

EVIDENCE THAT ASCHOFF BODIES OF RHEUMATIC MYOCARDITIS DEVELOP FROM INJURED MYOFIBERS

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That myocardial Aschoff bodies represent one of the most characteristic of all tissue reactions to rheumatic fever injury has long been recognized. Accumulated evidence indicates that certain of these lesions are probably peculiar to the heart disease of active rheumatic fever and of some cases diagnosed as rheumatoid arthritis. But the question of precisely which cardiac tissue elements undergo primary injury during the initial stages in the evolution of these myocardial Aschoff bodies has not been conclusively answered. Moreover, the origin of the large basophilic structural elements that are particularly characteristic of these lesions remains to be established. Since Aschoff's description of the lesions bearing his name (1) the now generally accepted theory has been steadily developed that interstitial non-myogenic collagen is the site of primary injury, and that damaged interstitial collagen fibers are the earliest recognizable lesions in the evolution of all myocardial Aschoff bodies. In these lesions the peculiar large basophilic structures, whether mono-, multi-, or non-nucleated, are generally believed to arise from undifferentiated and non-myogenic mesenchymal elements that proliferate in response to that interstitial collagen injury.

The purpose of this communication is to present data which show that many myocardial Aschoff bodies evolve from focal injury to cardiac myofibers. These data were obtained from lesions of the Aschoff body type that were induced in a very few among many rabbits repeatedly infected with group A streptococci (2, 3), and from myocardial Aschoff bodies in several subjects who succumbed to rheumatic fever.

Materials and Methods

Details concerning the group A streptococci employed, the techniques used to induce the experimental lesions of rheumatic type, and to prepare them for microscopic study, and extensive illustrated comparisons of the close structural similarity of these lesions with those in human rheumatic fever were presented in previous communications (2, 3).

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The experimental material here presented is from the hearts of 3 rabbits, respectively 5, 13, and 22 months of age. One developed a fatal illness terminating 8 days after the last of several cutaneous streptococcal infections, but had no demonstrable bacteriemia either ante- or postmortem; the others were sacrificed while sick 10 and 15 days respectively following the last infection; their autopsy blood cultures were negative. Careful microscopic examination of many sections stained to demonstrate bacteria, especially streptococci, revealed none in these lesions. The human hearts were from 12 patients, ranging from 1 to 19 years of age, who died during the first or second recognized attacks of active rheumatic fever. The duration of the fatal attack was apparently not longer than 6 weeks in the majority of these patients. They were selected from many fatal cases of rheumatic fever that were studied at the New York Hospital, Babies Hospital, and the Hospital of the Rockefeller Institute in New York City, and include one patient from the Johns Hopkins Hospital. Skeletal muscle from a 6½ year old child, who died with rheumatic fever at the Babies Hospital, was also studied. Sub-acute bacterial endocarditis was not present in any of these patients; and no microorganisms could be found in the cardiac or skeletal muscle studied.

The comparative procedure previously employed (3) to demonstrate the close structural similarity of the experimentally induced myocardial lesions and those of human subjects with active rheumatic fever is utilized in the present communication.

RESULTS

By study of the lesions of myocardial Aschoff body type found in the very small proportion of the many rabbits infected as above described, the following was usually demonstrated in these lesions: (a) The earliest visible and the principal lesions appear to be in myofibers; (b) The basophilic mono-, multi-, or non-nucleated structures at times appear clearly to be of myogenic origin; the basophilic cytoplasm of these structures sometimes represents sarcoplasm of damaged myofibers and at other times the cytoplasm of syncytial myogenic cell masses that occasionally give evidence of attempts at myofiber regeneration. When these lesions are stained with hematoxylin and eosin, fragments of disintegrating myofibers may be mistaken for fragments of swollen or fibrinoid collagen. As the stage of muscle fiber injury passes into one chiefly of healing it appears in some instances that the sites formerly occupied by myofibers or their fragments are replaced by newly formed collagen.

These findings in the experimentally induced lesions logically called for a reinvestigation of the Aschoff bodies that develop in the human myocardium and suggested that a study of them in their early stages might be essential to separating the histopathological features that follow immediately the rheumatic fever injury from those that result from a healing process in which new collagen fibers develop. Indeed, in the hearts studied minutely from 12 patients who died from active rheumatic fever a large proportion of myocardial Aschoff bodies, in their early stages, were demonstrated to originate in myofibers and to evolve essentially from injury to myofibers, and in a manner similar to that shown in the rabbit hearts. In these human lesions, moreover, the peculiar large basophilic mono-, multi-, and non-nucleated structures apparently represent the following: either (a) sarcoplasm of damaged myofibers or their frag-

ments in which muscle cell nuclei have proliferated and often collected toward the center of the fragment; or (b) reactive syncytial cell masses, probably of muscular origin, that have proliferated from beneath the sarcolemma and in the track of a damaged myofiber. This type of proliferation of multinucleated syncytial cell masses occasionally suggests an attempt at regeneration of cardiac muscle cells, as it does in some of the rabbit hearts. The sites of formerly injured and necrotic myofibers appear at times to have become occupied by thick new collagen. Thus it is conceivable that the formation of these new collagen fibers may mask the earlier evidence of lesions of myofibers, especially in myocardial Aschoff bodies studied in their later stages of evolution. Myocardial Aschoff bodies have been classically described as occurring in the interstices between bundles of myofibers and also in close proximity to arteries and veins. It must be emphasized that individual myofibers and varying sized bundles of myofibers occur throughout the human heart in these same interstices between larger bundles of myofibers, as shown in Figs. 20, 21, and 24; and they occur in close proximity to blood vessels as well (Fig. 11). When myofibers in these Aschoff body sites become damaged beyond recognition, it is understandable how one interpretation of the evolution of these Aschoff bodies would fail to consider involvement of myofibers within these sites, inasmuch as residua of destroyed myofibers may no longer be evident in later stages.

Varying degrees of cardiac myofiber damage and the consequence of that damage are illustrated in Figs. 1 through 30, taken from the hearts of rabbits repeatedly infected as above indicated and of patients with active rheumatic fever. In all it is possible to identify injured myofibers or fragments thereof in various stages of disintegration. Figs. 1, 8, and 10 illustrate various evidence of myofiber damage in one rabbit heart.

In Fig. 1, fragment A is clearly recognized as sarcoplasm, as is fragment B when sharply focussed. Enveloping these two fragments is a multinucleated cell mass that appears to arise beneath the sarcolemma and in the track of the disintegrating myofiber. This structure may be playing a phagocytic role. However, the distribution of nuclei throughout all portions of the basophilic cytoplasm differentiate this syncytial cell mass from a foreign body giant cell in which characteristically the cytoplasm is eosinophilic and the nuclei occur at the periphery of the cell. In Fig. 8 foci of disintegrating myofiber sarcoplasm are still more obvious than in Fig. 1; and multinucleated, apparently myogenic basophilic cell masses in intimate relationship to disintegrating sarcoplasm occur either as caps at the ends of or in columns alongside or within the tracks of damaged myofibers. In Fig. 10 entirely comparable multinucleated and apparently myogenic basophilic masses intimately surround foci of disintegrating myofiber sarcoplasm. There is also obvious but less marked damage of myofibers at the periphery of the myofiber lesions in Figs. 1, 8, and 10. In none of these lesions was there evident swelling of interstitial collagen.

It was the occurrence of these particular experimental lesions of cardiac myofibers that raised the question of whether comparable myofiber lesions occurred in rheumatic heart disease, and in particular in myocardial Aschoff

bodies. This question is clearly answered in the affirmative; for indeed myofiber lesions, quite similar to those illustrated from the rabbit, were found in the human rheumatic hearts.

For example, in both Figs. 1 (rabbit) and 2 (human) there are tiny fragments of myofiber sarcoplasm, which at A in Fig. 2 is surrounded by a basophilic multinucleated cell designated D that is quite like that designated F in Fig. 1; while in Fig. 3 (human) a tiny focus of even further degenerated myofiber sarcoplasm together with the basophilic multinucleated cell mass below it constitutes a lesion comparable to the lesions in Figs. 1 and 2. Both of these human lesions are seen to be in close proximity to blood vessels. In Fig. 3 an artery and an arteriole show considerable narrowing of their lumina by swelling and proliferation of endothelial cells.

The experimentally induced lesions of myofibers, illustrated in Figs. 8 and 10 strongly suggest that the multinucleated elements occurring in them are of muscular origin. In Fig. 8 (rabbit) proliferated basophilic and multinucleated cell masses about E, and probably of myogenic derivation, occupy much of the track of a disintegrating myofiber. Had this animal lived longer, further clearing of the now obvious masses of disintegrating sarcoplasm would conceivably have resulted in a lesion comprised of proliferated cells like that in Fig. 9, a well developed Aschoff body, but without unequivocal evidence of formerly existing degenerated myofibers therein. Indeed, the Aschoff body in Fig. 9 apparently represents a stage of myofiber necrosis considerably more advanced than that in the rabbit lesion shown in Fig. 8. The multinucleated cell masses are quite similar in both lesions. The empty spaces, designated E, F, and G, in the Aschoff body (Fig. 9) are probably myofiber tracks from which degenerated myoplasm has been absorbed. The fragments of easily recognized sarcoplasm H, I, and J, at the periphery of the Aschoff body strongly suggest progressive involvement of myofibers from the periphery inward toward the center of the lesion.

Freshly induced focal necrosis of myofibers is evident in Figs. 4 and 7 (rabbit), and more advanced myofiber necrosis is seen in the Aschoff bodies in Figs. 5 and 6. In Fig. 5 damaged but easily recognized myofibers or their fragments entirely surround and project into the Aschoff body in a way strongly indicating that the area of the entire lesion was formerly occupied by myofibers.

In the experimental lesion in Fig. 10 numerous foci of degenerated myofibers are seen. At C, D, and E masses of granular sarcoplasm are closely surrounded by syncytial structures consisting of basophilic cytoplasm and containing several nuclei. The syncytial cell masses F, G, and H appear to have moved from the periphery inward and toward the center of the tracks of these cross-sectioned damaged myofibers. Their derivation is obscure; but they certainly appear to be more intimately connected with myofibers than with other structures of mesenchymal derivation. Figs. 1 and 8 show this even better. Degenerated sarcoplasm surrounded by quite similar basophilic multinucleated syncytial

cells is evident in the human lesion in Fig. 2. Multiple nuclei occur in the centers of other myofibers in Fig. 10, as at A and B.

Damage to myofibers with proliferation of their nuclei, so well illustrated in the rabbit heart, is also evident in the human Aschoff bodies pictured in Figs. 11, 12, 14 to 16, 20, 22, and 24.

