degeneration appeared independent of the degree of fibrosis of the interstitium and the extent of collagen and fibroblast degeneration. Many patients with extensive myofilament loss had only moderate interstitial fibrosis. These observations may be due to the limited sampling technic. The presence and extent of accumulation of lipid droplets, osmiophilic dense bodies and myelin figures in muscle fibers appeared to be directly proportional, however, to the degree of myofilament loss. Similarly, the extent of collagen fraying and accumulation of granular material in the ground substance appeared to correlate with the degree of interstitial fibrosis. The ultrastructural changes in the mitral valve leaflets and the papillary muscles were remarkably uniform, irrespective of the clinical findings, the degree of mitral stenosis or the ultrastructural changes in the atrial appendage or atrium.

The fine structural changes in the muscle fibers of the atrium, atrial appendage and papillary muscle appear static in character. No acute changes such as smudging of myofilaments, vacuolation of mitochondria or disruption of the sarcolemma were noted. Deep infoldings of the sarcolemma and extrusion of the contents of the myofibers into the interstitium, reported by Lannigan and Zaki,[1] were not seen. The loss of myofilaments and the presence of degenerative by-products in the muscle fibers were interpreted as evidence of chronic or obsolete muscle damage. True Z-band proliferations, although present, were too infrequent to speculate on their possible significance.[18,19]

The fraying and fragmentation of collagen in the interstitial areas of the atrium, atrial appendage and papillary muscle and in the mitral valve were interpreted as evidence of continuing connective tissue remodeling of the stroma. Similar changes have been reported in ruptured chordae tendineae.[20,21] When collagen is subjected to collagenase,[16] accumulations of homogeneous material, fraying and fragmentation of the collagen, filamentous structures and electron-dense globules attached to the A-band area of intact collagen

fibers were noted. Immune-mediated collagen damage[16] also produced collagen fraying, although not as dramatically as enzymatic digestion.

Many of these criteria appear to be present in our material. In addition, in areas of collagen breakdown, there also was evidence of collagen formation similar to that of wound healing.[22] Mohos and Wagner[16] noted similar areas of presumptive collagen formation surrounding areas of both enzymatic and immune damage to collagen. These observations, although indicative of collagen damage, are not specific. Recently, Kaplan and Clemente[23] have demonstrated antibodies specifically directed against valvular fibroblasts in 93% of patients with acute rheumatic fever and in 30% of patients with inactive rheumatic heart disease. The significance of this finding is not clear, but it appears to suggest a possible immunologic mechanism for the valvular fibrosis of chronic rheumatic heart disease.

Recent electron microscopic studies[17] of collagen fibril depolymerization confirm previously reported experimental and human data. These workers demonstrated that depolymerization of the fibrils over the pH range 3.5 to 7.5 was associated with cleavage of the fibrils into short segments. This was followed by unwinding of the protofibrils and cleavage into protofibrillar particles. Polymeric collagen fibrils obtained from human ischemic skin exhibited a similar fragmentation pattern. Thus, it would now seem possible on the basis of detailed *in vitro* and *in vivo* experimental observations to determine by electron microscopic studies the integrity of collagen in disease states.

Although no Aschoff bodies were found, many perivascular collections of Anitschkow cells were seen. Around the larger vessels these cells were arranged in concentric rings. True vascular thickening could not be determined. None of the other stigmata of Aschoff bodies[24] were associated with these collections of Anitschkow cells. Saphir[24] stated that many so-called Aschoff bodies noted in the atrial appendages of patients undergoing mitral valvular surgery did not fulfill the histologic criteria of the Aschoff body. By light microscopy, the collections of Anitschkow cells noted in this report could easily be confused with Aschoff bodies and have been reported as Aschoff-like bodies.[14] This in no way implies that true Aschoff bodies cannot be found in the atrial appendages of patients with chronic rheumatic heart disease. In fact, Lannigan and Zaki[1] have described

the ultrastructure of lesions from such atrial appendages which fulfill all the criteria of the Aschoff body.

The most significant changes in chronic rheumatic heart disease appear to be progressive interstitial and valvular fibrosis associated with loss of muscle cells. Whether these two processes share a common stimulus is unknown. The continuing process in the rheumatic heart is myofiber damage with ultimate loss of structure and function. In parallel with these changes, there is apparent collapse and condensation of the preexisting stroma. Collagen is remodeled so that synthesis and breakdown of collagen fibers may be observed. Since the muscle changes are subtle, of long duration and not related to inflammation, several hypotheses exist.

