THE INDUCTION OF RHEUMATIC-LIKE CARDIAC LESIONS IN RABBITS BY REPEATED FOCAL INFECTIONS WITH GROUP A STREPTOCOCCI

COMPARISON WITH THE CARDIAC LESIONS OF SERUM DISEASE

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PLATES 21 TO 35

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In a previous communication (1) we presented data indicating that cardiac lesions, closely resembling those characteristic of rheumatic fever in man, had been induced in a small proportion of rabbits that had undergone multiple, successive skin infections with group A streptococci of several serological types. How the hypothesis leading to those experiments evolved is described elsewhere (2).

The purpose of this report is to submit additional examples of the rabbit cardiac lesions, together with representative human cardiac lesions from several fatal cases of active rheumatic fever; to describe them and their apparent evolution; and to compare and characterize the two groups, both as to their morphology and pathogenesis.

Methods, Materials, and Specimens Procured

Details of the group A streptococci employed, preparation of cultures, the cutaneous areas infected, the character of the local skin response to the first and succeeding inocula, variations in the intervals between inoculations, the methods employed to document the course of infection, and the techniques employed in preparing the tissues for microscopic study are all given in the first communication (1).

The streptococci had undergone many mouse passages, and in the case of some strains several rabbit passages in addition. They exhibited matt or mucoid colony forms after 18 to 24 hours' growth on moist rabbit blood agar, and produced large amounts of type-specific M protein (3) in Todd-Hewitt broth made with neopeptone.

After sustaining multiple successive streptococcal skin infections within 3 to 20 months, some rabbits sickened as indicated by various combinations of the following: elevated erythrocyte sedimentation rates for 1 to 2 weeks; leucocytosis; anorexia; weight loss; postexertional dyspnea; occasional transient pulmonary rales; tachycardia; and in a few instances markedly irregular cardiac rhythm (1). Many of the animals were allowed to recover (category A); a portion were sacrificed within 10 to 15 days following the last infection (category B); a few developed a severe illness that terminated fatally following the last infection (category C), whereas some controls for category C that were undergoing their *first* streptococcal infection survived. Rabbits of categories A, B, and C in addition to evincing definite symptoms of illness, had, as compared with controls, usually more rapid erythrocyte sedimentation rates,

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and developed in their blood sera higher antistreptolysin O titers (4) and more marked precipitin reactions with crude M extracts of both homologous and heterologous streptococci. It is in the rabbits of categories C and B which had succumbed or were sacrificed while sick that were found the fresh cardiac lesions closely resembling those of active rheumatic fever. Myocardial scarring and healed arterial lesions of the character seen in human rheumatic hearts occurred in some of these rabbit hearts and also in the hearts of other rabbits sacrificed after multiple streptococcal infections but without signs or symptoms of active disease just prior to sacrifice.

The material here presented was selected from the hearts of 7 rabbits: 3, belonging to category C, developed fatal illnesses that terminated between the 8th and 14th day after the last of several streptococcal infections but without demonstrable bacteremia either ante- or postmortem; the other 4, included in category B, were sacrificed within 10 to 15 days following the last infection and also had negative autopsy blood cultures. Careful microscopic examination of many sections specially stained to demonstrate bacteria has, moreover, revealed no microorganisms in these lesions. The human hearts were from 12 patients who died with active rheumatic fever. The lesions in these hearts showed no microorganisms on microscopic examinations.

The previous communication (1) contains a detailed composite description of the histological features of the lesions at various sites in the rabbits' hearts, together with photomicrographs illustrating some of these lesions. The present communication illustrates lesions from similar sites in the hearts of these rabbits and in the hearts of human subjects with active rheumatic fever.

Endocardial Lesions

In the gross the auricular side of the mitral valve in some rabbit hearts showed along the line of closure a row of fine, discrete opalescent elevations usually most marked on the aortic leaflet. Microscopically these elevations consisted of interstitial edema and valvulitis which in some instances can be clearly shown to have been more intense than in the contiguous valve tissue. Occasionally projecting from the auricular surface of the mitral valve of the hearts of these successively infected rabbits larger, firm white nodules and ridges of thickened valve were visible. Rows of fine verrucae, characteristic of active rheumatic valvular endocarditis of several weeks' duration, have not, however, been found on these rabbit heart valves. It should be noted that in man, moreover, verrucae are probably secondary to interstitial valvulitis of several weeks' duration, for careful microscopic study of valves of the hearts of patients dying early in an attack of rheumatic fever (5) reveals chiefly interstitial inflammation and in some instances palisades of endocardial and subendocardial cells similar to those found in these rabbits. For example (Fig. 1), in addition to obvious interstitial valvulitis there is on both surfaces of the mitral valve of rabbit 71-77 palisading of endo- and subendocardial cells quite similar to that found in the valves of some of our patients and comparable to that described by MacCallum (6) and von Glahn (7) in human auricular endocarditis. In an isolated area of this valve (Fig. 2) the proliferated cells are ar-

ranged in a definite microscopic nodule that is elevated above the contiguous endocardium. Beneath this, similar cells are arranged in a crescentic pattern, and between these two groups of cells there are fragmented elastica and swollen collagen. This is highly suggestive of an early verruca. Similar palisading of deeper layers of endocardial cells is seen in the aortic valve of a patient succumbing with rheumatic fever of many weeks' duration (Fig. 3), where areas of necrosis of the most superficial cells have fused into minute, frankly fibrinoid masses suggesting preverrucae. A possibly intermediate stage between those shown in Figs. 2 and 3 is illustrated in Fig. 4 from the heart of rabbit 71-77.

Lesions bearing close resemblance to each other have been found in the endocardia of the trabeculae carneae respectively of this rabbit (Fig. 6) and of a rheumatic patient (Fig. 5). Similar multiple contiguous endocardial lesions existed in this patient's endocardium at a mitral sulcus (Fig. 8); and cells in the superficial layers, especially where the pillows of proliferate touch one another, show necrosis. Comparable pillows in the mitral sulcus in rabbit 73-13 (Fig. 7) suggest comparable pathogenesis: stress and strain exerted on the surface layers of hinges containing tissues altered in a like manner.

In Fig. 9 from the aortic sulcus of a patient with active rheumatic fever are seen characteristic Aschoff or rheumatic granuloma cells. These large, irregularly shaped, mono- and multinucleated cells with basophilic and often indistinctly outlined cytoplasm are dispersed in a markedly altered connective tissue framework. Fig. 10 shows an entirely similar picture in the mitral sulcus of rabbit 71-77.

Myocardial Lesions

In myocardial granulomata the rabbit myocarditis approximates almost, if not absolutely, that of rheumatic fever in man. The descriptive adjectives for these lesions here employed follow those introduced by Gross and Ehrlich (8) to characterize the several architectural configurations of Aschoff bodies.[1]

The primary tissue injury in the submiliary myocardial granuloma and in the other lesions in rheumatic fever subjects is apparently in the connective tissue. In stained sections microscopic evidence of this injury ranges from slight turgescence of the collagen to marked swelling. The degree to which such swollen collagen fibers take up the eosin stain varies greatly in both intensity and distribution. To demonstrate stages thought to represent more advanced degrees of collagen alteration, Mallory connective tissue and Masson trichrome techniques are useful. With these methods, portions of a single, swollen collagen fiber may stain in a mottled fashion while other collagen fibers stain uniformly throughout like fibrin. Klinge (9) demonstrated with a silver impregnation

[1] In this article the use of the term Aschoff body is restricted to the *human rheumatic* submiliary granuloma; and the similar myocardial lesions in rabbits are designated simply submiliary granulomata.

technique that in the foregoing stages the fibrils of the collagen fibers were usually intact, but pushed apart by swollen ground substance (*Frühinfiltrat*). Focal lesions, however, sometimes occur in which markedly damaged collagen fibers show fragmentation that occasionally progresses to granular necrosis.

All degrees of focal collagen injury, described above, have been encountered in the myocardia of some rabbits successively infected intracutaneously with group A streptococci. Illustrated in Figs. 11 and 13 are interlacing networks of swollen collagen in reticular Aschoff bodies between bundles of myofibers in the heart of a patient succumbing fairly early in an attack of rheumatic fever. The altered collagen in these two lesions did not stain like fibrin with the Masson trichrome method. Fig. 12 illustrates comparable interlacing network of swollen collagen between bundles of myofibers in rabbit 71-80, sacrificed while sick 10 days after the last of 6 streptococcal infections. More marked alteration of an interlacing network of myocardial collagen is evident in Figs. 14 and 15 from, respectively, the heart of a patient succumbing early in an attack of rheumatic fever and of a rabbit dying with markedly irregular cardiac rhythm 8 days after the last of 5 infections. In the two latter lesions it is clearly evident that large portions of the altered collagen stain unequivocally like fibrin with Masson trichrome technique. In these five reticular lesions the amount of swollen collagen possibly outweighs in prominence the enmeshed proliferated granuloma or mesenchyme cells, which may not have had time to multiply further in response to injury before the death of the respective subjects. Incidentally, the fairly frequent proximity of submiliary myocardial granulomata to arteries is illustrated in Fig. 15 (rabbit) and Fig. 20 (human), and to altered arterioles or capillaries in Fig. 11 (human) and Figs. 19 and 21 from rabbits.

Contrasted with the foregoing reticular lesions, in which the swollen collagen forms an interlacing meshwork, are the mosaic Aschoff bodies illustrated in Figs. 16, 18, and 20. In these submiliary lesions the mesenchyme cells are lodged between fragmented collagen masses and the nodules are usually round, oval, or spindle-shaped. Quite similar nodular mosaic rabbit granulomata are illustrated in Figs. 17, 19, and 21.

Papillary muscle is commonly involved in rheumatic heart disease. In papillary muscles of both human and rabbit hearts there are few, if any, true connective tissue septa such as occur in myocardium elsewhere; therefore, the lesions in this muscle are found among the myofibers; and numerous disseminated lesions with resulting extensive destruction of myofibers may occur. A portion of such a human lesion is illustrated in Fig. 22, which shows swollen collagen throughout the lesion. Many stages of myofiber and sarcolemma alteration are evident. The least intense are seen at the borders of the lesion where individual myofibers with well marked striations pass into shadowy tubes and wavy, deeply staining fibers; while in the central portion of this lesion the end-stages of myofiber destru ction are largely obscured by numerous proliferated

mesenchyme cells. An apparently earlier stage in this type of myocardial lesion is illustrated in Fig. 23 from the heart of a rabbit that died with heart block 8 days after the last of 5 streptococcal infections. All stages of myofiber and sarcolemma alteration are evident. Especially prominent are the granule-containing tube-like shadows of sarcolemma. Definitely swollen collagen is evident throughout the lesion. The lesser degree of mesenchyme cell proliferation in the rabbit lesion compared with that in the human lesion can be explained by the termination of the rabbit disease before a comparable degree of mesenchyme cell proliferation had occurred in response to the collagen and myofiber injury.

Finally, in the end-stages of the granulomata, *viz.*, focal and diffuse scar formation, the human myocardial scars following rheumatic carditis (Fig. 24), and the scars in the heart muscle of these rabbits (Fig. 25) are entirely comparable. In both instances here cited a large proportion of the collagen fibers in the scars show distinct swelling, and most of these fibers partially or entirely stain like fibrin with connective tissue techniques. Dispersed throughout the fields of fibrinoid collagen in the scar of both the human and the rabbit lesions are proliferating mesenchyme cells. These fresh alterations superimposed on myocardial scars occur commonly in patients succumbing to a fresh attack of rheumatic fever after having sustained previous attacks of this disease. In this rabbit heart the myocardial scars were presumably induced by previous streptococcal infections, and the final streptoccal infection probably induced fresh alterations in these scars entirely similar to those found in the scars of this human heart.