In Figs. 11, 12, and 24 there occur on both sides of A multinucleated damaged myofiber fragments. In Fig. 14 multinucleated myofibers A and B clearly illustrate various stages of myoplasm degeneration and shrinking of the muscle fibers. Probable nucleated sarcoplasmic fragments occur throughout the Aschoff body. Fig. 15 shows myofiber damage in stages that progress from the periphery toward the center of an Aschoff body. In a portion of an Aschoff body the spacial relationship of a damaged multinucleated muscle cell to other members of a bundle of myofibers is shown in Fig. 16, in which still more intense myofiber damage is indicated throughout the picture. The relatively scanty amount of interstitial collagen in this lesion appears normal. Lower magnification of considerably more of this same Aschoff body shows in Fig. 20 that the lesion consists essentially of many greatly damaged myofibers located between normally appearing bundles of myofibers. Here again the interstitial collagen appears normal. Various kinds of nuclear response in injured myofibers or their fragments are seen in Fig. 22. The human mononucleated cell in Fig. 13 and multinucleated cell masses in Figs. 17 to 19 probably represent damaged myofibers.

That the Aschoff bodies, all from one patient, in Figs. 24 to 26 have evolved from necrosis of varying sized bundles of muscle fibers is clearly evident. Inasmuch as myocardial Aschoff bodies have classically been described as spindle-shaped, the spindle-shaped configuration of the areas of necrosis of myofiber bundles in the last two figures is noteworthy. Strikingly comparable myofiber necrosis in a rabbit heart is shown in Fig. 27. Considered in this light the myocardial Aschoff bodies in Figs. 9, 14, and 18 apparently represent progressive stages of necrosis of bundles of myofibers; in each of them are residua of former myofibers, either in the form of mono-, multi-, or non-nucleated fragments, or myofiber tracks into which syncytial cell masses, probably myogenic, have proliferated. The myocardial Aschoff body in Fig. 15 represents a stage intermediate in the evolution of these lesions from a time when myofibers, though damaged, can still be readily identified to the stage of a well developed Aschoff body, when residua of myofibers are either absent or difficult to identify.

Extensive necrosis of papillary muscle myofibers in the hearts respectively of a repeatedly infected rabbit and of a rheumatic fever patient are seen in Figs. 28 and 29.

Skeletal muscle may be similarly involved in rheumatic fever as illustrated in Figs. 31 and 32. In those lesions degeneration of myofibers is characterized by patchy loss of striation, both cross- and longitudinal. In both lesions there are columns of muscle cell nuclei within the center of damaged myofibers. The similarity of these fine focal lesions of the skeletal muscle fibers to those of a rheumatic heart, shown in Fig. 30, is striking.

In the lesions here shown neither fibrinoid change in collagen fiber ground

substance (*i.e.*, a portion of or an entire collagen fiber staining like fibrin) nor fibrinoid material between collagen fibers was found. Such fibrinoid material often occurs, however, in the myocardia of rheumatic fever patients and in some repeatedly infected rabbits, as illustrated in previous communications (2, 3). Among the several quite characteristic myocardial Aschoff bodies now shown, swollen collagen, evident in some, is not found in others. Thus these studies appear to demonstrate that myocardial Aschoff bodies can evolve without evidence of primary injury to interstitial collagen. Indeed, the human Aschoff bodies and the experimentally induced lesions here illustrated of Aschoff body type appear to have evolved from primary injury to myofibers.

DISCUSSION

Gross and Ehrlich (4, 5), believing that myocardial Aschoff bodies are invariably the result of injury to interstitial collagen, concluded, however, that their interpretation of the life cycle of these lesions would have to be confirmed by animal experiment. The present investigation has been the outcome of findings in myocardial lesions, closely resembling myocardial Aschoff bodies, in a very few among many rabbits subjected to repeated focal infections with group A streptococci (2, 3). Such bacteria have repeatedly been found in the human focal infections that are followed occasionally by attacks of rheumatic fever.

In contrast with the accepted theory that all myocardial Aschoff bodies are consequent on injury to interstitial collagen, the present studies demonstrate that a large proportion of myocardial Aschoff bodies in the several rheumatic hearts studied are the result of injury to muscle fibers. Moreover, in contrast with the view generally held that myocardial Aschoff bodies characteristically consist essentially of damaged collagen and non-myogenic mesenchyme cells that have proliferated in response to interstitial collagen injury, the present studies demonstrate the following: that in the several rheumatic fever patients studied the structures most peculiar to myocardial Aschoff bodies were damaged muscle fibers, their fragments or residua, and syncytial cell masses, probably of muscular origin that proliferated in response to that muscle fiber injury.

The question is pertinent of how these latest findings stand in relation to those of previous studies of rheumatic myocardial Aschoff bodies. It has previously been suggested by several observers, cited below, that some cells in myocardial Aschoff bodies are derived from myofibers; but subsequently these suggestions were generally rejected as the thesis was widely developed that myocardial Aschoff bodies invariably evolve from lesions of interstitial collagen.

Before Aschoff described in detail the myocardial lesions that bear his name, the following changes had been observed in the hearts of rheumatic fever patients: Goodhart (6) observed cellular proliferation near cardiac blood vessels and between myo-

cardial fasciculi; Romberg (7) and Bret (8) emphasized the occurrence of abnormal large cells in those sites; and Vaisse (9) described focal myocardial necrosis and granulation replacement of other myocardial foci after several rheumatic fever attacks; in addition to muscle fiber changes Krehl (10) emphasized the common occurrence of arteritis and arteriolitis where damaged and proliferated intimal and medial elements often markedly narrowed the lumina of small and medium sized myocardial vessels.

Aschoff (1) emphasized that Aschoff bodies occur in close proximity to small or medium sized blood vessels, and stated that they are specific for rheumatic fever. He concluded that the characteristic large cells invariably arise from vascular adventitial cells. Schmorl (1) questioned whether they might not derive from myofibers. Geipel (11), observing that they occur in interstitial tissue distant from as well as close to blood vessels, considered the large granuloma cells to arise from wandering vascular adventitial elements, and ascribed damage to cardiac myofibers to erosion by adjacent Aschoff bodies (12). He also described necrosis of skeletal muscle in rheumatic fever. Aschoff and Tawara (13) subsequently denied a myofiber origin for Aschoff body cells. Coombs (14) emphasized the role of endothelial proliferation in partial or complete occlusion, with or without thrombosis, of small myocardial blood vessels. Saigo (15) briefly mentioned that giant cells might be of myogenic origin in some Aschoff bodies in one rheumatic heart. Huzella (16) reported lesions like myocardial Aschoff bodies in skeletal muscles from rheumatic fever patients. He believed that some giant cells originated from muscle fibers. But Aschoff (16) and Fraenkel (16) insisted that all myocardial Aschoff bodies represent reactions of non-myogenic connective tissue elements to injury. Whitman and Eastlake (17), on the other hand, believed they could trace in one rheumatic heart the origin of some Aschoff body cells from myofibers, and stated that Aschoff bodies may develop from minute infarcts. Swift (18) held that the giant cells of myocardial Aschoff bodies arise from vascular endothelium. He reemphasized the occurrence of endarteritis and thrombosis of small cardiac blood vessels and considered that the nutrition of cardiac muscle cells would immediately be disturbed when their blood supply was thus compromised. MacCallum (19) pointed out that Aschoff bodies near myocardial vessels occur at some distance from rather than within or intimately surrounding the blood vessels.¹ He stated that the large cells are not derivatives of cardiac muscle fibers. In contrast Letulle, Bezancon, and Weil (20) brought evidence highly suggestive of the formation of myocardial Aschoff body giant cells from muscle fibers by fragmentation of the myofibers and amitotic division of the nuclei within the sarcoplasm. Talalajew (21) emphasized the primary role of interstitial collagen swelling and necrosis in the pathogenesis of all Aschoff bodies as did Gross and Ehrlich (22, 4, 5). Klinge and his coworkers (23) stressed that fibrinoid swelling (Frühinfiltrat) of interstitial collagenous ground substance is the conspicuous feature of the early lesion, and believed that the large cells characteristic of myocardial Aschoff bodies arise from non-myogenic mesenchymal elements. They regarded the damage to cardiac and

¹ Thus, with respect to location, the discrete Aschoff body that develops near a cardiac blood vessel differs importantly from the lesion of the peri-, poly-, or panarteritis nodosa type that develops within and intimately surrounds a segment or all of the circumference of the vessel wall.

skeletal muscle fibers as secondary to injury to perimysial collagen, and did not attribute a myogenic origin to any element found within myocardial Aschoff bodies.

Some investigators, assuming that rheumatic fever subcutaneous nodules are histopathologically identical with myocardial Aschoff bodies, have utilized their findings in the former to explain the latter (24, 25), with result in the simplified concept that all myocardial Aschoff bodies, like subcutaneous nodules, consist essentially of a central focus of damaged collagen, within or around which are found certain large cells of non-myogenic mesenchymal origin that have proliferated in reaction to that collagen damage. As Gross and Ehrlich (4) pointed out, however, one cannot logically assume that the histopathological process is identical in subcutaneous nodules and myocardial Aschoff bodies, even though both probably arise under the influence of common etiological factors. Certainly, there are striking histological differences, especially in their early stages. The hallmarks of myocardial Aschoff bodies are the peculiar large, often ragged edged, polymorphous, basophilic cytoplasmic masses containing one or more nuclei, but at times apparently without nuclei. As shown in the present studies these structures are injured muscle fibers, their fragments or residua, and syncytial cell masses, probably of muscular origin, that have proliferated in reaction to muscle fiber injury. They can often be differentiated from the multinucleated cells found in rheumatic lesions elsewhere as well as from the multinucleated giant cells commonly present in chronic inflammatory lesions in many other diseases.

In active rheumatic myocarditis there occur numerous focal lesions consisting of a central core of collagen within or around which are found large basophilic cells; and there also occur strands of stringy material, often intensely eosinophilic and generally thought to be either damaged collagenous ground substance that stains like fibrin or fibrinoid connective tissue ground substance between collagen fibers. Among such strands basophilic cells may be interspersed. In interpreting the significance of such fibrinoid in rheumatic hearts, the following observations are pertinent: Some collagen fibers in normal tissue, *e.g.* corium and uterus, may stain in a patchy fashion like fibrin with connective tissue staining techniques; in the myocardia of patients who denied having had an attack of rheumatic fever and who succumbed to a quite different disease, *i.e.* advanced post-alcoholic cirrhosis of the liver, foci of collagen have been found to stain like fibrin in the absence of any histological evidence of rheumatic fever in the heart or other tissues; in the myocardia of other patients who have previously undergone attacks of rheumatic fever before succumbing to advanced post-alcoholic cirrhosis, some of the thick collagen fibers in focal myocardial or dense paravascular scars have also been found to stain like fibrin in the absence of cells of the Aschoff body type: indeed, there was no clinical or histological evidence of active rheumatic fever at the time of death; and in such hearts a considerable amount of collagen in scarred valves has likewise been found to stain like fibrin in the absence of active valvulitis. Much collagen in such cirrhotic livers also stains like fibrin.² These observations, together with

² Unpublished observations by the author.

those that form the basis for this report, indicate that in interpreting the significance of fibrinoid collagen intermingled with basophilic cells in rheumatic fever myocardia the following must be considered: (a) that some of the large basophilic cells in such lesions may be myogenic elements resulting from advanced myofiber necrosis but showing no landmarks necessary for identifying them as such; and (b) that some collagen, including fibers showing fibrinoid, may be components of scar laid down subsequent to myofiber necrosis either in a previous rheumatic attack or during the final one; and (c) that some of that collagen may have become freshly altered during the final attack. The presence of fibrinoid material between interstitial collagen fibers, however, seems invariably to indicate relatively recent injury. On the above mentioned bases might be explained the presence of fibrinoid collagen fibers in the myocardial lesions illustrated in Figs. 24 and 25 of a previous communication (3). The first lesion from a patient who died during the last of several attacks of rheumatic fever, shows myocardial scars as well as fresh myofiber necroses. Collagen fibers in the scar are thick and many stain partially or entirely like fibrin (fibrinoid). The second lesion from a rabbit dying after the last of 8 infections, likewise illustrates both myocardial scars and fresh myofiber necroses. Many collagen fibers in these scars are thick and exhibit fibrinoid alteration quite similar to that evident in the human heart. The rabbit myocardial scars developed following necrosis of myofibers that was presumably induced by previous streptococcal infections; but the final streptococcal infection may have induced fibrinoid change in some collagen of the myocardial scars. This process conceivably paralleled the induction of fibrinoid alteration in some collagen of the human myocardial scars during the final of multiple attacks of rheumatic fever. It is noteworthy, however, that in the characteristic myocardial Aschoff bodies and in the experimental myocardial lesions of Aschoff body type, illustrated in the present communication, neither fibrinoid change in interstitial collagen fibers nor fibrinoid material between interstitial collagen fibers was found, although swollen collagen fibers were found in some of these lesions.