One hypothesis suggests that, once set in motion by the original insult, progressive myosclerosis follows as a subclinical process. This would be similar to the progressive subclinical hepatic sclerosis that may follow heptatitis. Such continuing processes may be due to immunologic phenomena, as in autoimmune responses. A second hypothesis advocates that the rheumatic patient is genetically susceptible to toxic bacterial products, especially those derived from group A β-hemolytic streptococci. Repeated exposure to cardiotoxic agents may sustain the myodegenerative processes. Finally, hemodynamic alterations in themselves may be responsible for the evolving pattern of the cardiac pathology. It may well be that all of these hypotheses are operative in sequence or simultaneously.

Previous studies[25–29] have established the primacy of connective tissue damages as the earliest recognizable structural alteration in acute rheumatic carditis. Acute rheumatic inflammation shows that the Aschoff body evolves as a response to the focal fibrinoid changes in the connective tissue ground substance.[25,27,28] Anitschkow cells, unique cardiac histiocytes, appear; some transform into typical Aschoff cells. Thus, Anitschkow cells may reflect a low-level continuing stimulus.

These observations would appear to be at variance with the extensive and detailed studies of Murphy.[30,31] However, Murphy's studies were primarily based on light microscopic evaluations of human and animal cardiac tissue. The assumption was made that the Aschoff cell was derived from injured cardiac myofibers and smooth muscle. This hypothesis advocated at least two kinds of Aschoff bodies. While attractive in concept, the hypothesis did not explain the presence of Aschoff bodies in areas devoid of all muscle elements, the histochemical characteristics of the Aschoff body, the

electron microscopic demonstration of Anitschkow cells as a separate identifiable cell system and the need to postulate two mechanisms for evolution of the Aschoff body.

Our investigations have demonstrated that because of the close topographic relationship of Anitschkow cells to the myofiber, in areas of focal damage, it is often difficult if not impossible to resolve the cellular events with the resolution of the light microscope. It is possible then, to visualize what appears to be Anitschkow cells arising from cardiac myofibers and smooth muscle. With the resolution of the electron microscope, the nuclei of damaged striated and smooth muscle cells in the heart develop chromatin patterns similar to the Anitschkow cell.[14] However, Murphy's studies have served to clarify the range of muscle cellular alterations in rheumatic heart disease.[30,31]

The ultimate fate of the Aschoff body is loss of all cellular elements with replacement by dense collagen.[29] Perivascular scars may be the only residual evidence of previous rheumatic carditis. However, acute rheumatic carditis is also associated with a toxic myocarditis and it is this latter process that accounts for fatality. The end-result of myocarditis is healing by fibrosis. Thus, the patients with chronic rheumatic heart disease may be in a static or stable equilibrium with all of these on-going processes. At the time of surgery, these patients represent end-stage cardiac disease.

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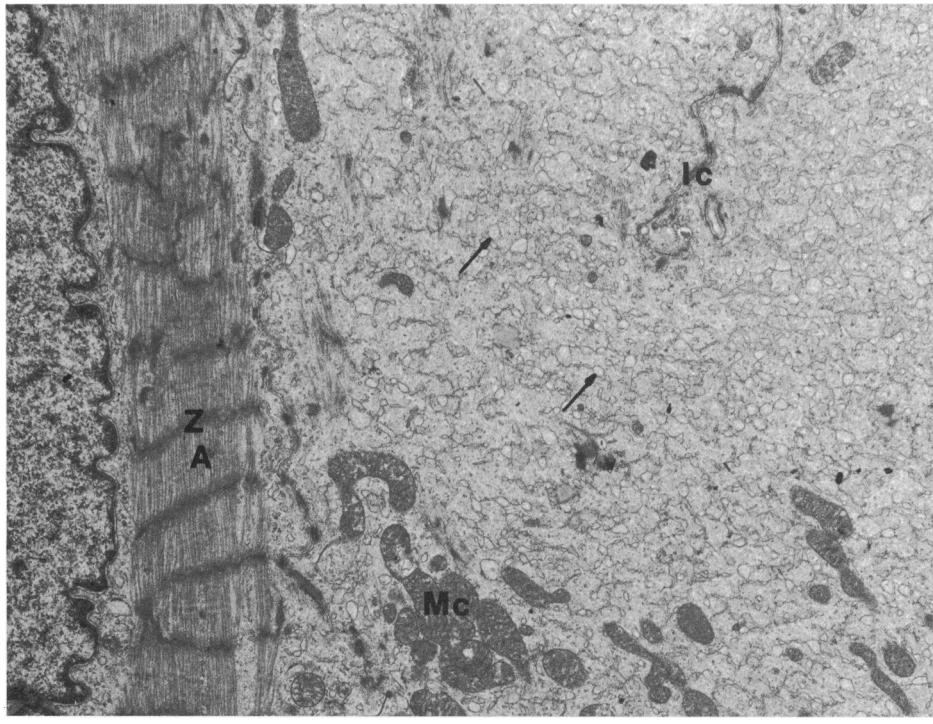
## Legends for Figures