Lesions of Cardiac Blood Vessels

It is generally recognized that certain lesions of the blood vessels are almost as characteristic of rheumatic fever as are the interstitial myocardial granulomata. Vascular lesions of this disease occur in all ramifications of the coronary arteries as well as in many other blood vessels. The simplest microscopically visible lesion is a swelling of the vascular endothelial cells into oval or cuboid forms; this narrows the lumen of the small vessels, which on cross-section often resemble actively secreting tubular glands, as is well illustrated in an arteriole (Fig. 19) in a rabbit heart near a myocardial granuloma. Oval endothelial swelling in a capillary at the edge of a reticular Aschoff body is shown in Fig. 22. Similar vascular abnormalities occur frequently in subcutaneous rheumatic nodules. Occasionally one side of an arteriole is more intensely involved than another, and the hyperplastic cells are crowded into a crescent-shaped mass (Fig. 11); and suitable staining often reveals a splitting of the internal elastica close to this eccentric hyperplasia. These lesions of fine blood vessels have been encountered in the hearts of both the rabbit and the human rheumatic subjects here discussed.

A more advanced lesion is shown in Fig. 26 from rabbit 70-66 and in Fig. 27 from a human rheumatic heart: obliterating verrucous arteritis due to intense proliferation of the endothelial and subendothelial cells, followed by necrosis of the proliferate. A somewhat similar lesion is seen in other acute infectious diseases (rickettsial in particular). Obliterating endarteritis involving small coronary blood vessels was described in fatal human rheumatic fever by Krehl (10) long before the classical description of the Aschoff body; it has been present in a number of our patients. Karsner (11) has emphasized the fact that arterial verrucre resemble the verrucous lesions occurring in acute rheumatic valvulitis.

While Figs. 26 and 27 show in the paravascular tissue distinct collagen swelling and mesenchyme cell proliferate, more marked paravascular collagen injury is illustrated in Fig. 31 from the heart of rabbit 71-77 and in Fig. 30 from a human rheumatic heart. In each of these lesions perivascular edema is evident. The areas of intensely damaged collagen surround and extend into paravascular tissue adjacent to the vessels. This intensely eosinophilic collagen stains like fibrin with Masson trichrome, Mallory connective tissue, and Weigert hematoxylin and eosin techniques. Interspersed in this altered collagen are mesenchyme cells of the type found in myocardial interstitial granulomata. This distinctive vascular lesion was first described by von Glahn and Pappenheimer (12) who considered it to be specific for rheumatic fever. The striking similarities between these human and rabbit lesions are noteworthy. Possibly much of the comparatively dense paravascular collagen in the human lesion (Fig. 30) developed during previously observed attacks of rheumatic carditis, and the intense frankly fibrinoid alteration of this collagen during the latest attack. The reactions in the arterial intima and media are further evidence of recent injury to this blood vessel. Similarly, because this rabbit (71-77) arterial lesion (Fig. 31) resembles so closely that from the human heart (Fig. 30) just considered, we feel that the rabbit had undergone at least one prior attack of cardiac vasculitis. This, in fact, is indicated in Fig. 29 from this rabbit, which shows endarteritis polyposa, in which the polyp is composed of well organized scar tissue; and at the base of the polyp there is distinct splitting of the internal elastica with medial and adventitial alterations. As seen in Fig. 31 from this rabbit the frankly fibrinoid alteration of the paravascular collagen together with the reactions in the arterial intima and media is evidence of recent injury. Indeed, this rabbit succumbed with markedly irregular cardiac rhythm 8 days after the last of 5 successive focal streptococcal infections.

Coronary endarteritis polyposa, as illustrated in Fig. 29 from rabbit 71-77, has developed in several of our repeatedly infected rabbits. This lesion, designated endarteritis verrucosa by Holsti (13), is well illustrated by him in small arteries of peritonsillar tissue in two cases of relapsing arthritis and chronic rheumatic arthritis. In an extensive study of the coronary arteries in 66 cases

of active rheumatic fever, 34 cases of inactive rheumatic heart disease, and 50 non-rheumatic cases Gross, Kugel, and Epstein (14) found coronary endarteritis polyposa in three subjects, all with active rheumatic fever.

In the human rheumatic lesion of endarteritis polyposa (Fig. 28) the section passes through the attachment of the finger-like polyp to the vessel wall. The human verrucous lesion (Fig. 27) in healing might well become the lesion of endarteritis polyposa seen in Fig. 28 (human) and Fig. 29 (rabbit). The healing and conversion of verrucae to fibrous polyps in blood vessels may be quite comparable to the healing of valvular endocardial verrucae.

Still more advanced arterial lesions are illustrated in Figs. 32 through 37. Figs. 33, 35, and 37 are from fatal cases of rheumatic fever; Figs. 34 and 36 are from rabbits sacrificed respectively 11 days after 11 different focal streptococcal infections, and 10 days after 9 infections. Neither of these rabbits showed signs or symptoms of disease when sacrificed. Microscopically there were in these hearts several similar advanced arterial lesions and small foci of myocardial scarring, but no fresh myocardial granulomata. Fig. 32 is from a rabbit that developed a severe disease terminating fatally on the 14th day after the last of 8 focal streptococcal infections. There were present intense valvulitis, many areas of myocardial scarring (Fig. 25), and numerous fresh discrete and conglomerate myocardial granulomata. In all these human and rabbit arteries the marked alterations are internal to the internal elastic lamella; hence, they are intimal lesions. A striking feature is splitting and beading, and hyperplasia of the internal elastica, sometimes into a meshwork in which areas of increased numbers of smooth muscle cells and collagen fibers are enclosed by elastic mantles. In these arteries the media shows only slight alteration, usually in the form of moderate swelling of the smooth muscle nuclei; at other times there are focal areas of injury with a response in the form of small granulomata as in Fig. 32. At times the nuclei of the mesial muscularis are swollen with their long axes directed radially—Fig. 36. Sometimes certain segments of the vessel wall are more markedly involved than others (Figs. 32, 33, 35, 36, and 37). The lumina of all these vessels are markedly narrowed, occasionally practically obliterated as in Figs. 34 and 37. The laminated arrangement of several irregular layers of musculo-elastic tissue separated by heavier elastic membranes often in concentric rings suggests repeated and successive reactions to an injurious agent or agents. Both von Glahn and Pappenheimer (12) and Gross, Kugel, and Epstein (14) have called attention to the apparent uniqueness of this type of lesion in rheumatic fever subjects.

Noteworthy in all the cardiac blood vessel lesions in these rabbits is the absence of reaction resembling peri- or panarteritis nodosa.

In a few of these rabbit hearts there are found focal proliferation and necrosis of auricular and ventricular epicardial cells with frankly fibrinoid alteration of epi- and subepicardial collagen; focal scarring in these sites is also occa-

sionally seen. Although the more florid degrees of pericarditis are readily recognized in rheumatic subjects, some succumbing to the disease may show only small focal areas of epicarditis similar to those found in the rabbits.

Finally, in the aortae of a few of the animals under consideration there has occurred a patchy aortitis quite comparable to that occasionally encountered in rheumatic fever subjects, as illustrated in Fig. 38 from a rabbit and in Fig. 39 from a rheumatic patient. There is focal splitting and fragmentation of the elastica interna, with overlying intimal plaques of swollen interlacing collagen containing large mono- and multinucleated cells, and small mononuclears. Sometimes these proliferated cells are collected into minute granulomata (Fig. 38), but generally they are more diffusely distributed. Swelling of adventitial collagen that occasionally stains like fibrin with connective tissue techniques is seen in some of these rabbit and human rheumatic aortae.

DISCUSSION

The evidence presented here and previously (1) together with that derived from study of many other cardiac lesions, both human and rabbit, indicates that in the hearts of some rabbits subjected at varying intervals to successive focal infections with group A streptococci of several serological types, the following lesions were induced: (*a*) myocardial interstitial submiliary granulomata; (*b*) a variety of lesions of the cardiac blood vessels; (*c*) granulomatous endocarditis and valvulitis; and (*d*) occasionally localized epicarditis. And comparison of these lesions with those from fatal cases of rheumatic fever indicates that these experimentally induced lesions are quite similar to those found in human rheumatic carditis. The rabbit myocardial interstitial granulomata and certain of the cardiac blood vessel lesions appear, moreover, to be those that are, individually and in combination, peculiarly characteristic of rheumatic fever in man. Furthermore, neither comparable lesions nor spontaneous interstitial myocarditis have been found in normal control rabbits, in those dying or sacrificed after one intracutaneous infection, in those immunized with groups A or C streptococcal vaccines, or in rabbits that died or were sacrificed after a single intravenous inoculation with any of several types of group A streptococci.

So far as we are aware, the myocardial interstitial submiliary granulomata, the vascular, and mural endocardial lesions here described have not been previously induced in laboratory animals infected with streptococci or other microorganisms, either with or without bacterial or non-bacterial adjuvants. The question naturally arises: How do these lesions individually or in combination compare with those induced in rabbits by parenteral injections of foreign serum or one of its fractions? This question is pertinent because the rabbit cardiac lesions induced by foreign serum or its fractions are considered by some investigators to be essentially those characteristic of human rheumatic fever carditis.

Schick's (15) careful clinical studies of the *Nachkrankheiten* of scarlet fever, among them serous migratory polyarthritis and endocarditis, had suggested to him that these sequelae are "allergic" in nature. After the hemolytic streptococcal etiology of scarlet fever was established, the close identity of postscarlatinal rheumatism and carditis with poststreptococcal rheumatic polyarthritis and heart disease suggested a common pathogenesis. Weintraud (16), after studying the clinical resemblance of the polyarthritis of rheumatic fever and that of serum disease, predicated that the pathogenesis of rheumatic fever was related to an anaphylactic reaction to bacterial products in a body sensitized by infection. The analogies between these two diseases remained largely on a clinical basis until Klinge and his coworkers directed attention to histopathological resemblances in some of the lesions induced in rabbits by repeated injections of horse serum and those which they described in the tissues of patients who had succumbed to rheumatic fever. Klinge (17) induced an intraarticular Arthus phenomenon by injecting horse serum into the knee joints of previously subcutaneously sensitized rabbits and discovered that the reaction was featured by fibrinoid swelling of the ground substance in the synovia and periarticular collagen, followed by granulomatous inflammation about the altered collagen. He described similar lesions in human rheumatic polyarthritis. He also described in some of these rabbits perivascular granulomata that he considered analogous to Aschoff bodies. Vaubel (18) found that in the hearts of rabbits subjected to repeated subcutaneous and intravenous injections of horse serum there occurred vascular lesions resembling periarteritis nodosa, thromboangeitis obliterans, and rheumatic arteritis; sometimes there was also granulomatous valvular endocarditis. Frequently foci of fibrinoid swelling of collagenous ground substance was found within these vessels. The relative frequency and intensity of these lesions were roughly proportional to the number of serum injections administered to the animals. Junghans (19) induced severe valvular endocarditis and extensive panarteritis in the hearts and other organs of rabbits that had received only two or three successive subcutaneous and intravenous injections of pig serum, which is primarily much more toxic for rabbits than is horse serum; hence, the element of toxicity was added to that of allergic inflammation. While other investigators, Apitz (20), and Masugi and associates (21), confirmed these findings, Bruun (23), using horse serum 6 months old instead of comparatively fresh serum, such as that employed by Klinge, was unable to induce in rabbits an analogue of Aschoff's nodule. Indeed, Aschoff (22) stated that in his opinion none of the experimentally induced lesions up to that time had duplicated the structure of the myocardial submiliary granulomata characteristic of rheumatic fever.

Renewed interest in this subject was subsequently aroused by the experiments of Rich and Gregory (24–26) who induced lesions chiefly of the periarteritis nodosa type in the hearts and other tissues of rabbits, and sometimes granulomatous endocarditis with large single or repeated intravenous injections of horse serum. While these investigators' attention was directed originally towards the pathogenesis of periarteritis nodosa as a manifestation of anaphylactic hypersensitivity to various foreign antigens, they felt that serum-induced cardiac lesions of rabbits in their basic characteristics resembled those of rheumatic fever. Other investigators, by similarly administering the second intravenous dose of serum approximately 2 weeks after the first, or by employing chemically defined fractions of beef or horse serum, or by giving one massive

intravenous injection of the antigen have induced in rabbits cardiac vascular lesions that are likewise generally of the peri- or panarteritis nodosa or "allergic" type (Hopps and Wissler (27), McKeown (28), Ehrich, Seifter, and Forman (29), and More and McLean (30)). Hawn and Janeway (31) found that one injection of bovine serum albumin induced more vasculitis and endocarditis than did bovine gamma globulin; but More, Waugh, and Kobernick (32), by injecting two massive doses of this globulin into 17 rabbits that were unilaterally nephrectomized, induced granulomatous valvulitis in 9 animals and coronary panarteritis in 2. Wissler, Smull, and Lesh (33) found that horse serum albumin was more capable of inducing "acute" panarteritis than were other fractions; whereas a mixture of alpha and beta globulins induced "chronic" arteritis characterized by collections of mononuclear cells in the arterial adventitia; but the photomicrographs cited show panarteritis.