The long existing moot question, usually answered in the negative, has again recently been raised: Do the myocardial Aschoff bodies, long considered so very characteristic of rheumatic heart disease, occur as manifestations of other diseases?

In two cases of disseminated lupus erythematosus Rich (25) found a few myocardial lesions that he deemed of the Aschoff body type. They were similar if not identical with certain rheumatic myocardial lesions comprising collagen or intercollagen fibrinoid with interspersed basophilic cells. Mallory (26) reported finding such myocardial lesions that he considered typical Aschoff bodies in a case diagnosed as disseminated lupus erythematosus with polyarteritis nodosa and rheumatoid arthritis. Rich (25), and Bauer, Kulka, and Giansiracusa (27) encountered myocardial Aschoff bodies in two cases of generalized periarteritis nodosa.

These five instances have been cited as evidence that myocardial Aschoff bodies are not pathognomonic of rheumatic heart disease. But it has long been recognized that generalized necrotizing vascular lesions of the peri-, poly-, or panarteritis nodosa type occasionally occur in cases of rheumatic fever (1, 28, 29), and several have occurred after scarlet fever. Furthermore, rheumatic fever not uncommonly exists without being recognized clinically. It seems important, therefore, to consider the following possibility: that the two isolated cases reported as examples of non-rheumatic generalized periarteritis nodosa in which Aschoff bodies developed may indeed have been instances of clinically unrecognized rheumatic fever with associated generalized vascular lesions of the peri- or panarteritis nodosa type.

With respect to the three isolated cases that have been diagnosed histopathologically as disseminated lupus erythematosus in which myocardial Aschoff bodies were reported, it is pertinent to mention that in long and intensive study of very many cases of disseminated lupus erythematosus neither Klemperer (30) nor Baehr (31) has ever observed in this disease the myocardial Aschoff bodies so characteristic of rheumatic heart disease. Rich (25) has shown that valvular and verrucous endocardial lesions entirely similar to those of rheumatic fever may occur in disseminated lupus. The previously cited observations of Rich and of Mallory seem to have shown that there occur in some patients with disseminated lupus erythematosus myocardial lesions resembling certain of those found in rheumatic heart disease; but that those disseminated lupus myocardial lesions are identical with the myocardial Aschoff bodies so peculiarly characteristic of rheumatic heart disease has certainly not been established.

Although focal myofiber necroses occur in many diseases, the human Aschoff bodies evolving from myofiber damage, as detailed in the present report, appear to be peculiarly characteristic of heart disease that occurs in rheumatic fever patients and in some cases diagnosed as rheumatoid arthritis. It has previously been suggested that the chief difference between the focal myocardial lesions in disseminated lupus erythematosus and non-rheumatic periarteritis nodosa, on the one hand, and typical rheumatic myocardial Aschoff bodies, on the other, is the more marked swelling and fusion of affected collagen fibers in the latter lesions (25). The results of the present studies strongly suggest, however, that the most distinguishing histological feature of rheumatic heart disease, and of myocardial Aschoff bodies in particular, are the peculiar lesions of cardiac myofibers. And it is here proposed that the term myofiber Aschoff body be used to designate this lesion. The terms Aschoff body and myocardial Aschoff body ought, henceforth, to be used advisedly and not to include a variety of cardiac lesions.

The question of whether certain of the myogenic syncytial cell masses in the rabbit and human lesions described in these studies represent attempts at myofiber regeneration cannot be answered conclusively from the data available. That this may be the case is suggested, however, in some of the lesions

observed, and strikingly so in the rabbit lesions shown in Fig. 10. Pertinent to this question are previous studies on the histopathogenesis of regeneration of skeletal muscle.

Zenker (32) concluded that regeneration after hyaline changes in the rectus abdominis muscle was effected entirely by extra-muscular connective tissue cells, but Waldeyer (33) believed that the regenerative and phagocytic cells lying within the sarcolemma of such damaged myofibers originated from muscle nuclei. Volkmann (34) likewise considered all the cells within the sarcolemma of damaged human and experimentally injured rabbit skeletal muscle to be of muscular origin. Forbus (35) damaged skeletal muscle in several species of animals by several methods. At the center of the lesions necrosis of all muscle and collagenous connective tissue occurred; but toward the periphery, where injury was less severe and sarcolemma persisted, regenerative changes were evident. He thought that removal of necrotic muscle was effected by non-muscular phagocytic cells, but that muscle regeneration was accomplished by cells developing from the nuclei and sarcoplasm of injured muscle fibers.

The regenerative muscle elements just mentioned, often occurring just beneath the sarcolemma, are multinucleated long spindle cells or syncytial cytoplasmic cell masses that structurally appear quite like the many myocardial syncytial cell masses illustrated in the rabbit and human Aschoff body-type lesions in the present communication. With respect to the question of the possibility of cardiac myofiber regeneration one might draw an analogy, on the one hand between extensive necrosis of cardiac muscle as seen in Figs. 28 and 29 and the extensive necrosis in the center of Forbus' experimental lesions, and on the other between the focal lesions of cardiac myofiber Aschoff body type and those at the periphery of Forbus' lesions. This suggests that the likelihood of regeneration of cardiac muscle cells may be inversely proportional to the severity of injury to the myofibers, including their sarcolemmas. It is yet to be determined whether in rheumatic fever the cardiac myofiber damage, focal or extensive, represents infarction resulting from narrowing or occlusion of blood vessel lumina, caused by damaged and proliferated intimal and medial elements or by thrombosis; or is due to a direct action on muscle fibers of some poison(s) elaborated either by streptococci, by their interaction with host tissue, or to a toxic agent called out from other host tissue in response to this interaction.

It is here emphasized that the results of this investigation do not exclude the possibility of injury to collagen in sarcolemma intimately surrounding muscle fibers any more than they exclude injury to other components of muscle fibers in the cardiac myofiber lesions of rheumatic heart disease.

These studies provide additional evidence that close experimental homologues of myocardial Aschoff bodies have been induced in a very few among many rabbits subjected to repeated focal infections with group A streptococci of different serological types; and thus they support the concept that the myo-

cardial lesions characteristic of rheumatic fever develop in only a certain few among many patients who have experienced successive focal infections with group A streptococci of several different serological types.

SUMMARY

Comparative studies on the histopathogenesis of experimentally induced lesions of myocardial Aschoff body type in rabbits and of many myocardial Aschoff bodies from several active rheumatic fever patients have revealed the following:

Almost invariably these experimental lesions and very frequently the myocardial Aschoff bodies studied in their early stages have been shown to originate in and evolve from lesions of heart muscle fibers.

The mono-, multi-, and non-nucleated cell masses, most characteristic of myocardial disease of the rheumatic type, appear to be damaged muscle fibers, their fragments, and syncytial cell masses of probable muscular origin that proliferate from beneath the sarcolemma and in the tracks of damaged muscle fibers in reaction to that damage.

In addition to destructive changes in cardiac muscle fibers an attempt at myofiber regeneration may occur in some myocardial Aschoff bodies.

The most distinguishing histologic feature of the myocardial Aschoff bodies in rheumatic heart disease are the peculiar lesions of muscle fibers. Therefore, it is proposed that they be designated as myofiber Aschoff bodies in order to indicate their origin more accurately.

The results of these investigations contrast with the widely accepted theory that all myocardial Aschoff bodies originate as injured interstitial collagen, and that, as they evolve, they consist of damaged interstitial collagen intermingled with cells of non-myogenic derivation that proliferated in response to that collagen injury.

These studies, furthermore, provide evidence that experimental homologues of rheumatic myocardial Aschoff bodies have been induced in a very few among many rabbits subjected to repeated focal infections with group A streptococci of different serological types. Hence, they support the concept that the myocardial Aschoff bodies of rheumatic fever are induced by repeated infections with group A streptococci of several different serological types; even though only a certain few among the many patients so infected develop these lesions.

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EXPLANATION OF PLATES

The photographs were made by Mr. Julian Carlile and Mr. Richard Carter.

In no rabbit in this series were streptococci found either in blood cultures or in the cardiac lesions.

PLATE 30

FIG. 1. Rabbit 80-65; sacrificed while quite sick 12 days after the second streptococcal infection. Although blood cultures were repeatedly negative this animal received intramuscular injections of penicillin from the 5th to the 11th day following the last infection in an attempt to enhance the chance for recovery.