**Fig 1**—Portion of a muscle fiber from the left atrial appendage in which there is diffuse loss of myofilaments. The myofilaments in the remaining sarcomeres appear normal; Z (*Z*) and A (*A*) bands are distinct. In areas of myofilament loss there are collections of mitochondria (*Mc*), and the sarcotubular system is condensed and dilated. A portion of an intercalated disc (*Ic*) is present (× 7500).

**Fig 2**—An area of extensive myofilament loss in a muscle fiber from the left atrium. In the remaining sarcomeres (*M*) there is slight thinning of the myofilaments, but the Z bands and A bands are distinct. The area of extensive myofilament loss is filled with mitochondria (*Mc*) and glycogen (*G*). In the center of this area the remaining myofilaments resemble smooth muscle filaments (*SM*) with spindle-shaped densities (*arrows*) which have a crystalline appearance resembling Z-band material (× 7500).

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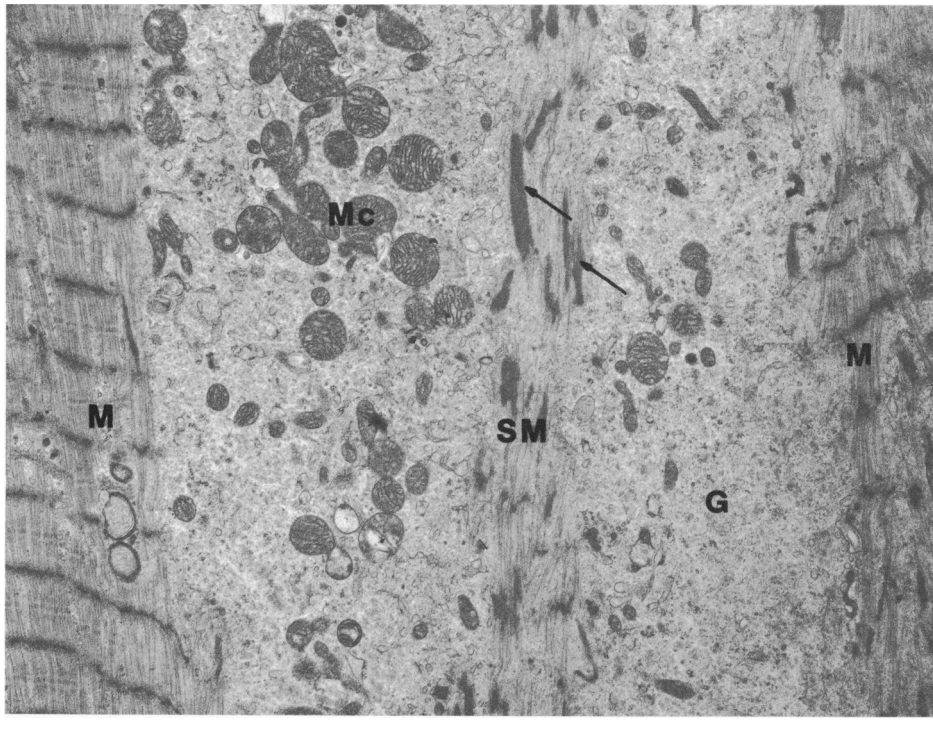