Peri- or panarteritis nodosa is generally considered to be the characteristic manifestation of anaphylactic hypersensitivity induced by foreign serum in the hearts and other tissues of man and lower animals; while this lesion has been occasionally described in fatal rheumatic fever, it is not a common or a characteristic feature of this disease. It is, moreover, noteworthy that in the hearts of the rabbits here described, that have undergone repeated focal group A streptococcal infections, peri- or panarteritis nodosa is conspicuously absent. The acute and healed lesions in the cardiac arteries of these rabbits, on the other hand, bear striking resemblance to those found by us in fatal rheumatic carditis and considered by von Glahn and Pappenheimer (12) and Gross and his associates (14) to be highly characteristic of rheumatic fever. In the finer branches of these rabbits' coronary arteries, there were also found both fresh and healed lesions quite similar to those first described in fatal rheumatic fever by Krehl (10).

It is generally recognized that the peculiar histologic hallmark of rheumatic fever in the human heart is the myocardial interstitial submiliary granuloma, the Aschoff body (34). While so called "Aschoff-like bodies" have been described in the hearts of animals with serum disease, most of the published illustrations appear clearly to represent segmental arteritis of the peri- or panarteritis nodosa type.

More and McLean (30) found no "Aschoff-like lesions" in the myocardia in a large group of rabbits having carditis induced with large intravenous injections of horse serum, but they found panarteritis in 60 per cent of these rabbits. And in unilaterally nephrectomized rabbits receiving two massive injections of bovine serum gamma globulin, More, Waugh, and Kobernick (32) found a few myocardial foci of mononuclears like those described in normal rabbits by Miller (35); and these foci were also present in their control animals; but no lesions resembling Aschoff bodies were found. In about half of their experimental animals, however, panarteritis was present. Wissler, Smull, and Lesh (33) described the infrequent "Aschoff nodules" they found in rabbits to which they had given two successive doses of horse serum or its fractions, as focal periarterial inflammation made up of various mononuclear and occasionally poly-

nucleated cells, and rarely with significant fibrinoid alteration of the collagen. These lesions could be interpreted as being segmental panarteritis.

The "Aschoff body–like structures" referred to by Ehrich *et al.* (29) in the hearts of rabbits sustaining large intravenous injections of horse serum were described as perivascular accumulations of mesenchyme cells; and it is noteworthy that these lesions developed simultaneously with arteritis of the peri- or panarteritis or "allergic" type. Inasmuch as this arteritis was at times observed to be segmental, it seems probable that the "Aschoff body–like structures" represented segmental arteritis of the peri- or panarteritis or "allergic" type. These segmental arterial lesions appear to resemble closely those observed in human serum disease by Clark and Kaplan (36). The latter authors concluded that the periarterial lesions in human serum disease did not closely correspond with the Aschoff nodules of rheumatic fever.

The data cited above in connection with serum-induced carditis suggest the possibility that the rabbit myocardium may not be capable of developing granulomata in consequence like those of rheumatic fever. That under suitable circumstances it does have this capacity is, however, established by the results here presented; for in some of these rabbits repeatedly infected with group A streptococci there have occurred myocardial interstitial submiliary granulomata, often unrelated to arteries, that are strikingly similar to the most characteristic of all human rheumatic fever lesions, the Aschoff bodies.

The valvular intersititial and endocardial lesions in these rabbits bear striking resemblance to those encountered in human subjects who succumbed early to active rheumatic carditis. It is, nevertheless, noteworthy that several investigators cited above, as well as others, have described analogous granulomatous valvular endocarditis and/or interstitial valvulitis in rabbits subjected to injections of foreign protein. In human rheumatic fever neither the early nor later stages of valvulitis and endocarditis are necessarily pathognomonic of rheumatic fever, for as Rich (37) has emphasized, entirely similar valvular and verrucous endocardial lesions may occur in disseminated lupus erythematosus. It seems apparent, therefore, that interstitial valvulitis and valvular endocarditis are less characteristically pathognomonic in both human disease and in experimentally induced carditis than are myocardial submiliary granulomata and certain lesions of cardiac blood vessels. The same statement applies to focal epicarditis, although in the occasional epicardial lesion found among rabbits here described, the element of fibrinoid alteration in collagen was more marked than that noted by Wissler and coworkers (33) in their rabbits injected twice with horse serum or its fractions.

It should be noted that the course of the final disease in the rabbits repeatedly infected with streptococci did not follow, in general, that usually observed in patients with rheumatic fever; *viz.*, phase 1, initiating group A streptococcal infection; phase 2, apparent quiescence; phase 3, rheumatic manifestations. With wider application of laboratory techniques for observing patients, it has been

found, however, that during phase 2 there occur not infrequently such indicators of a continuing disease state as persisting or relapsing abnormal erythrocyte sedimentation rates, leucocytosis, and sometimes abnormal electrocardiograms. Malaise, abnormally high pulse/temperature ratios, with the patients either at rest or after moderate exercise, and simple arthralgia have similar connotations. Occasionally phase 2 is apparently very brief, especially in patients having a superinfection with a streptococcus of a type different from that which infected him a few weeks previously. Indeed, such super infections suggested to Rantz and his coworkers (38) that reinfection with streptococci of a new type might be an important pathogenetic factor in rheumatic fever. It is difficult to evaluate this suggestion from their data, because most of the superinfections occurred within the period when phase 3 was observed to occur among our patients following infection with group A streptococci of a single type (Watson *et al.* (39)). As group A streptococci are not natural pathogens for rabbits, it might be expected that their responses might differ from those encountered in man. In fact, accelerated local response to focal infection is a common phenomenon in rabbits that have previously sustained focal infections with streptococci.

In comparing serum disease in animals on the one hand and rheumatic fever in man on the other, it is necessary to consider four different combinations of variables; *viz.*, two hosts and two probable etiological factors; hence logically there arises a hazard in stating that the two diseases are analogous in their pathogenesis simply because they have certain manifestations in common. Comparable manifestations may, however, point the way to fruitful investigations of these possibilities. Indeed, Aschoff (22) emphasized the importance of applying the same etiologic stimulus to different species of animals and comparing their responses if one is to establish common causes for those responses. We would add that it might be equally important to provide an association between the experimental animal and the etiological agent under consideration approximately similar to that which occurs in man, the natural host for that agent. Group A streptococci are not natural pathogens for the rabbit, hence may elicit different responses in this species than in man. Nevertheless, by studying the results of a succession of human group A streptococcal infections and then submitting rabbits to a somewhat comparable series of infections there have been induced in some of these rabbits cardiac lesions so similar to those peculiarly characteristic of fatal rheumatic fever in man that the conclusion seems justified that common pathogenetic factors are operative in both this rabbit disease and in human rheumatic fever. And it seems probable that among various factors the pathogenesis of both abnormal conditions is attended by altered host reactivity to group A streptococci that had been induced by previous infection with these microorganisms.

SUMMARY

Cardiac lesions like those characteristic of rheumatic fever in man have been induced in a small portion of rabbits that were subjected to successive focal infections with group A streptococci of several serological types.

Fresh myocardial interstitial granulomata so induced bear striking resemblance to Aschoff bodies, the histologic hallmarks of human active rheumatic fever; and the fresh and healed lesions found in the cardiac valves, endocardia, epicardia, blood vessels, and aortae of some of these rabbits are homologous with those characteristic of rheumatic fever in man.

These experimental myocardial and vascular lesions and those of human rheumatic fever differ in several important respects from the lesions of experimental and human serum disease.

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EXPLANATION OF PLATES

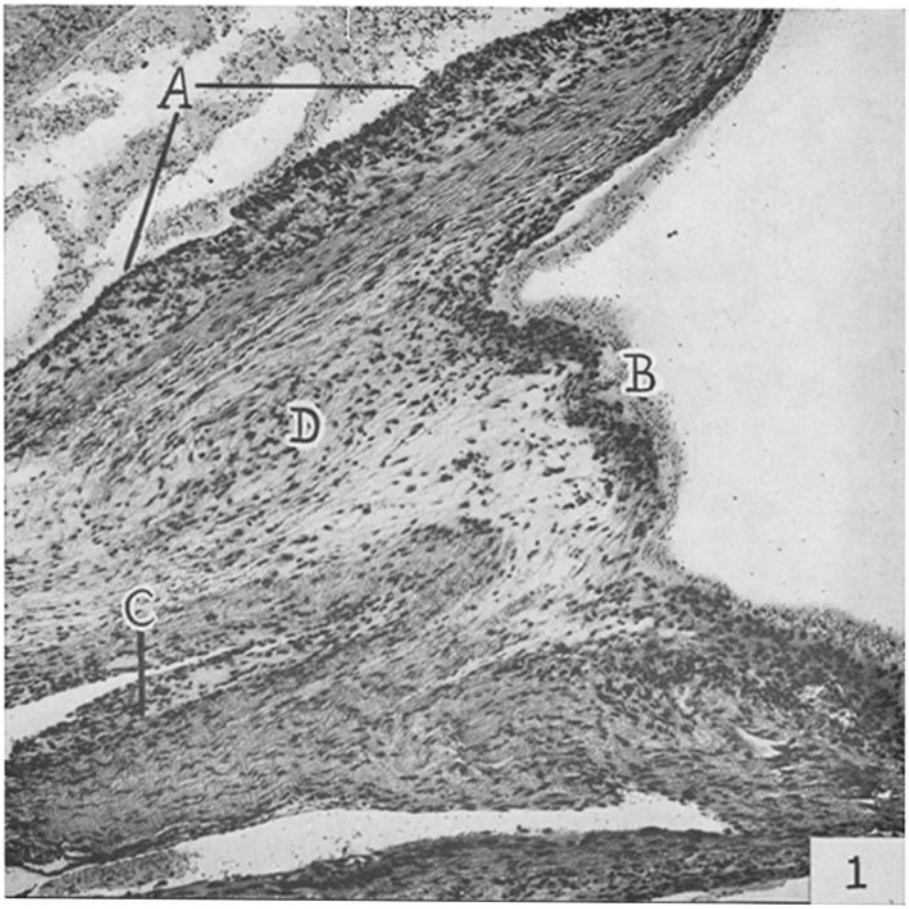
The photographs were made by Mr. Julian Carlile and Miss Patricia Allen.

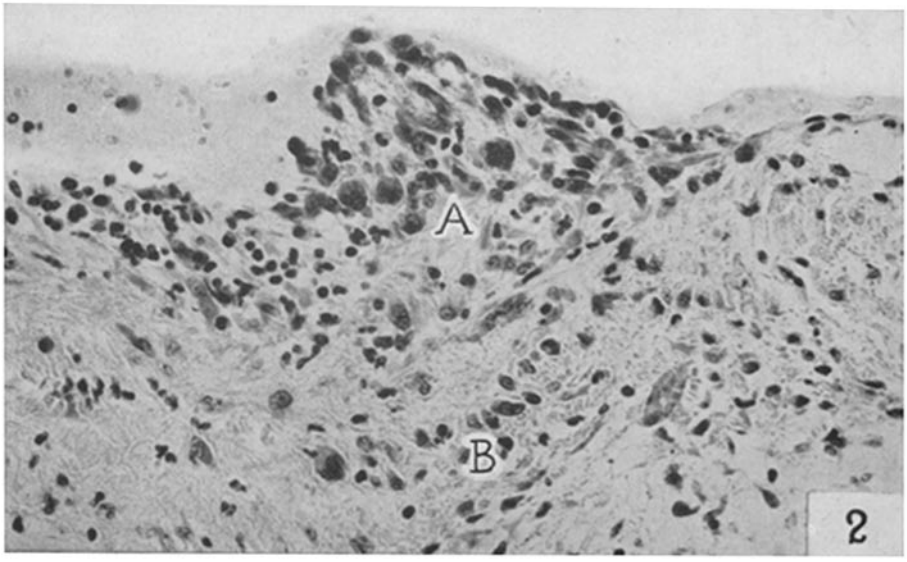
In no rabbit of this series were streptococci found either in blood cultures or in the cardiac lesions.