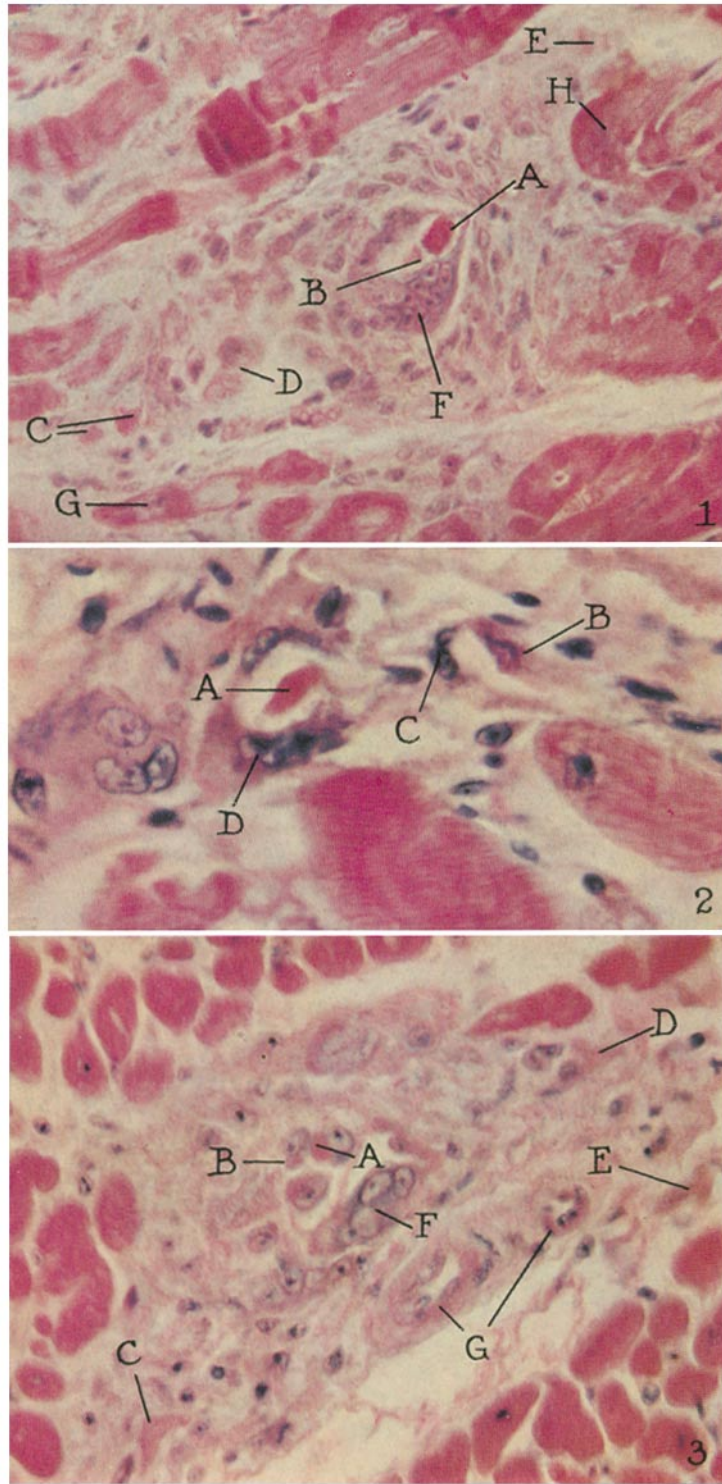
Lesion in left ventricle of heart, A, B, and C, degenerated myofiber fragments. D and E, very indistinct but still identifiable residua of myofibers. F, basophilic and multinucleated syncytial cell mass, probably myogenic, that envelops fragments A and B, and differs structurally from a foreign body giant cell; very similar cell masses in the same rabbit heart are shown in Figs. 8 and 10, and in the human lesions in Figs. 2, 3, and 9. G and H, myofibers with damaged myoplasm and large vesicular nuclei. Marked alteration of contiguous myofibers. Giemsa. $\times 454$.

FIG. 2. From a 6 year old girl who died about 2 months after onset of disease early associated with albuminuria and transient hypertension. Death about 4 days after onset of an upper respiratory infection (autopsy 7127, Babies Hospital). Although rheumatic heart disease was not diagnosed clinically, nevertheless, very numerous, well developed and characteristic myocardial Aschoff bodies were found throughout this heart.

Lesions in left ventricle of heart. A and B, fragments of myofibers. C and D, basophilic and multinucleated syncytial cell masses, probably myogenic, and like F in Figs. 1 and 3. See Figs. 11 and 30 from this same subject. \times Hematoxylin and eosin. $\times 765$.

FIG. 3. From a 14 year old boy who died about 4 months after onset of the first recognized attack of rheumatic fever, and 2 months after tonsillectomy (autopsy 8620, New York Hospital).

Aschoff body in left ventricle of heart. A and B, apparent residua of myofiber fragments like A and B in Figs. 1 and 2. C, D, and E, degenerated myofiber fragments like C in Fig. 1. F, basophilic and multinucleated syncytial cell mass, probably myogenic, and like F in Fig. 1 and D in Fig. 2. G, Artery and arteriole with narrowed lumina caused by endothelial swelling and proliferation. Giemsa. $\times 460$.



(Murphy: Development of Aschoff bodies from injured myofibers)

PLATE 31

FIG. 4. Rabbit 71-80; sacrificed while sick 10 days following the last of 6 focal infections.

Lesion in left ventricle of heart, showing a focal area of fresh necrosis of myofibers. Hematoxylin and eosin. \times 531. Compare with figures below.

FIG. 5. From a 10 year old boy who died after about 3 months of active rheumatic fever (autopsy 325, Rockefeller Institute Hospital).

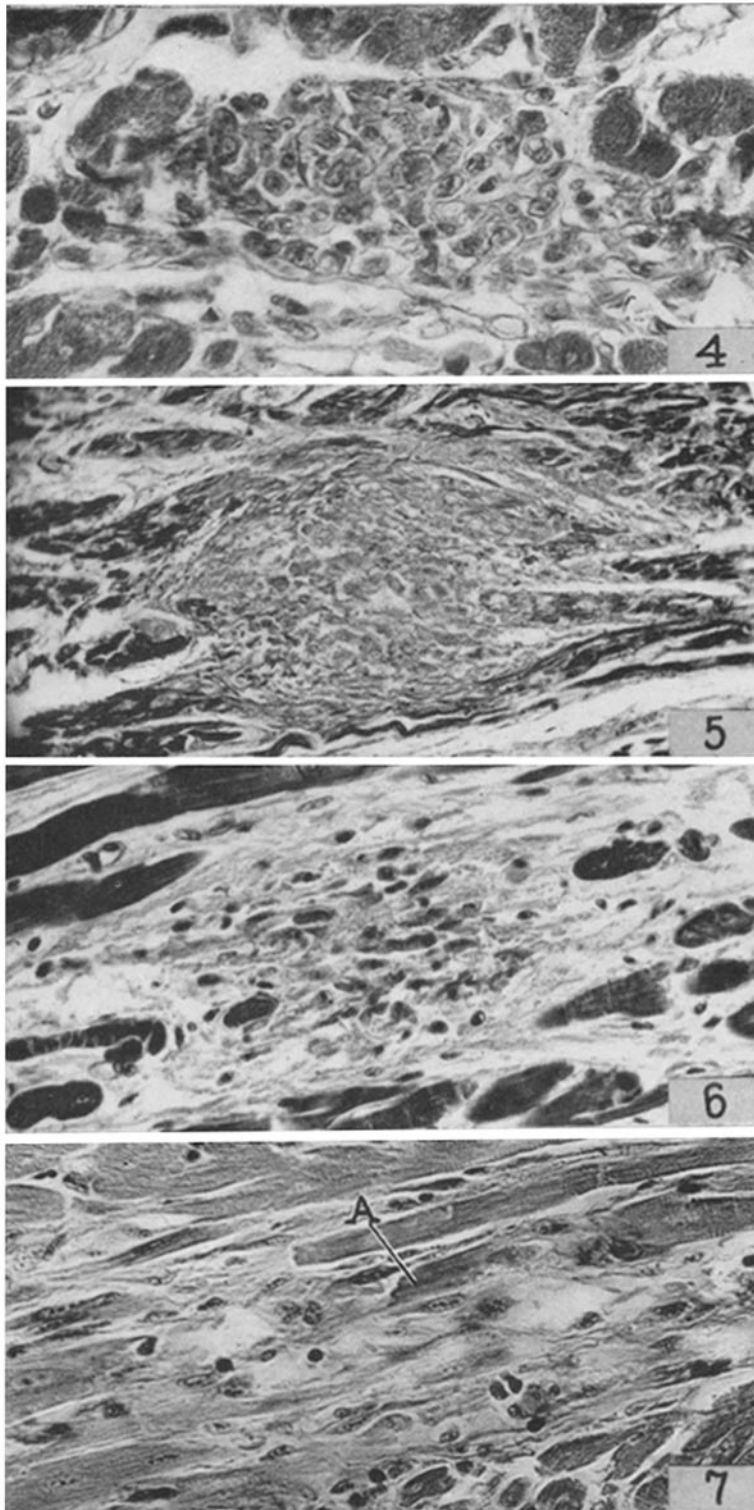
Aschoff body in left ventricle of heart, showing a focal area of necrosis of myofibers very similar to but larger than that in Fig. 4. Damaged but easily recognized myofibers or their fragments entirely surround and project into the Aschoff body in a way strongly indicating that the site of the entire lesion was formerly occupied by myofibers that have undergone great damage. Weigert-hematoxylin and eosin. \times 132.

FIG. 6. From a 13 year old girl who died about 6 weeks after onset of an upper respiratory infection, and 3 weeks after the first symptom of the second recognized attack of rheumatic fever (autopsy 716, Rockefeller Institute Hospital).

Aschoff body in interventricular septum of heart, showing numerous varying sized fragments of myofibers. Collagen appears normal in this lesion stained with Masson trichrome technique. \times 375.

FIG. 7. Rabbit 71-77; died after developing markedly irregular cardiac rhythm 8 days following the last of 5 focal infections.

Focal area of fresh necrosis and fragmentation of myofibers in left ventricle of heart. Note at A the myofiber fragment with jagged edge like that at D in the human lesion in Fig. 22. Hematoxylin and eosin. \times 344.



(Murphy: Development of Aschoff bodies from injured myofibers)