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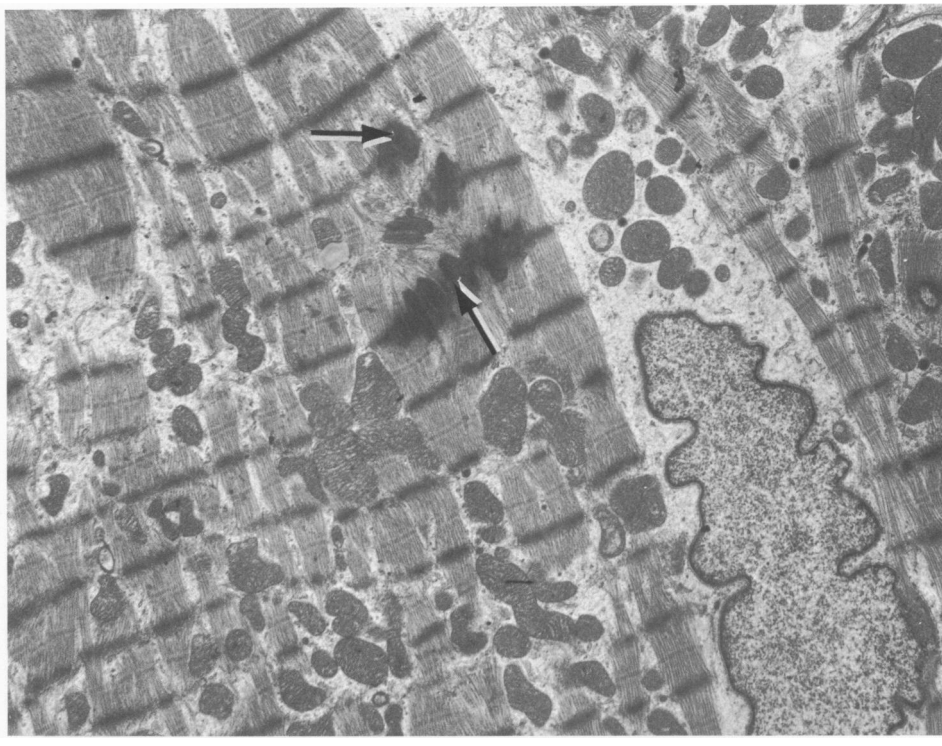

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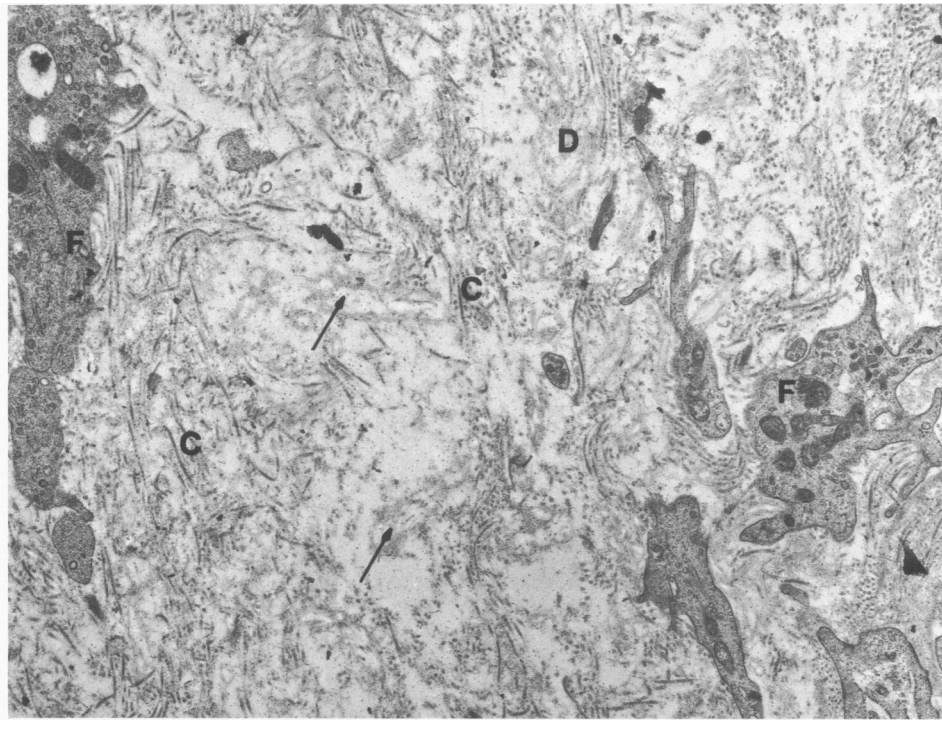
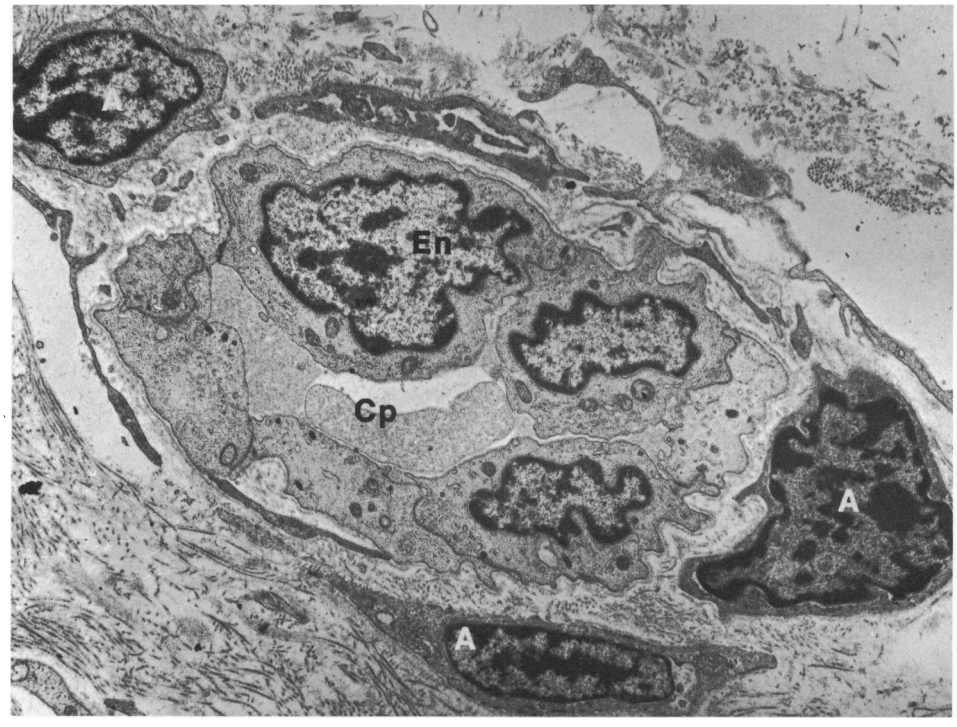