PLATE 21

FIG. 1. Rabbit 71-77; died after developing markedly irregular cardiac rhythm 8 days following the last of 5 infections. Endo- and subendocardial palisade on ventricular (*A*) and auricular (*B*) sides of mitral valve; *C*, comparable involvement of chordae tendineae; *D*, interstitial valvulitis. Hematoxylin and eosin. × 82.

FIG. 2. Rabbit 71-77; Mitral valve. Proliferation of valvular endocardial cells with breaking of superficial elastic membrane forming a projecting nodule (*A*) of large mono- and multinucleated cells with vesicular nuclei and basophilic cytoplasm; similar cells above *B* arranged in crescentic pattern at base of nodule; fragmented elastica and swollen collagen between these two groups of cells; this lesion is highly suggestive of early verruca formation. Hematoxylin and eosin. × 286.



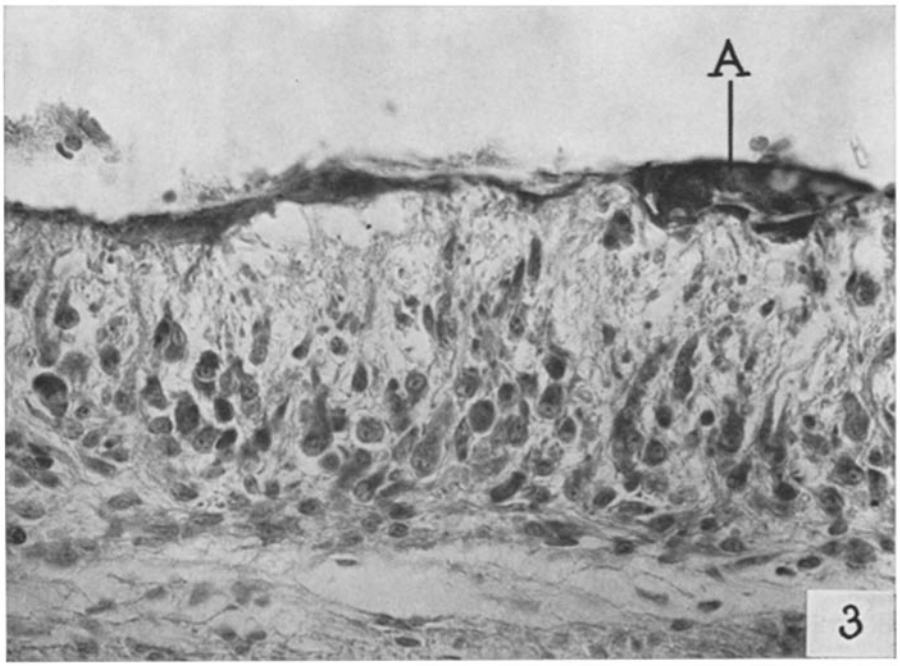


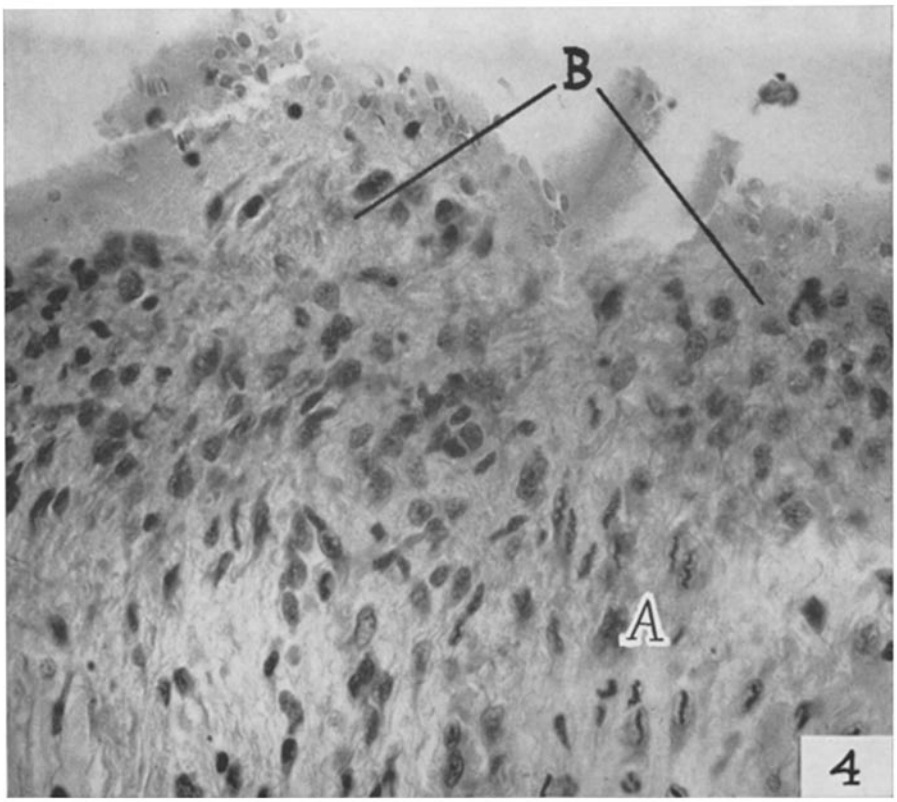
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 22

FIG. 3. From a 28 year old woman who died with active rheumatic heart disease (autopsy 582, Rockefeller Institute Hospital). Aortic valve palisade of large mono- and multinucleated cells with vesicular nuclei and basophilic cytoplasm; necrosis of superficial cells to form a flat microscopic preverruca (*A*). Eosin-methylene blue. × 454.

FIG. 4. Rabbit 71-77; higher magnification of mitral valve at *B* in Fig. 1. Palisade of large mono- and multinucleated cells with vesicular nuclei and basophilic cytoplasm; numerous cells of the "Anitschkow myocyte" type surrounding *A*; *B*, most superficial portions of palisade have broken through valvular endothelium and internal elastic membrane. Hematoxylin and eosin. × 443.



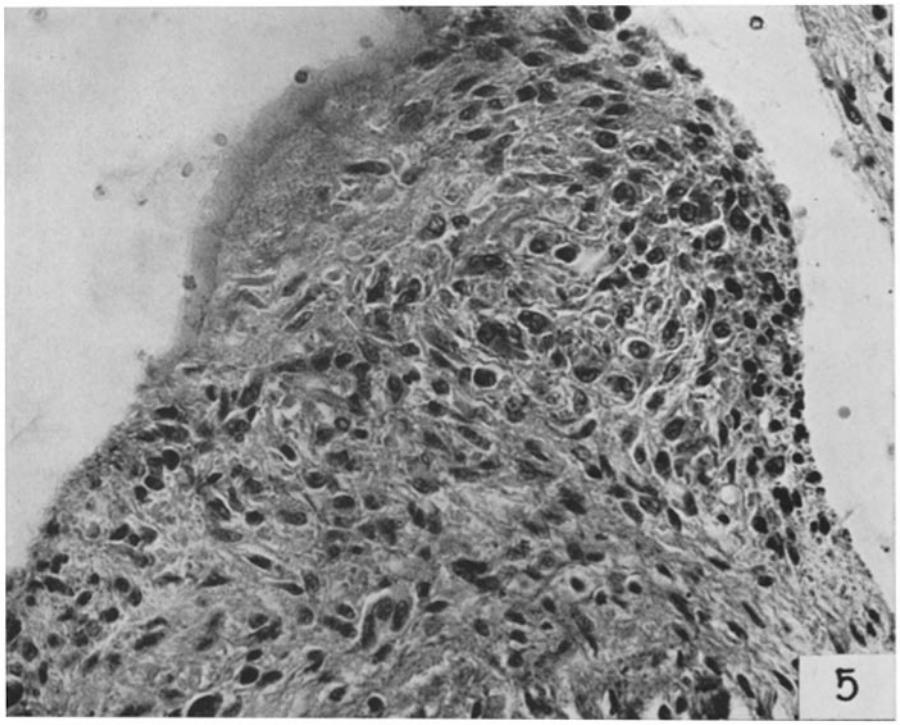


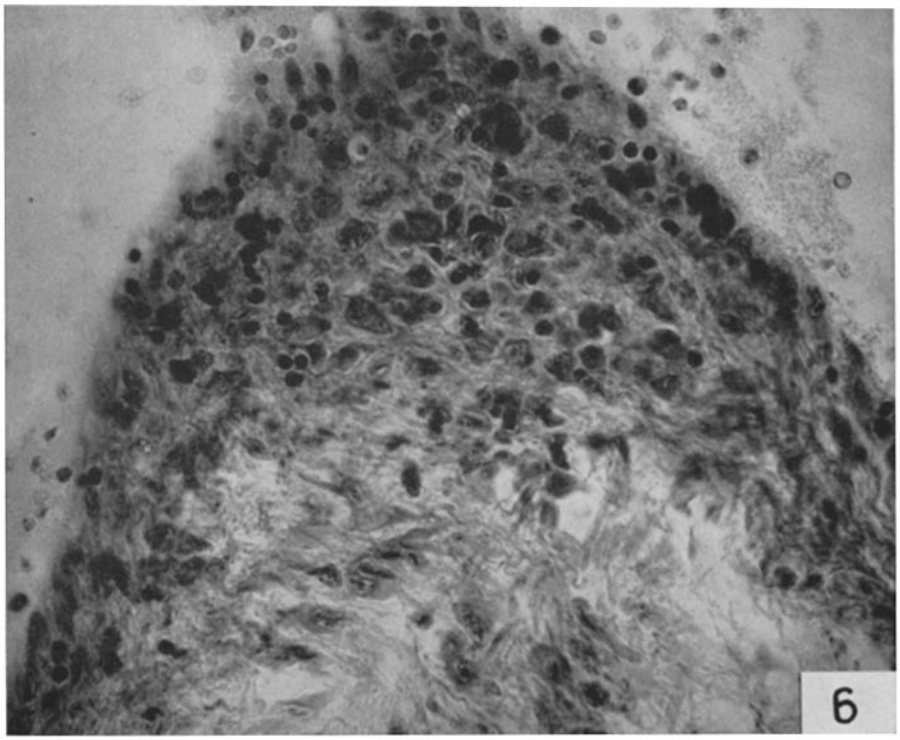
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 23

FIG. 5. From a 10 year old boy who died after 3 months of active rheumatic fever (autopsy 325, Rockefeller Institute Hospital). Nodule of large mono- and multinucleated cells among masses of swollen collagen at tip of trabecula carneae. Masson trichrome. × 388.

FIG. 6. From rabbit heart referred to in Figs. 1, 2, and 4. Similar lesion at tip of trabecula carneae. Giemsa. × 437.