PLATE 32

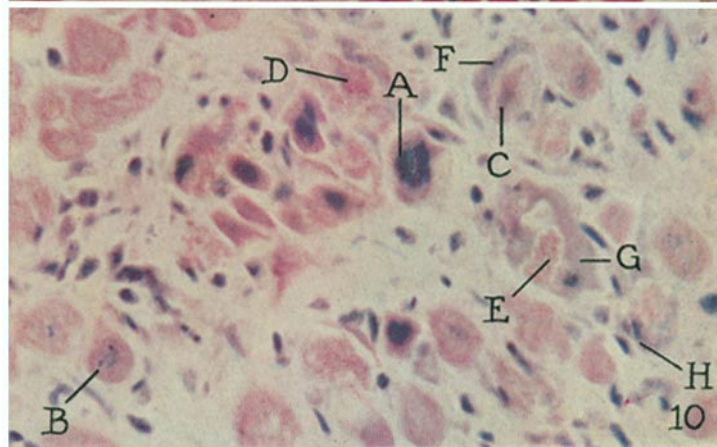
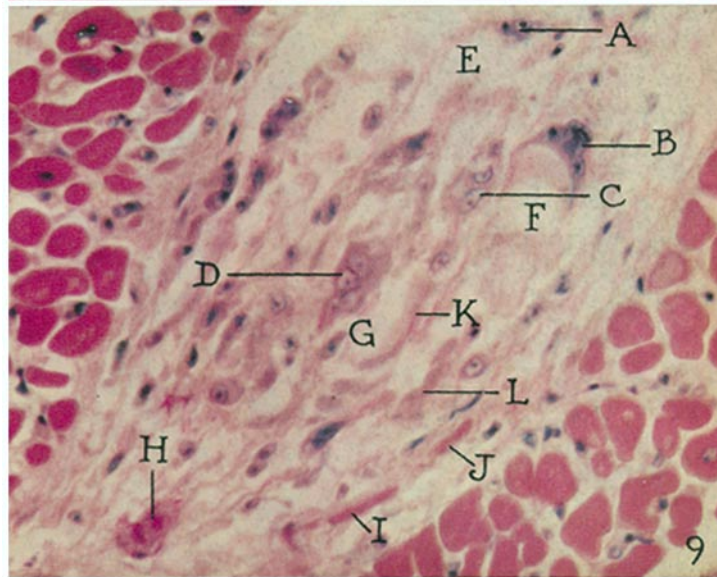
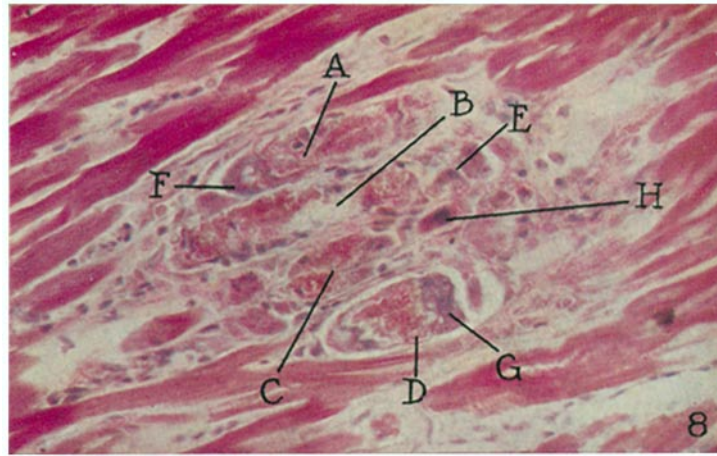
FIG. 8. From left ventricle of *rabbit* heart referred to in Fig. 1. Experimental lesion like an early Aschoff body and showing fresh necrosis of myofibers. A, B, C, and D, obliquely directed tracks of degenerated myofibers. Note in this picture how proliferated basophilic and multinucleated cell masses surrounding E occupy a considerable segment of the track of a disintegrating myofiber, as is also seen in other portions of the figure. F and G, basophilic and multinucleated syncytial cell masses occurring as caps at one pole of disintegrating myofibers. Compare with the very similar syncytial cell masses in Figs. 1 and 10 (*rabbit*) and Figs. 2, 3, and 9 (*human*). H, multinucleated myofiber fragment.

Had the animal lived longer further clearing of the now obvious masses of disintegrating sarcoplasm would have left a structure of proliferated cells like that in Fig. 9, a well developed Aschoff body, but without unequivocal evidence of the former existence of myofibers in the site of this granuloma. Giemsa. $\times 288$.

FIG. 9. From left ventricle of *human* heart referred to in Fig. 3. A, B, C, and D, basophilic and multinucleated syncytial cell masses like those in Figs. 1 and 8 (*rabbit*) and Figs. 2 and 3 (*human*). E, F, and G, empty spaces, but probably obliquely directed tracks of former myofibers from which necrotic myoplasm has been absorbed.

This Aschoff body apparently represents a stage of myofiber necrosis considerably more advanced than that in the *rabbit* lesion shown immediately above. The easily recognized fragments of myofibers, H, I, and J at periphery of Aschoff body together with the possibly further degenerated muscle fragments at K and L are very suggestive of involvement of myofibers in decreasing degrees of intensity from the center toward the periphery of the Aschoff body; this also appears to be the case in the Aschoff bodies in Figs. 5, 6, 14, 15, 18, 20, 25, and 26. Giemsa. $\times 420$.

FIG. 10. From left ventricle of *rabbit* heart referred to in Figs. 1 and 8. A and B, multinucleated myofibers. C, D, and E, masses of necrotic and granular sarcoplasm. The basophilic syncytial cell masses F, G, and H appear to have moved from the periphery of the tracks of cross-sectioned damaged myofibers, and inward toward the centers of these tracks. The very intimate association of syncytial structures with necrotic sarcoplasm masses suggest an attempt at myofiber regeneration. Giemsa. $\times 493$.



(Murphy: Development of Aschoff bodies from injured myofibers)

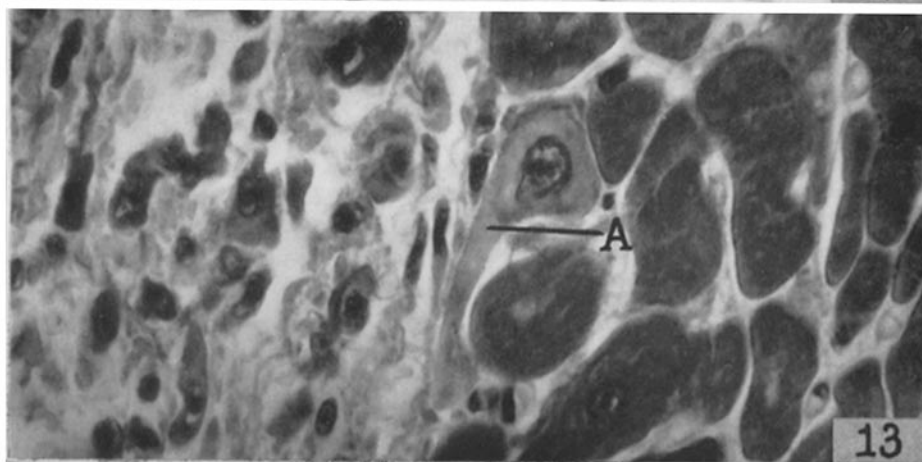
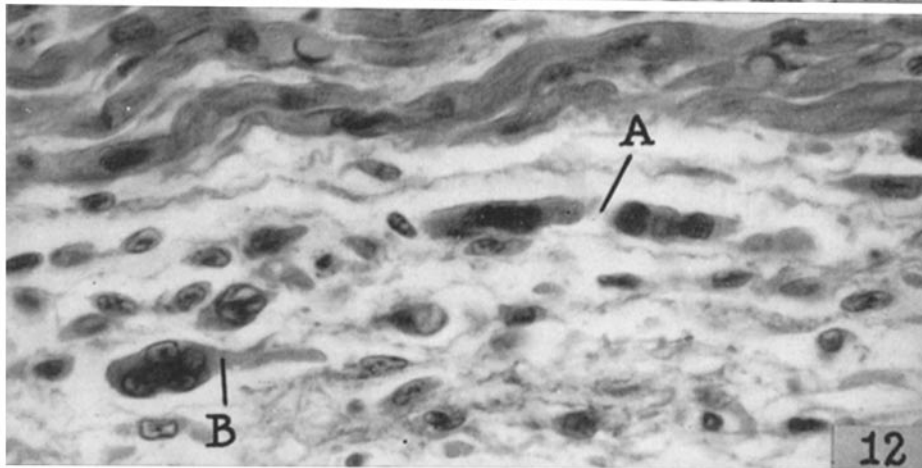
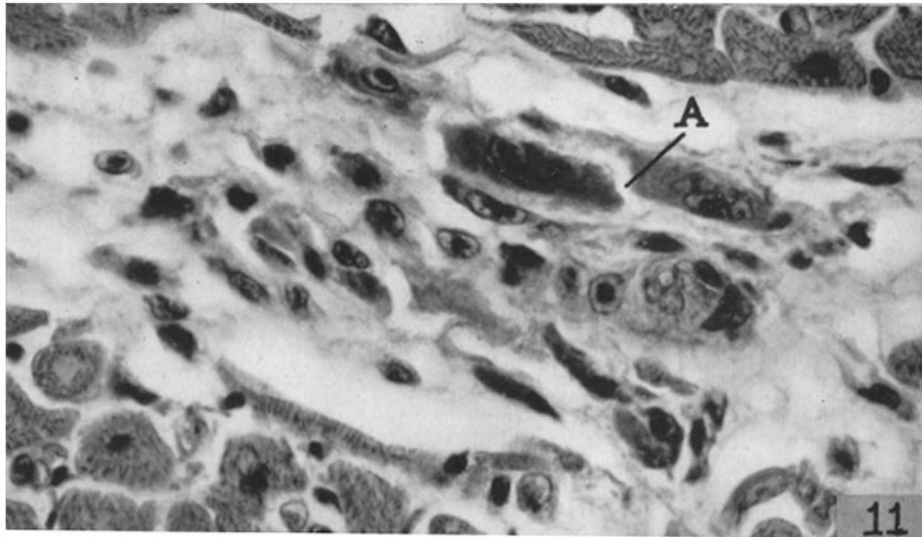
PLATE 33

FIG. 11. From left ventricle of *human* heart referred to in Fig. 2. In this Aschoff body the only multinucleated structures are on both sides of the space, indicated by A, in the track of a markedly damaged myofiber; these structures appear clearly to represent a damaged myofiber that has broken into two almost equal parts toward the centers of which multiple muscle cell nuclei have collected; similar appearance in the fragments on both sides of A in the Aschoff bodies in Figs. 12 and 24. These multinucleated myogenic structures are close to a small blood vessel. Hematoxylin and eosin. $\times 710$.

FIG. 12. From an 8 year old girl who died about $5\frac{1}{2}$ weeks after onset of the first recognized attack of rheumatic fever (autopsy 8627, New York Hospital).

Aschoff body in right ventricle of heart. A, probable damaged myofiber track containing two basophilic and multinucleated myofiber fragments quite comparable to those in Figs. 11 and 24. B, basophilic and multinucleated structure with tail of degenerated cytoplasm, apparently a damaged myofiber, like those in Figs. 13, 17, and 18. Note close similarity of the structure at B to the damaged but easily recognized multinucleated myofiber at A in Fig. 16. Hematoxylin and eosin. $\times 710$.

FIG. 13. From the interventricular septum of the *human* heart referred to in Fig. 6. A, probable injured myofiber with large vesicular nucleus at margin of an Aschoff body. Masson trichrome. $\times 820$.



(Murphy: Development of Aschoff bodies from injured myofibers)

PLATE 34

FIG. 14. From a 3½ year old girl who died 6 weeks after onset of sore throat and 1 week after the first complaint of joint pain (autopsy 8450, New York Hospital).

Aschoff body in left ventricle of heart. A and B, damaged, fragmented and easily recognized multinucleated myofibers at periphery. There is no fibrinoid change in the swollen interstitial collagen of this lesion. The many cell masses like C and D with dusky red granular cytoplasm seen in this Aschoff body are highly suggestive of damaged muscle elements and it is quite conceivable that this Aschoff body represents in fact a later stage of necrosis of a bundle of myofibers than that pictured in Figs. 8, 9, 15, 24 to 26. Masson trichrome. $\times 540$.

FIG. 15. From a 19 year old man who died about 3 months after onset of the second recognized attack of rheumatic fever (autopsy 319, Rockefeller Institute Hospital).