**Fig 3**—Focal Z-band thickening (*arrows*) in myofiber from the left atrium. The remainder of the myofiber is normal in appearance (× 7500). **Fig 4**—In the interstitial areas of the left atrium there is a diffuse increase of collagen (*C*) and elastic fibers (*arrows*). Areas suggestive of collagen fraying (*D*) are evident even at this low power. The entrapped fibroblasts (*F*) are normal in this area (× 7500).

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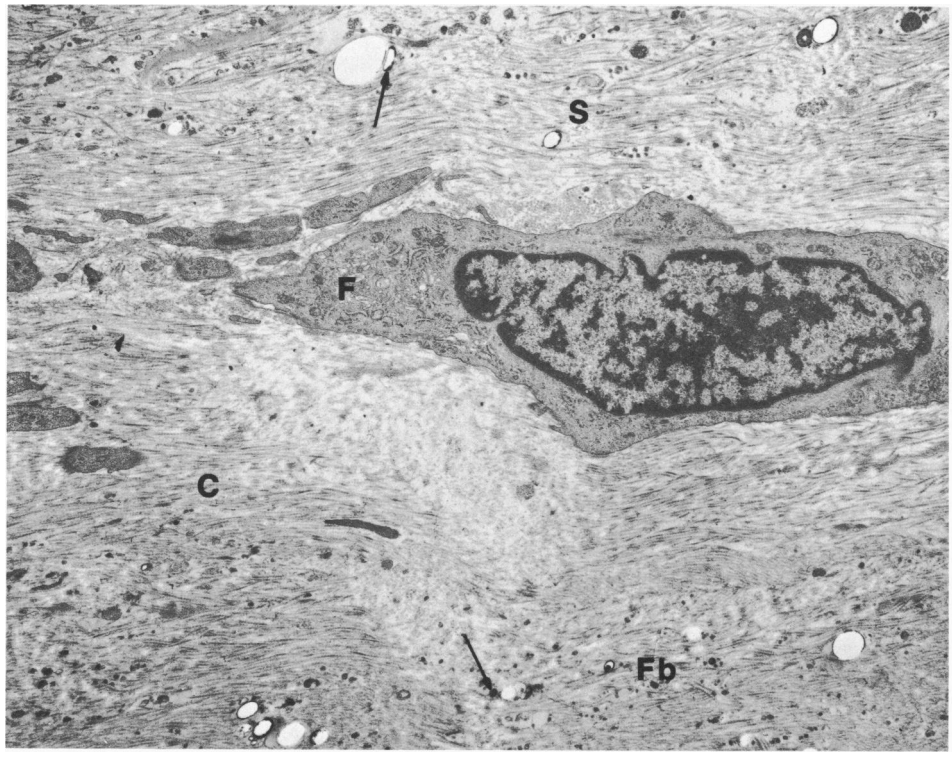


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**Fig 5**—Collections of Anitschkow cells (*A*) are prominent around capillaries (*Cp*), especially in the mitral valve. The endothelial cells (*En*) have tight junctional complexes and prominent micropinocytotic vesicles (× 6250). **Fig 6**—In the mitral valve the distinction between spongiosa (*S*) and fibrosa (*Fb*) is blurred. The valve is composed of dense collagen (*C*) and elastic fibers within which are trapped fibroblasts (*F*). Between the collagen fibers are dense bodies (*arrows*) and vacuoles which represent foci of calcification (× 7500).