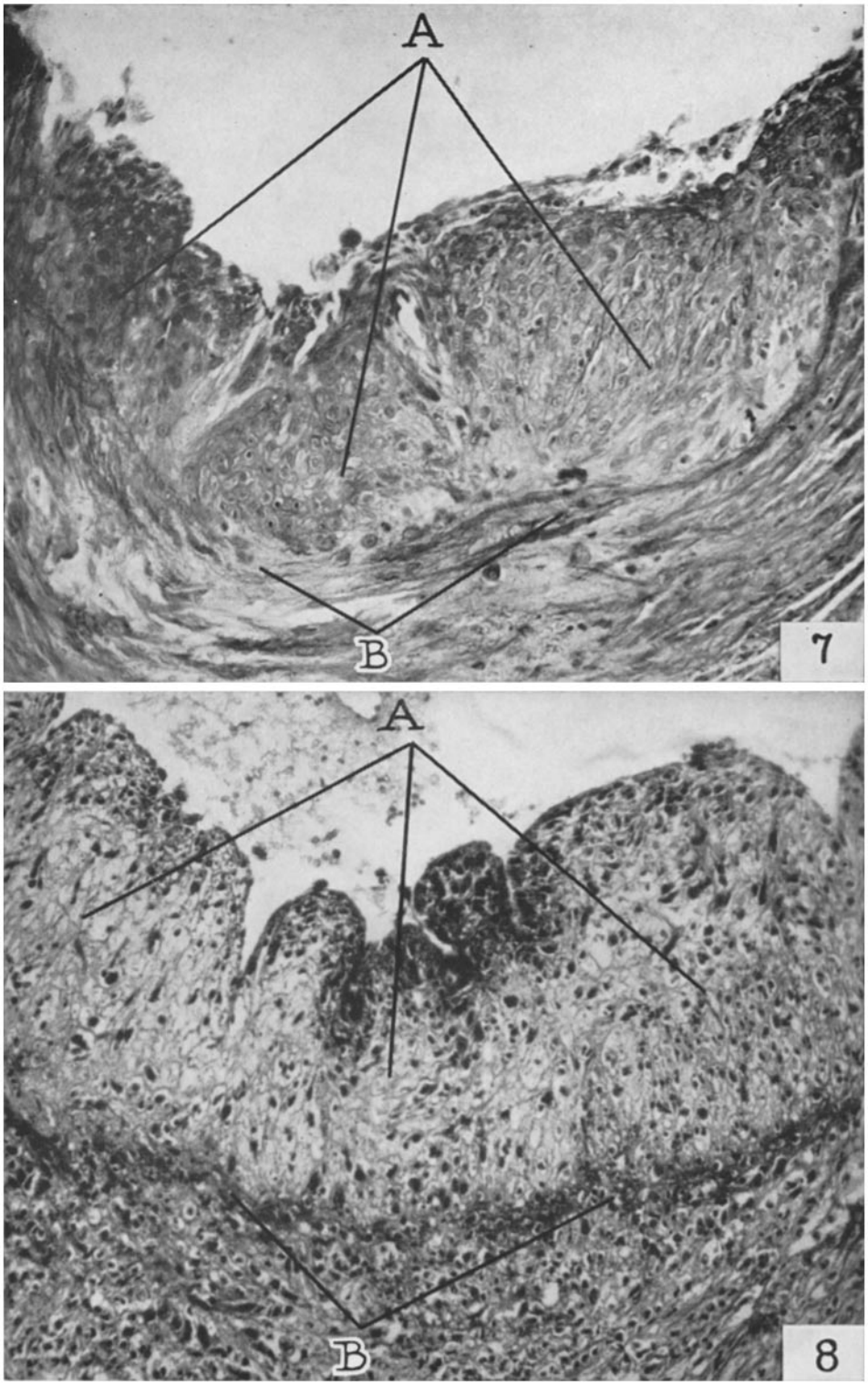


(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 24

FIG. 7. Rabbit 73-13; sacrificed 15 days after the last of 4 infections, the last of which was a superinfection. *A*, polypoid palisading of endo- and subendocardial cells within network of swollen collagen in mitral sulcus; *B*, fragmented internal elastic lamella. Weigert-hematoxylin and eosin. × 235.

FIG. 8. From human heart referred to in Fig. 5. *A*, polypoid palisading of endo- and subendocardial cells within network of swollen collagen in a mitral valve sulcus with necrosis of some of the most superficial cells; *B*, fragmented internal elastic lamella. Weigert-hematoxylin and eosin. × 235.

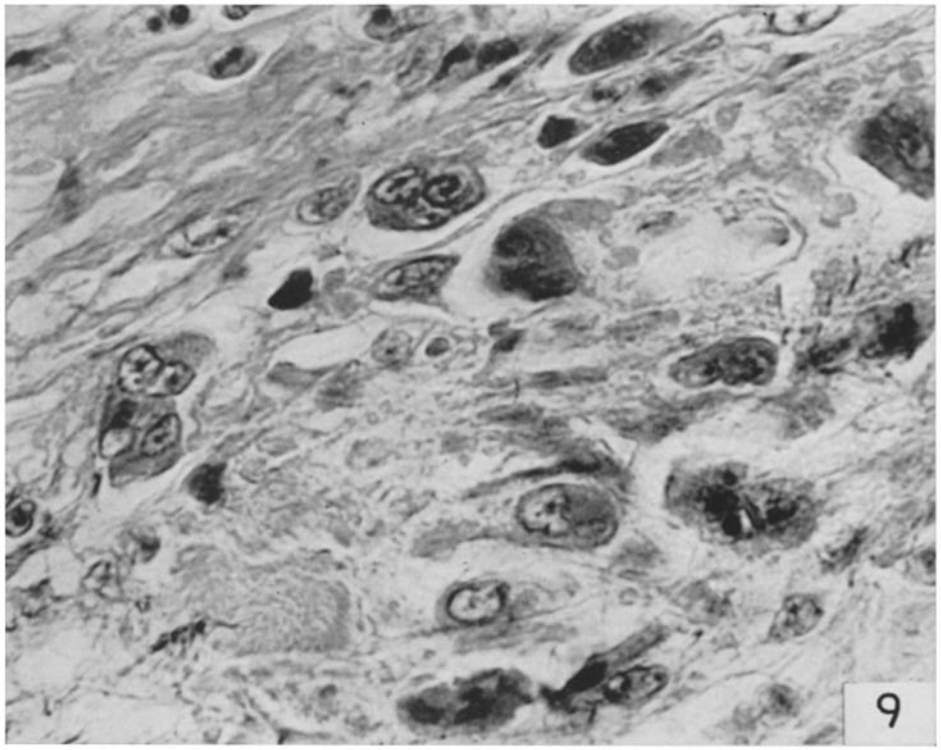


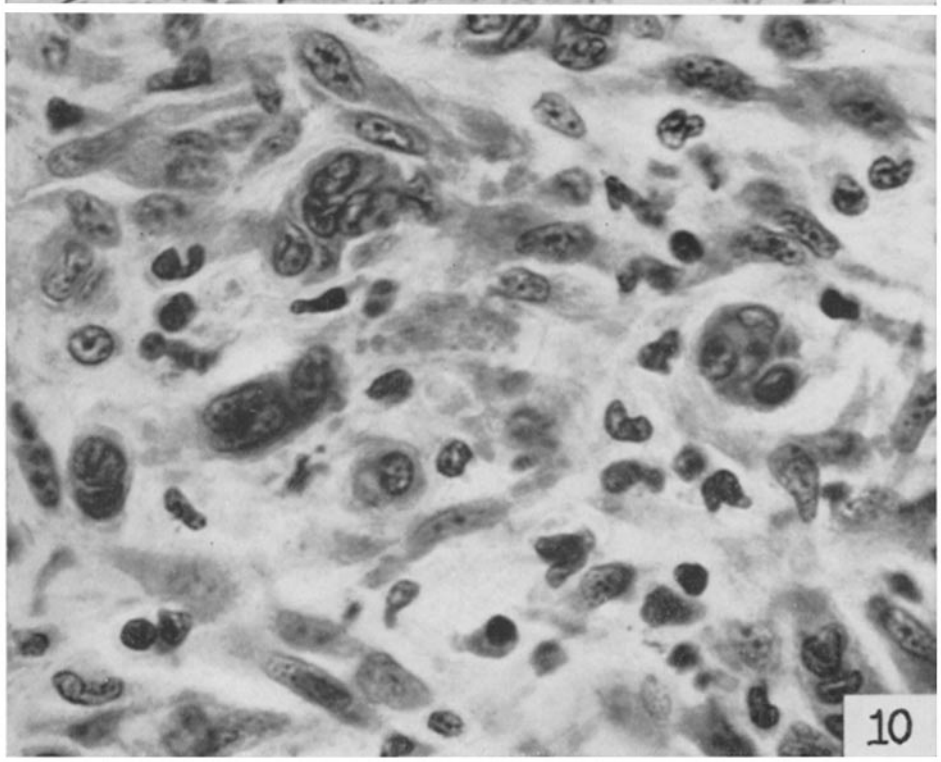
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 25

FIG. 9. From human heart referred to in Figs. 5 and 8. Dispersed among greatly altered collagen fibers in aortic sulcus are mono- and multinucleated granuloma cells, characteristic of rheumatic fever. Weigert-hematoxylin and eosin. × 886.

FIG. 10. Similar lesion in mitral sulcus of rabbit heart referred to in Figs. 1, 2, 4, and 6. Hematoxylin and eosin. × 887.





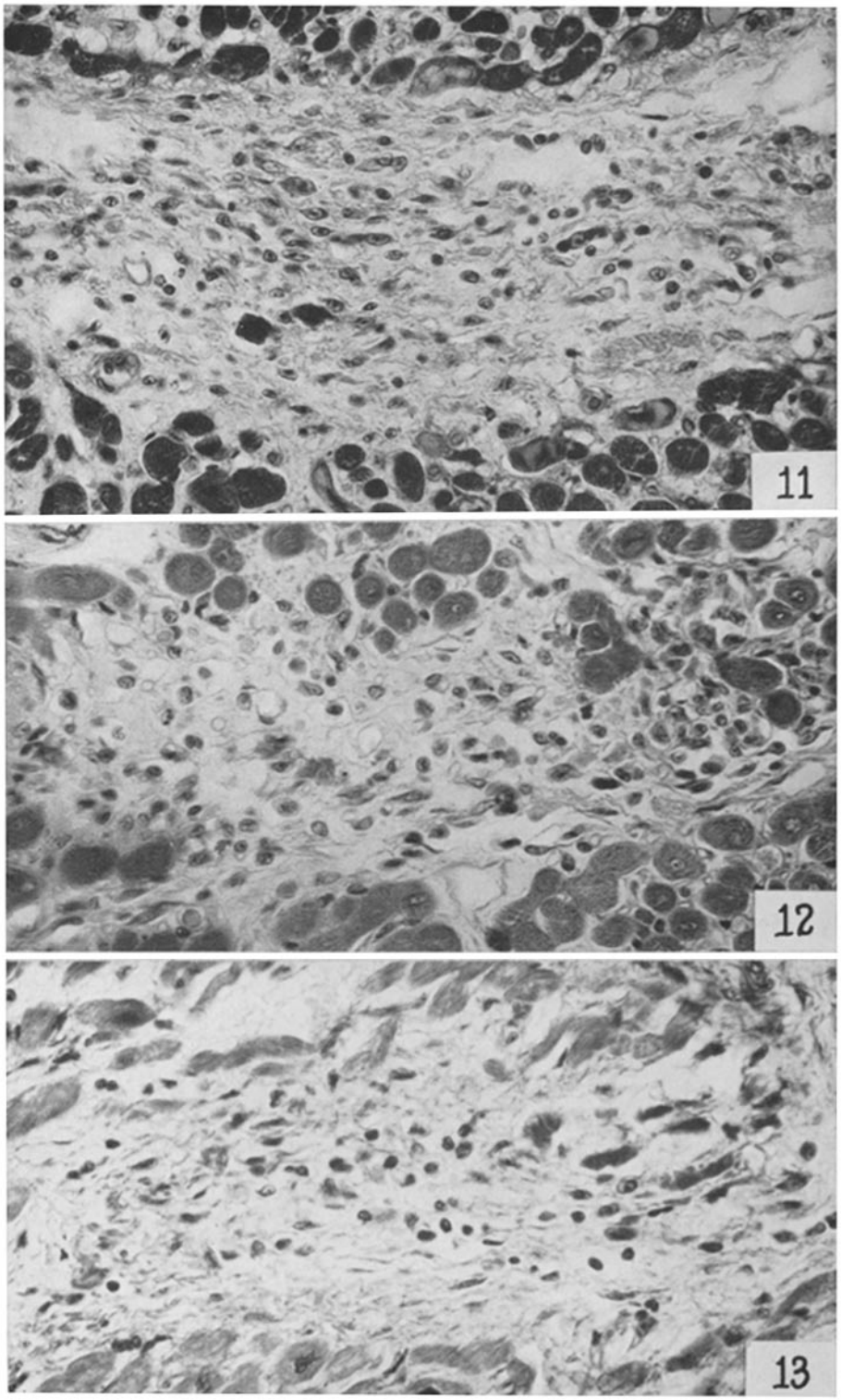
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 26

FIG. 11. From right ventricle of human heart referred to in Figs. 5, 8, and 9. Diffuse reticular Aschoff body in myocardial interstitium; many mononucleated and rare multinucleated granuloma cells dispersed in an interlacing network of swollen collagen that does not stain like fibrin with Masson trichrome method; definite alteration of adjacent myofibers. Arteriolitis, left lower corner. × 376.