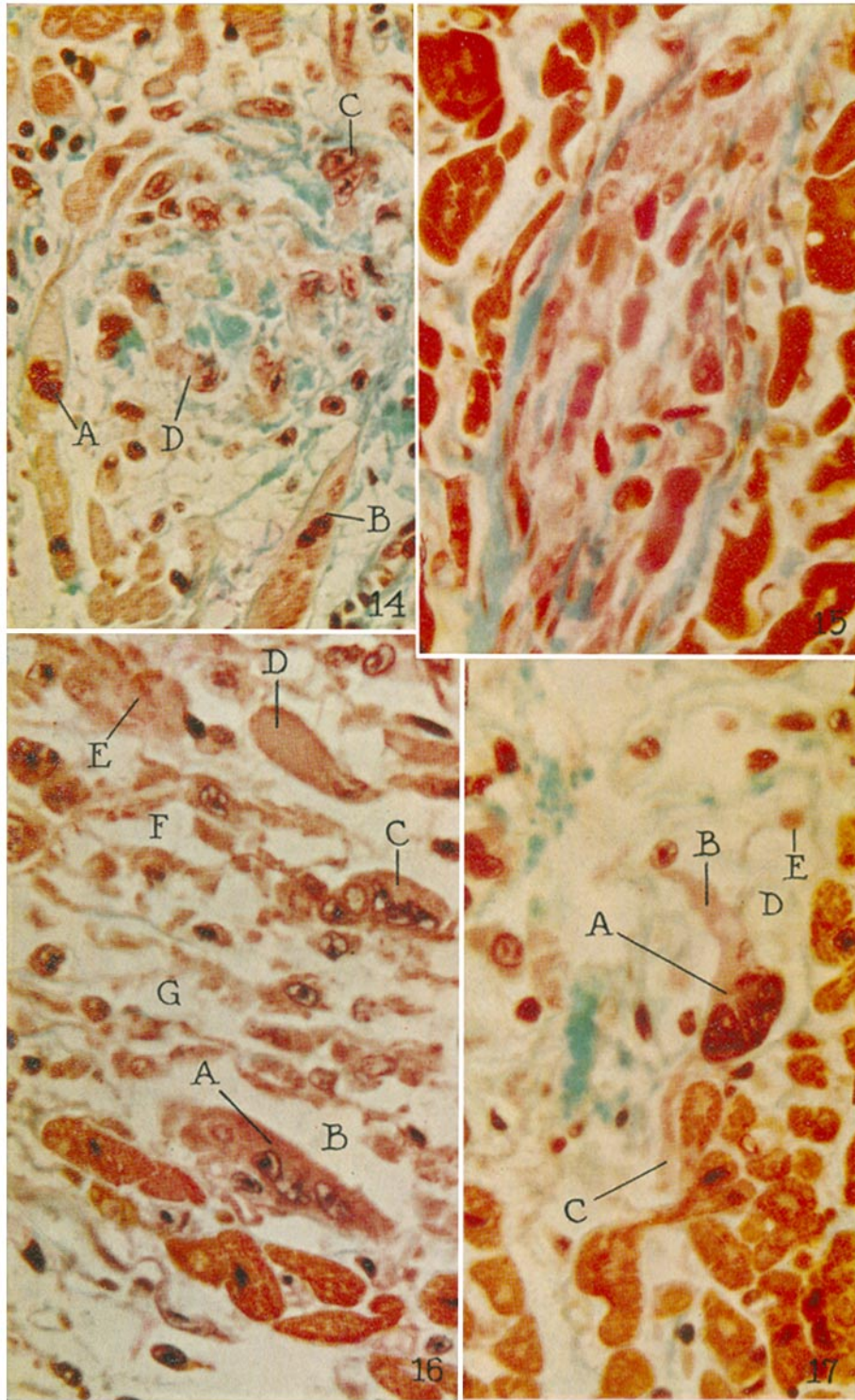
Left ventricle of heart. Aschoff body showing degrees of myofiber damage that decreases in intensity from the center toward the periphery; similar gradations in the Aschoff bodies in Figs. 5, 6, 9, 14, 16, 18, 20, 24 to 26. Orange-brown staining fragments of damaged myofibers are the principal constituents of this Aschoff body. Between these fragments relatively sparse amounts of collagen are seen that, although occasionally swollen, stain normally. Damaged myofiber with two nuclei in the left lower corner. Masson trichrome. $\times 575$.

FIG. 16. From a 6½ year old girl who died 5 weeks after onset of scarlet fever and 1 week after the first complaint of marked pain in right ear (ear drum ruptured spontaneously). No evident arthritis (autopsy 6061, Babies Hospital). Numerous well developed Aschoff bodies throughout myocardium.

Left ventricle of heart. Portion of an Aschoff body that is shown more completely in a lower magnification in Fig. 20. A, disintegrating ragged edged, multinucleated myofiber, showing its spacial relationship to the other myofibers below that stain normally. B, track of damaged myofiber A. C, multinucleated cell, quite similar to that at A and very probably a damaged myofiber. D and E, probable myofibers showing still greater disintegration. F and G, tracks probably occupied formerly by myofibers but now containing only residual fragments and syncytial myogenic structures. The small amount of interstitial collagen in this lesion appears normal. Masson trichrome. $\times 682$.

FIG. 17. From an 8½ year old boy who died 4 weeks after onset of the first recognized rheumatic fever symptom, shoulder pain (autopsy 6142, Babies Hospital).

Left ventricle of heart. A, multinucleated cell with disintegrating processes B above and C below. Compare C with the similar portion of the damaged myofiber in Fig. 13. D, track probably occupied by upper portion of this cell when normal. E, tiny fragment of degenerated myofiber. This multinucleated cell is very probably a damaged myofiber. Note its very close similarity to the multinucleated myofiber at A in Fig. 14. Interstitial collagen in this lesion though swollen in places still stains normally. Masson trichrome. $\times 710$.



(Murphy: Development of Aschoff bodies from injured myofibers)

PLATE 35

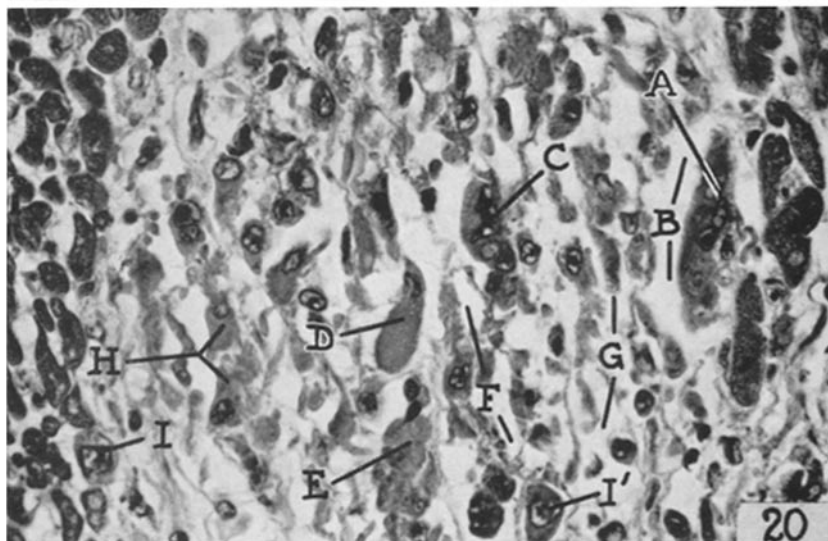
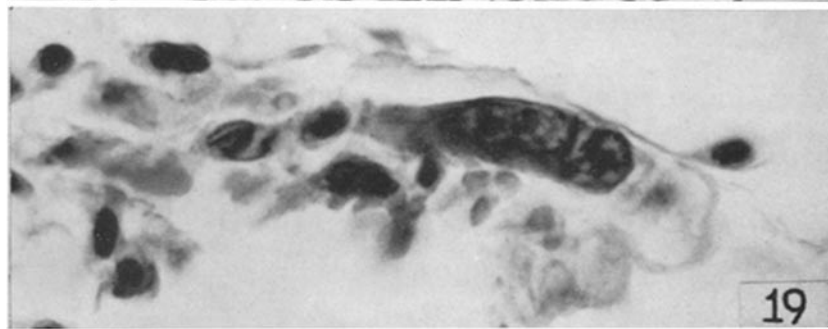
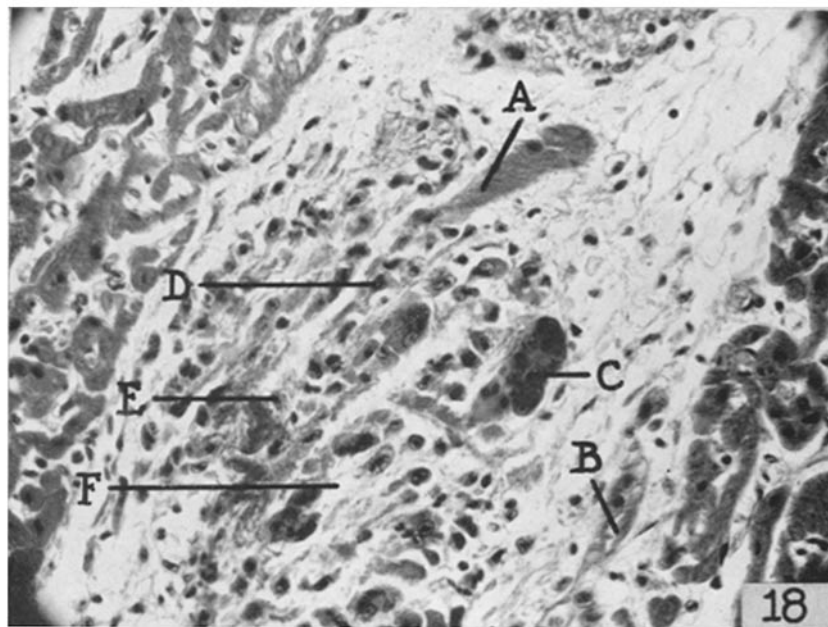
FIG. 18. From a 1 year old malnourished Chinese boy who died about 10 weeks after onset of anorexia and irregularly recurring bouts of fever, and 3 weeks after a series of convulsions (autopsy 6717, Babies Hospital). Very numerous quite characteristic myocardial Aschoff bodies throughout heart.

Left ventricle of heart. Typical Aschoff body apparently representing necrosis of a whole bundle of myofibers between larger bundles. A and B, easily recognized myofiber fragments, the lower portions of which are frankly necrotic. C, basophilic, multinucleated cell, probably a myofiber, and almost identical with the multinucleated cell at A in Fig. 17. Compare with A in Fig. 14. D, E, and F probably represent tracks of necrotic myofibers as indicated in Fig. 8, 9, 11, 12, 16, and 20. The scanty amount of interstitial collagen in this lesion appears normal. Masson trichrome. $\times 470$.

FIG. 19. From interstitium between large bundles of myofibers in left ventricle of the *human* heart referred to in Fig. 17. The long multinucleated cell is probably a damaged myofiber, showing necrosis of the portion on the left. Compare with similar cells in Figs. 11, 12, 14, 16, 17, 18, 20, and 24. Masson trichrome. $\times 1080$.

FIG. 20. The myocardial Aschoff body, a small portion of which is seen in Fig. 16. Letters employed in Fig. 16 also are used in this figure to indicate identical structures. H, fragmented myofiber.