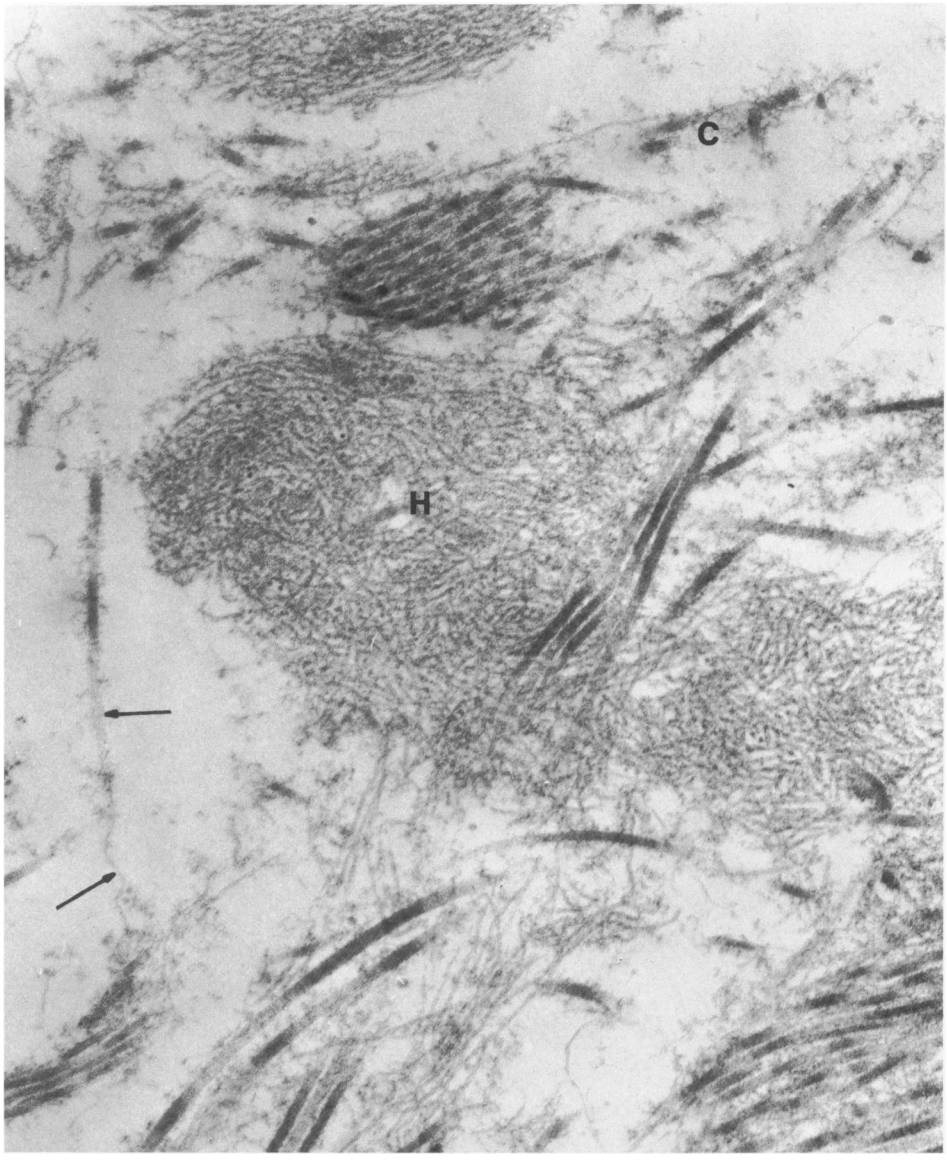


**Fig 7**—At higher magnification, the collagen fibers in the mitral valve leaflet are focally fragmented (*C*) and frayed (*arrows*). Accumulations of fibrillar material (*H*) lie between the collagen fibers (× 63,000).