FIG. 12. Rabbit 71-80; sacrificed while sick 10 days following the last of 6 infections. Similar reticular granuloma in myocardial interstitium; alteration of adjacent myofibers. Masson trichrome. × 399.

FIG. 13. Similar reticular granuloma in myocardial interstitium of heart referred to in Figs. 5, 8, 9, and 11; alteration of adjacent myofibers. Weigert-hematoxylin and eosin. × 420.

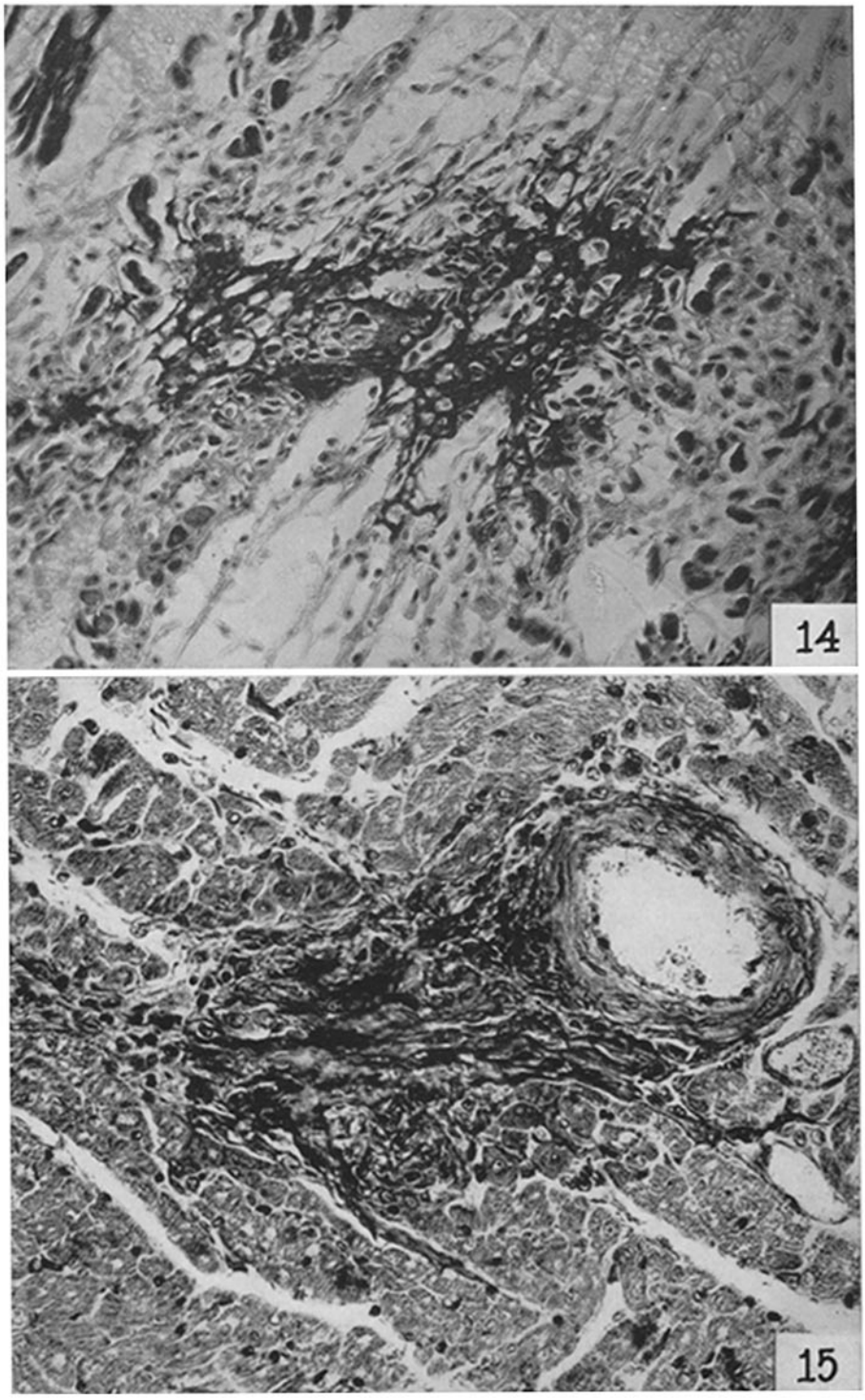


(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 27

FIG. 14. From a 50 year old man who died about 2 weeks after apparent onset of active rheumatic fever (autopsy 40, Rockefeller Institute Hospital). Lesion in left ventricle of heart; interlacing network of swollen collagen (much of which stains unequivocally like fibrin) embracing many mono- and occasional multinucleated rheumatic granuloma cells; extensive necrosis of myofibers. Masson trichrome. × 248.

FIG. 15. From the rabbit heart referred to in Figs. 1, 2, 4, 6, and 10. Lesion in right ventricle consisting of network of swollen collagen (much of which stains unequivocally like fibrin) embracing several mono- and occasional multinucleated granuloma cells; necrosis of myofibers prominent; lesion involves adventitia of artery on the right. Peri- or panarteritis nodosa absent. Masson trichrome. × 357.



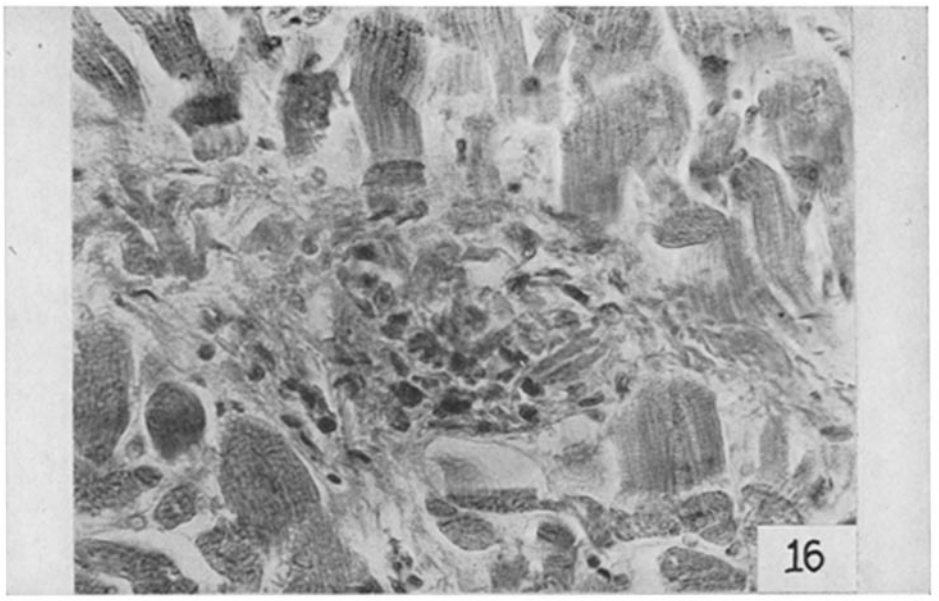
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

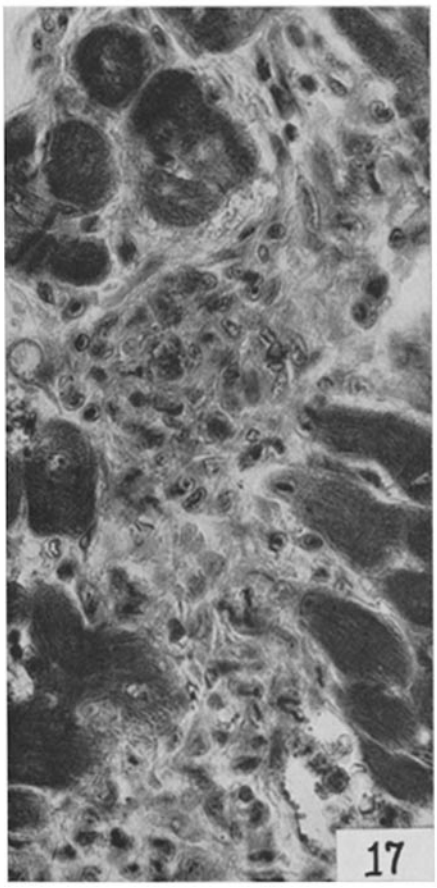
PLATE 28

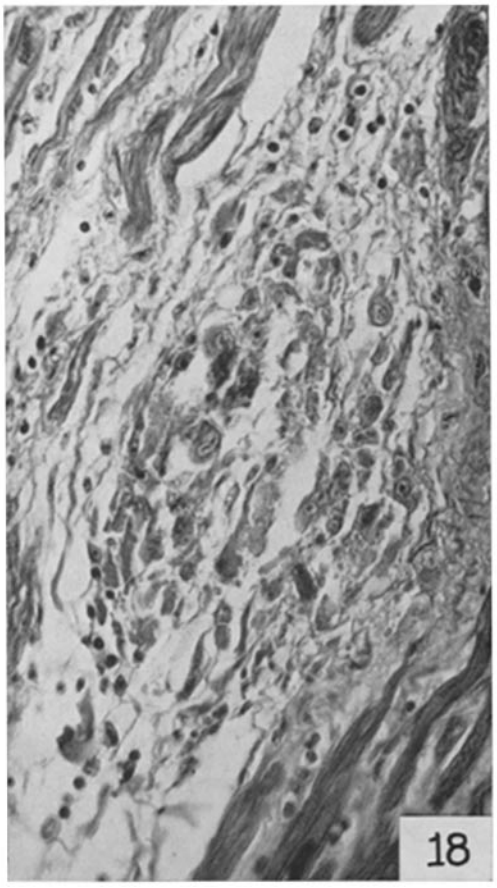
FIG. 16. From a 19 year old man who died 3 months after onset of a severe second (recognized) attack of rheumatic fever (autopsy 319, Rockefeller Institute Hospital). Mosaic Aschoff body in myocardial interstitium in interventricular septum; mono- and occasional multinucleated granuloma cells lodged between masses of swollen collagen fibers, only very few of which exhibit small portions that take the stain for fibrin with Masson trichrome method. × 444.

FIG. 17. From the heart of the rabbit referred to in Fig. 12. Entirely similar mosaic granuloma in myocardial interstitium in left ventricle. Masson trichrome. × 443.

FIG. 18. From a 17 year old girl who died with active rheumatic heart disease (autopsy 26-48, Roosevelt Hospital). Mosaic Aschoff body in myocardial interstitium in interventricular septum; altered collagen and granuloma cells similar to the lesions in Figs. 16 and 17. Masson trichrome. × 354.