This Aschoff body, located between easily recognized bundles of myofibers at extreme right and left, has almost certainly evolved from necrosis of numerous myofibers; this also appears to be the case in the Aschoff bodies in Figs. 6, 9, 14, 15, 18, 25, and 26. The portion of this lesion in the colored picture in Fig. 16 shows better the myogenic character of the structures involved. The cell at I' appears similar to the one at I, a damaged muscle cell. The interstitial collagen in this lesion is scanty and appears normal. Masson trichrome. $\times 500$.



(Murphy: Development of Aschoff bodies from injured myofibers)

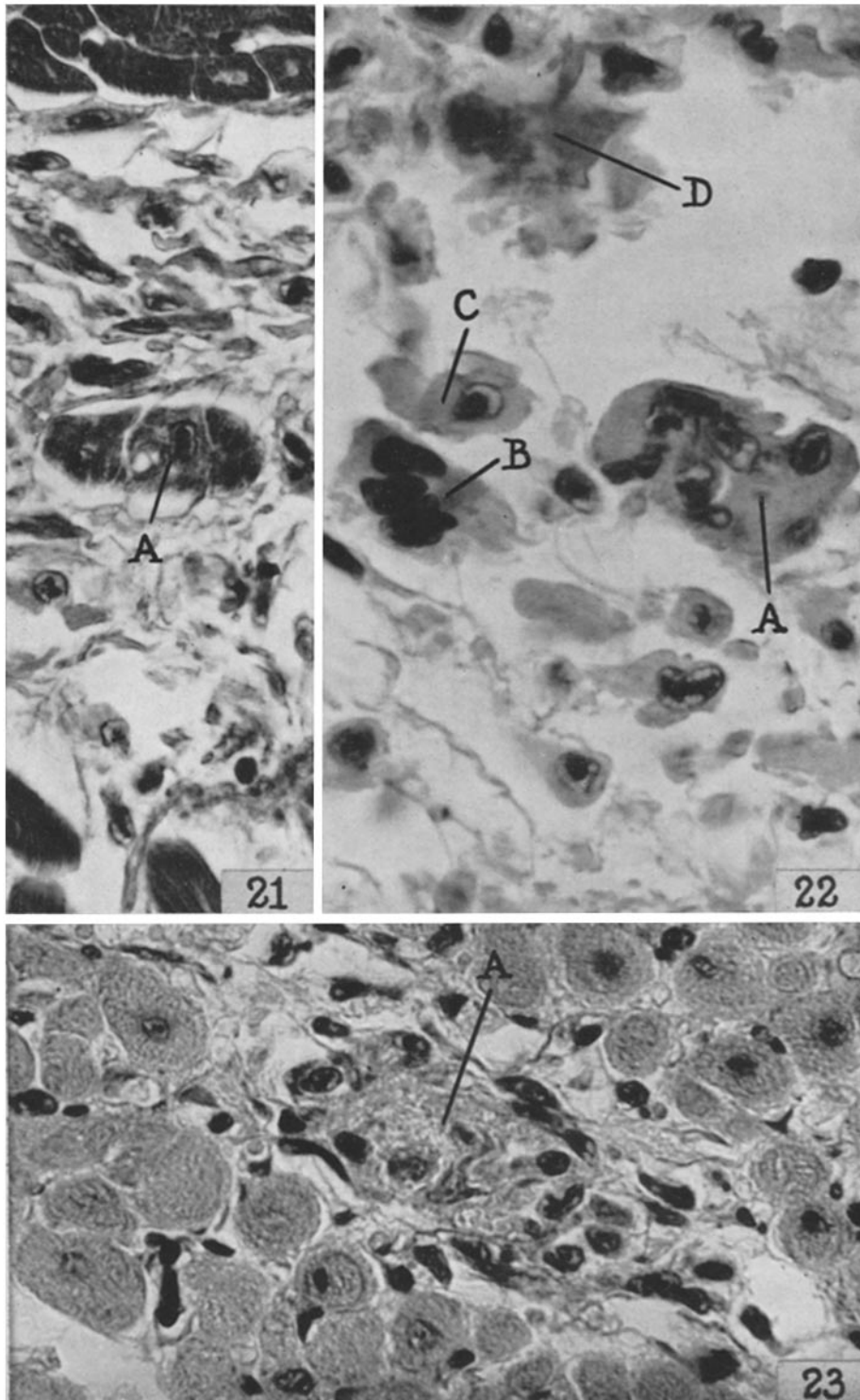
PLATE 36

FIG. 21. From interventricular septum of *human* heart referred to in Figs. 6 and 13. A, small bundle of damaged myofibers; this demonstrates that between large bundles of myofibers the myocardial interstitium is also the site of smaller aggregates of myofibers. Masson trichrome. $\times 850$.

FIG. 22. From a 10 year old girl who died 5 weeks after onset of tonsillitis and during ensuing second attack of rheumatic fever. First attack 1 year earlier (autopsy 7136, Babies Hospital).

Left ventricle of heart. From large Aschoff body lying between large bundles of myofibers. A, disintegrating, ragged edged, and multinucleated Aschoff body myofiber mass similar to A in Fig. 16. B, C, and D, probable fragments of myofibers. Microscopically B can be seen to have 7 nuclei. In the neighborhood of these masses is a very scanty amount of collagen that stains normally. Compare the jagged edged structure at D with the jagged edged and obvious fragmented myofiber at A in Fig. 7. Masson trichrome. $\times 1100$.

FIG. 23. From the left ventricle of the *rabbit* heart referred to in Fig. 4. A, necrosis of an entire small bundle of myofibers situated between larger bundles. This lesion is like a small human myocardial Aschoff body. Weigert-hematoxylin and eosin. $\times 692$.



(Murphy: Development of Aschoff bodies from injured myofibers)

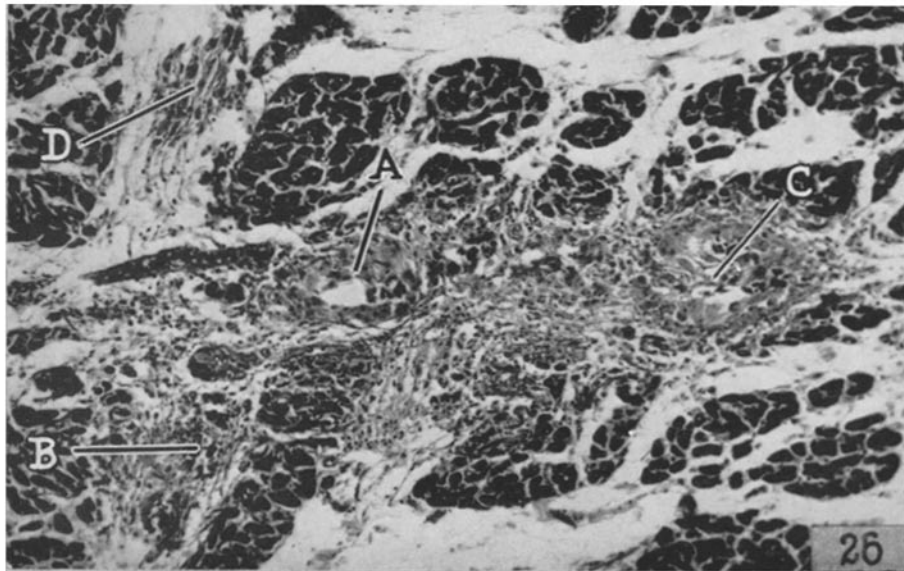
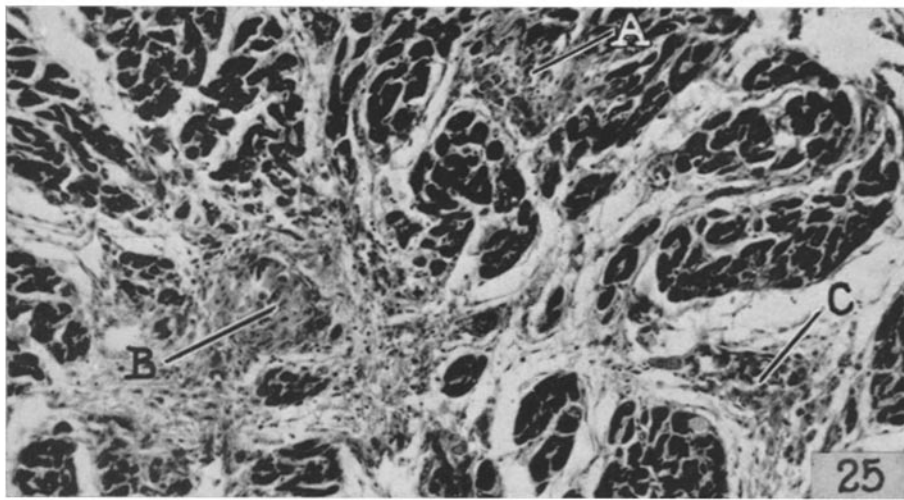
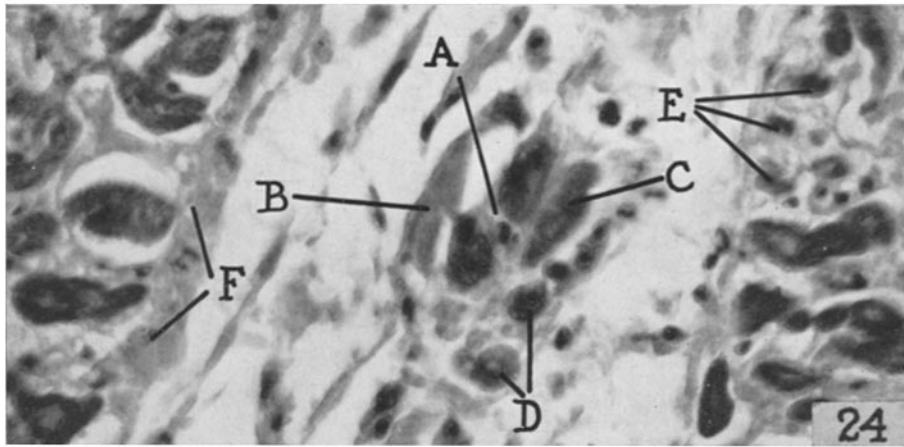
PLATE 37

FIG. 24. From a 15 year old boy who died following the second recognized attack of rheumatic fever. Death occurred about 1 month after the beginning of irregularly recurring fever and hive-like skin lesions, 9 days after onset of abdominal pain, and 6 days after first joint symptoms (autopsy 18944, Johns Hopkins Hospital).

Left ventricle of heart. Discrete small Aschoff body, probably evolving from necrosis of a small bundle of myofibers. C, easily recognized myofiber that shows cross-striations. The multinucleated structures above and below the space A, and similar to myofibers shown in Figs. 11 and 12, probably represent a damaged myofiber that has broken into two basophilic fragments containing multiple myofiber nuclei at their centers; microscopically, 6 nuclei are recognizable in the upper fragment and 5 in the lower one. Lower fragment resembles somewhat the basophilic and multinucleated structures at D. B., damaged myofiber mass that has shrunken to the left of its track. E, damaged and shrunken myofibers. Numerous other damaged myofibers at left and right of this Aschoff body. F, swollen collagen that does not stain as fibrinoid. No fibrinoid in collagen fibers or between them at any place within or near this Aschoff body. Masson trichrome. $\times 393$.

FIG. 25. From another portion of left ventricle of human heart referred to in Fig. 24. A, B, and C, fresh necrosis of bundles of myofibers. No fibrinoid interstitial collagen in or adjacent to these lesions. Phosphotungstic acid-hematoxylin. $\times 116$.

FIG. 26. From still another portion of the left ventricle of the human heart referred to in Fig. 24. A, B, and C, spindle-shaped early Aschoff bodies evolving from necrosis of bundles of myofibers. D, spindle-shaped Aschoff body, probably representing necrosis of a bundle of myofibers but lacking myofibers intact enough to be recognized as are some in area C. No fibrinoid interstitial collagen in or adjacent to these lesions. Phosphotungstic acid-hematoxylin. $\times 113$.



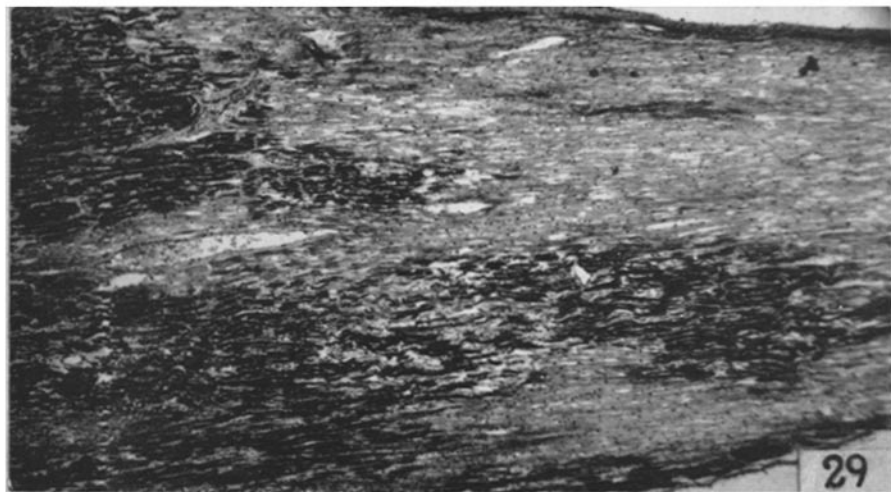
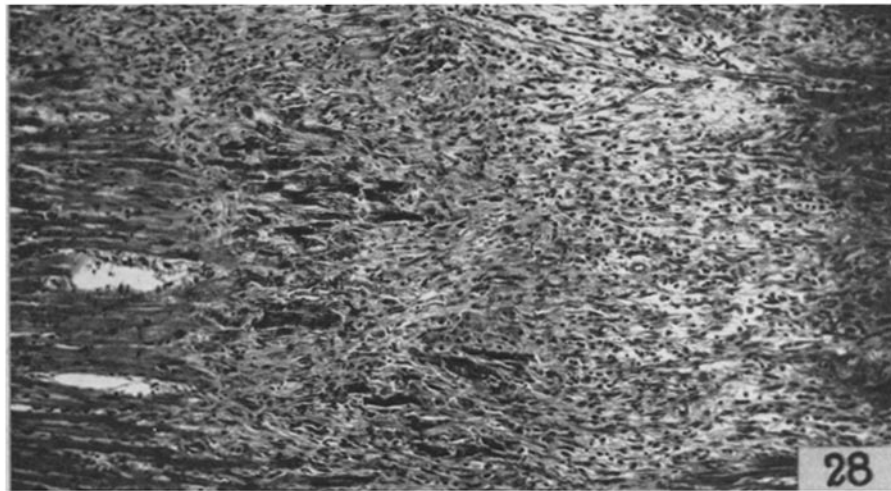
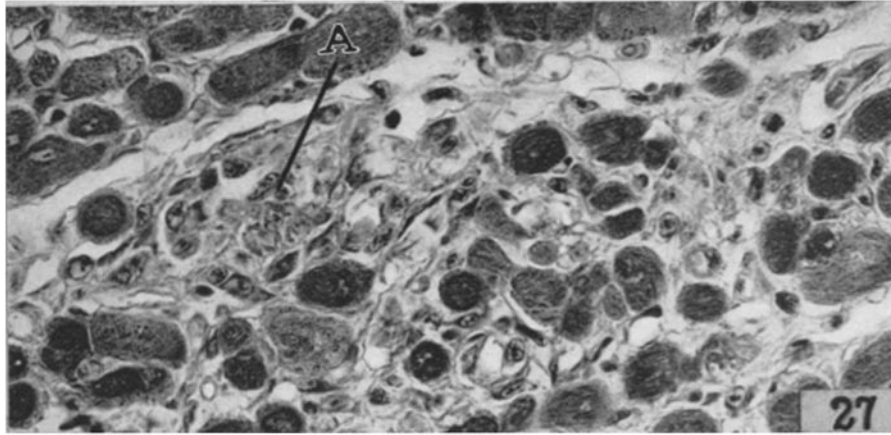
(Murphy: Development of Aschoff bodies from injured myofibers)

PLATE 38

FIG. 27. From the left ventricle of *rabbit* heart referred to in Figs. 4 and 23. A, fresh necrosis of a bundle of myofibers that is strikingly like that in Figs. 25 and 26 from a *human* rheumatic heart. Note extensive damage of myofibers throughout this area. Giemsa. $\times 476$.

FIG. 28. From papillary muscle of the *rabbit* heart referred to in Fig. 7. Fresh and massive necrosis of myofibers. Hematoxylin and eosin. $\times 90$.

FIG. 29. From papillary muscle of the *human* heart referred to in Fig. 5. Fresh and massive necrosis of myofibers. Masson trichrome. $\times 42$.



(Murphy: Development of Aschoff bodies from injured myofibers)

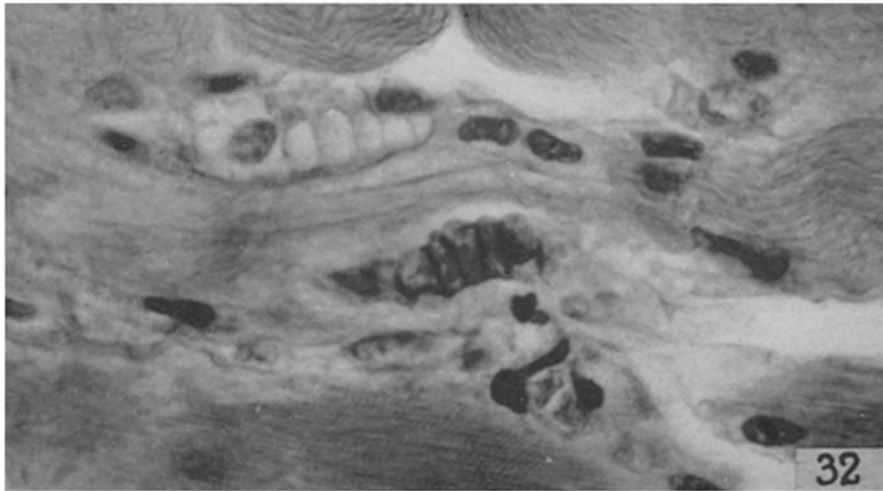
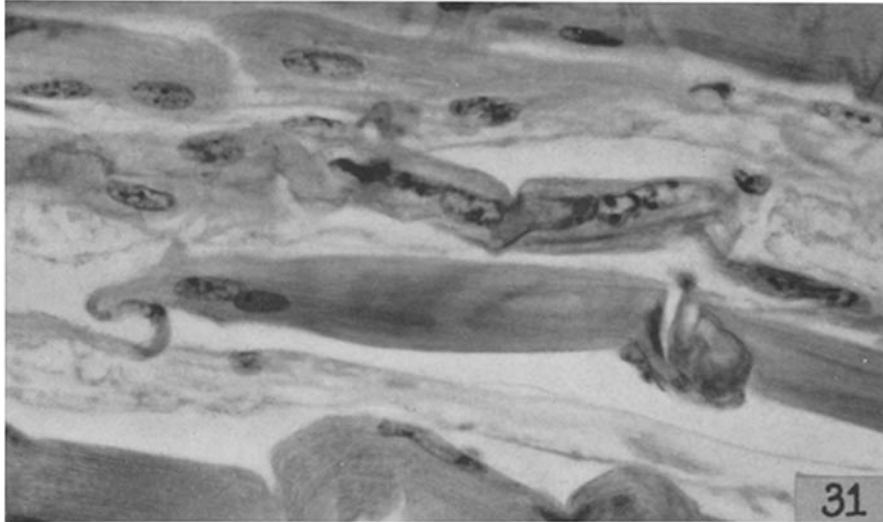
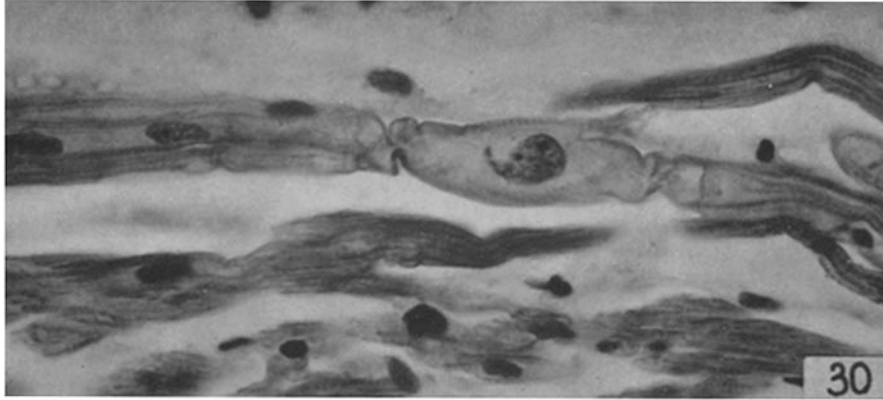
PLATE 39

FIG. 30. From left ventricle of human heart referred to in Figs. 2 and 11. Marked degeneration of a myofiber. Note changes in the upper fiber comparable to those in the diaphragmatic muscle fiber near the center of Fig. 31. Hematoxylin and eosin. \times 630.

FIG. 31. From a $6\frac{1}{2}$ year old girl who died $3\frac{1}{2}$ weeks after complaining of pain in back of legs (autopsy 6238, Babies Hospital).

Aschoff bodies in myocardium. Diaphragm. Marked degeneration of a myofiber with multiple nuclei arranged in a column. Hematoxylin and eosin. \times 620.

FIG. 32. From diaphragm of subject mentioned in Fig. 30. Marked loss of cross-striation in a myofiber that shows accordian-like close grouping of multiple nuclei. Hematoxylin and eosin. \times approximately 650.



(Murphy: Development of Aschoff bodies from injured myofibers)