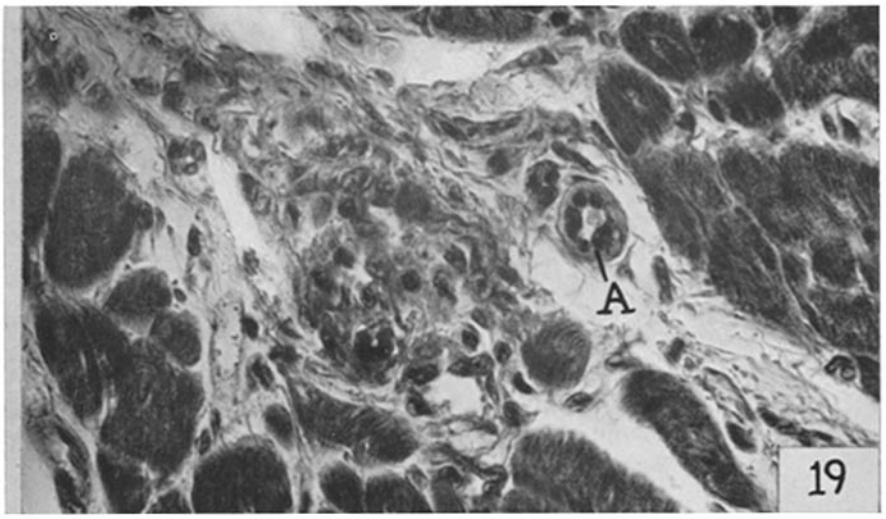
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

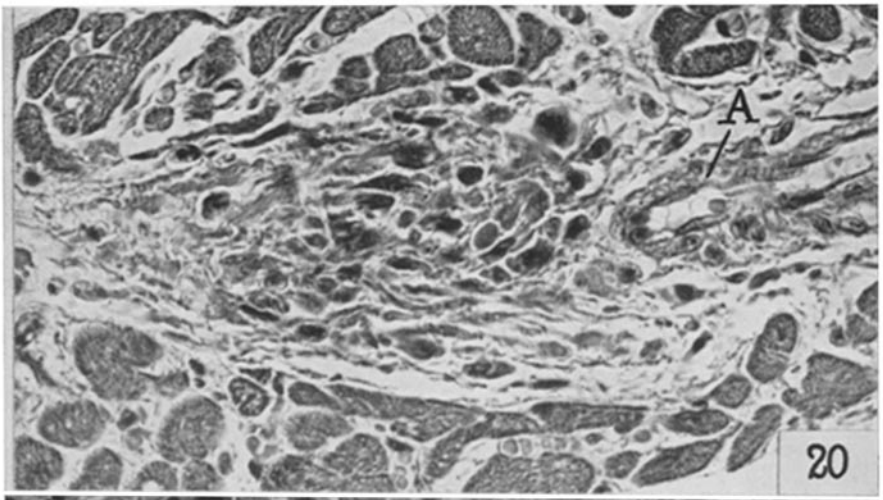
PLATE 29

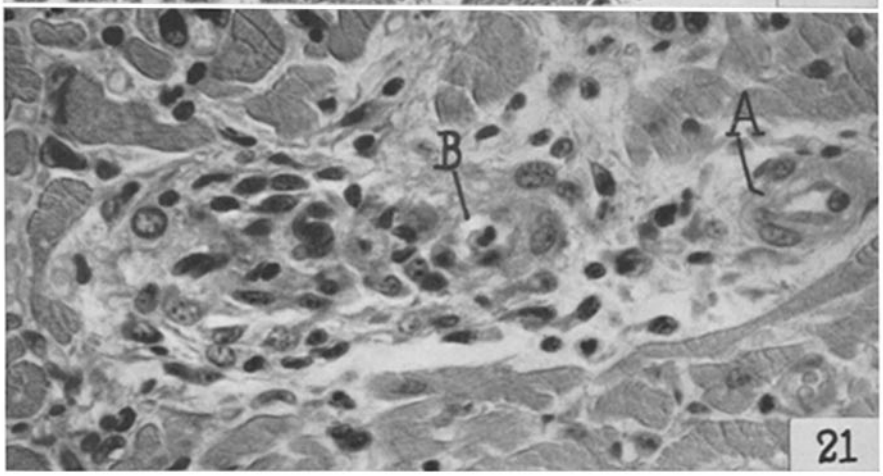
FIG. 19. From rabbit heart referred to in Figs. 12 and 17. Mosaic myocardial interstitial granuloma close to an arteriole, *A*, the endothelial cells of which are swollen; granuloma cells lodged between masses of swollen collagen. No panarteritis nodosa. Masson trichrome. × 523.

FIG. 20. From a 7 year old girl who died with active rheumatic fever (autopsy 37034, Bellevue Hospital). Similar mosaic myocardial interstitial Aschoff body situated in left ventricle close to an artery, *A*, the endothelial cells of which are swollen. Panarteritis nodosa absent. Hematoxylin and eosin. × 517.

FIG. 21. Rabbit 70-66; died 10 days after last of 9 infections. Similar mosaic myocardial interstitial granuloma situated in left ventricle close to artery, *A*, and in close association with arteriole, *B*. Panarteritis nodosa absent. Hematoxylin and eosin. × 510.





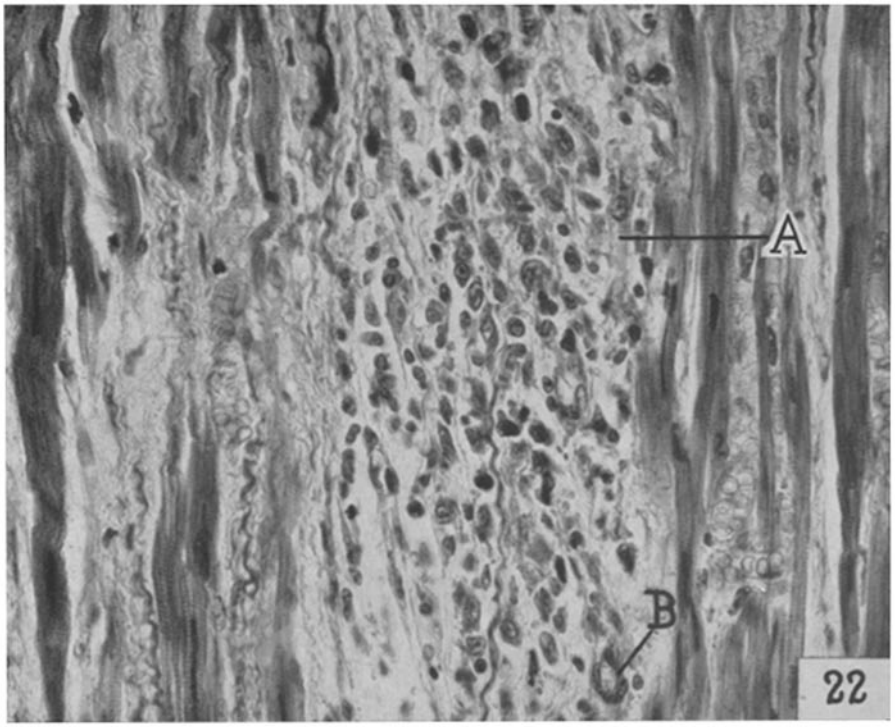


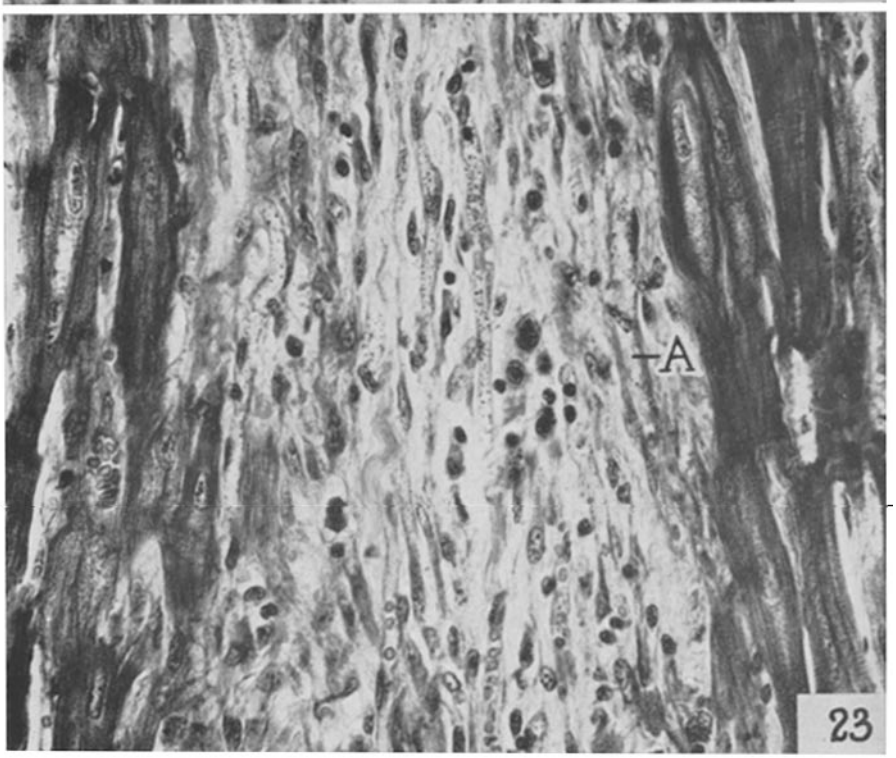
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 30

FIG. 22. From a 16 year old girl who died with active rheumatic fever of about one month's duration (autopsy 220, Rockefeller Institute Hospital). Mosaic Aschoff body in cardiac papillary muscle; mono- and very occasional multinucleated granuloma cells interspersed between masses of swollen collagen and partially obscured fragments of necrotic myofibers (*A*) and sarcolemma; only portions of an occasional collagen mass take the stain for fibrin with Masson trichrome method; necrosis of myofibers more clearly evident at borders of lesion. Swelling of endothelial cells of capillary at *B*. × 404.

FIG. 23. From heart of rabbit referred to in Figs. 1, 2, 4, 6, 10, and 15. Apparent earlier stage in a process similar to that in Fig. 22. All stages of myofiber (*A*) and sarcolemma alteration evident. Only portions of an occasional collagen mass take the stain for fibrin with Masson trichrome method; lesser degree of mesenchyme cell proliferation in this rabbit lesion as compared with human lesion in Fig. 22 possibly related to termination of the rabbit disease (8 days' duration) much earlier than the human disease (one month's duration). × 409.



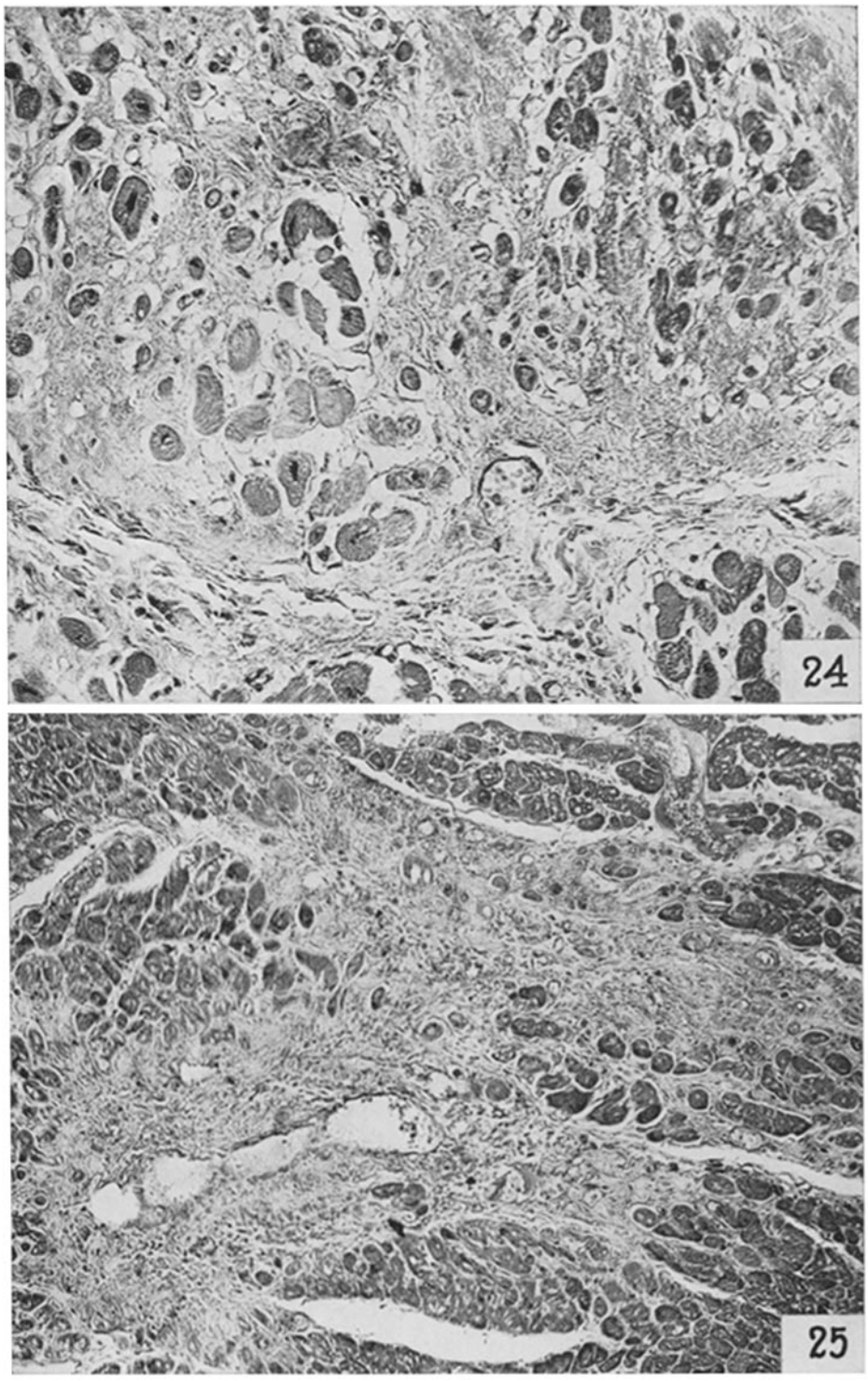


(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 31

FIG. 24. From a 9 year old girl who died during the last of several attacks of rheumatic fever (autopsy 189, Rockefeller Institute Hospital). Marked myocardial scarring in left ventricle. Most of the collagen in the scars shows distinct swelling and numerous fibers partially or entirely stain like fibrin with Masson trichrome method. Mesenchyme cells dispersed throughout the fields of fibrinoid collagen. × 261.

FIG. 25. Rabbit 70-58; died 13 days following last of 8 infections; marked myocardial scarring in left ventricle. Most of the collagen exhibits the identical apparently fresh alterations described for that in Fig. 24. Mesenchyme cells dispersed throughout the fields of fibrinoid collagen. Masson trichrome. × 261.



(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

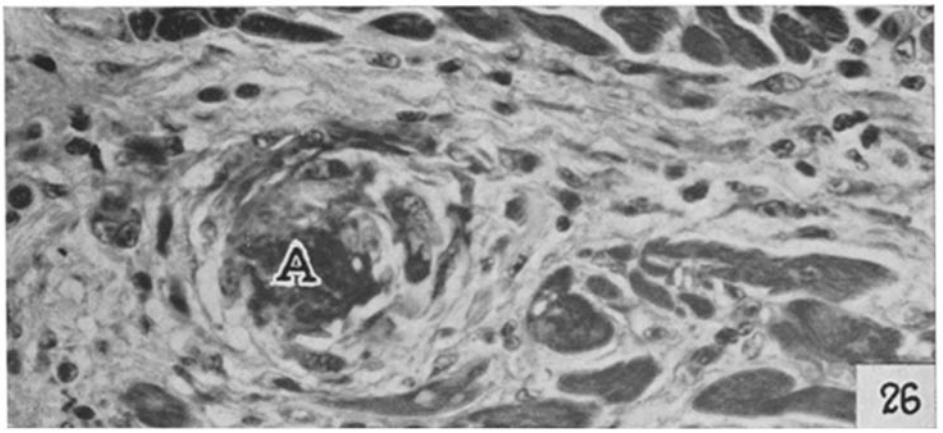
PLATE 32

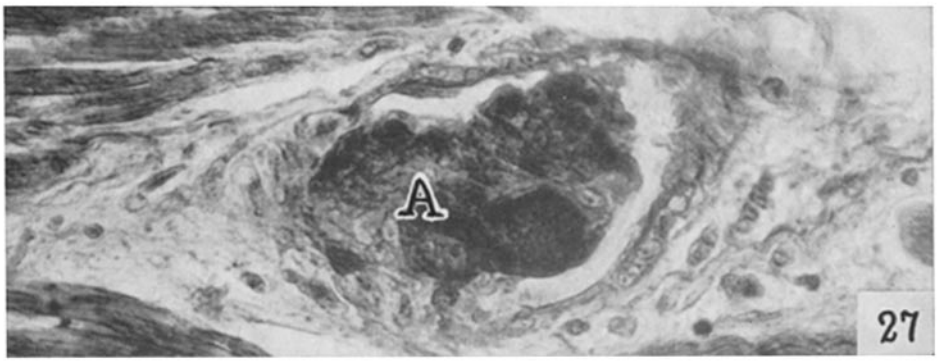
FIG. 26. From rabbit heart referred to in Fig. 21. Verrucous arteritis (verruca at *A*) in left ventricle; intense proliferation and necrosis of endothelial and subendothelial cells obliterating lumen of artery; panarteritis nodosa absent; proliferation of mesenchyme cells in adventitia and among swollen collagen fibers in adjacent interstitium. Masson trichrome. × 576.

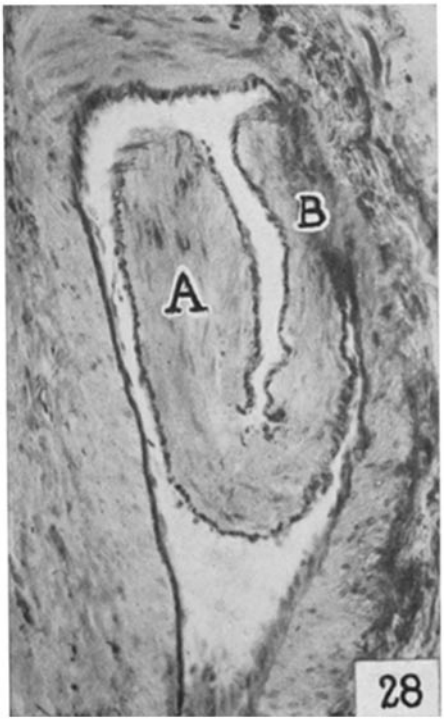
FIG. 27. From a 6 year old girl who died during a severe second (recognized) attack of rheumatic fever (autopsy 197, Rockefeller Institute Hospital). Verrucous arteritis (verruca at *A*) in right ventricle; same changes as in lesion of Fig. 26; panarteritis nodosa absent. Masson trichrome. × 576.

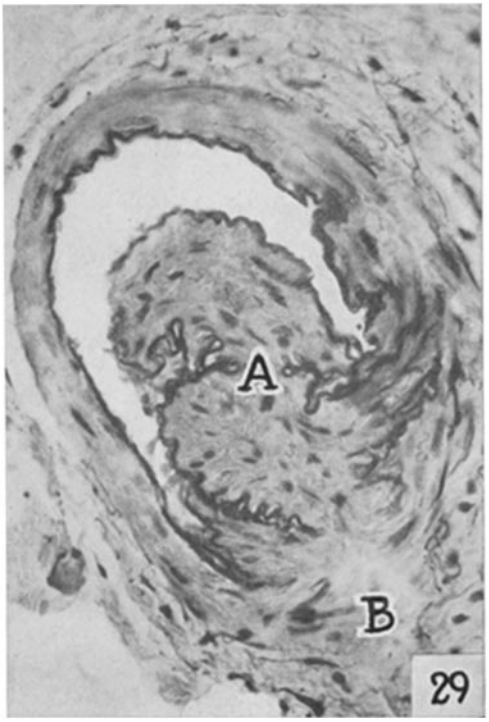
FIG. 28. From an 11 year old girl who died during the last of several attacks of rheumatic fever (autopsy 426, Rockefeller Institute Hospital). Endarteritis polyposa in subepicardium; *A*, polyp arising from vessel wall at *B*. This lesion may represent the healed stage of a verruca such as occurs in Fig. 27. Weigert-hematoxylin and eosin. × 225.

FIG. 29. From subendocardium of left ventricle of the rabbit heart referred to in Figs. 1, 2, 4, 6, 10, 15, and 23. Endarteritis polyposa; *A*, centrally placed, organized polypoid mass within lumen of artery; *B*, disrupted media and external elastica. It might be expected that healing of the verrucous lesion within the human artery in Fig. 27 would result in polypoid endarteritis as occurs in this rabbit artery. Weigert-hematoxylin and eosin. × 432.









(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 33

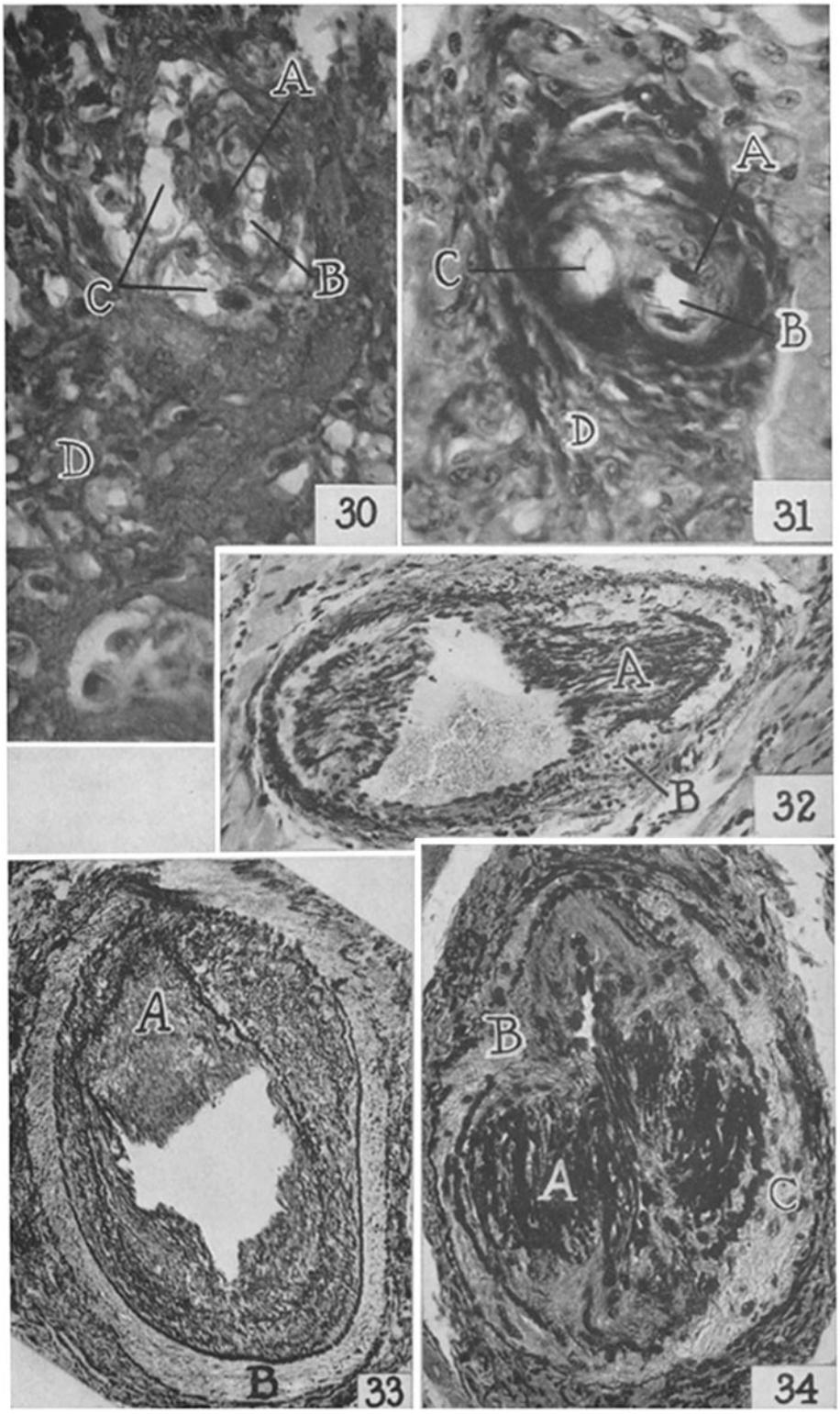
FIG. 30. From a 17 year old girl who died during the last of several attacks of rheumatic fever (autopsy 179, Rockefeller Institute Hospital). Arteriolar lesion in auricular retro-aortic myoepicardial wedge showing the following: *A*, marked swelling and hyperplasia of endothelial cells; *B*, narrowed lumen; *C*, perivascular edema; *D*, dense paravascular interlacing network of swollen collagen staining like fibrin (with connective tissue techniques) and embracing only a few proliferated mesenchyme cells. This is not the lesion of panarteritis nodosa. Weigert-hematoxylin and eosin. × 542.

FIG. 31. From left ventricle of rabbit heart referred to in Figs. 1, 2, 4, 6, 10, 23, and 29. Similar arteriolar lesion showing: *A*, hyperplasia of endothelial cells; *B*, narrowed lumen; *C*, perivascular edema; *D*, dense paravascular interlacing network of swollen frankly fibrinoid collagen in which are dispersed a moderate number of mesenchyme cells. This is not the lesion of panarteritis nodosa. Weigert-hematoxylin and eosin. × 542.

FIG. 32. From right ventricle of rabbit heart referred to in Fig. 25. Artery showing intimal musculo-elastic hyperplastic lesions, *A*; *B*, small granuloma in media. Weigert-hematoxylin and eosin. × 171.

FIG. 33. From left ventricle of human heart referred to in Fig. 18. Artery showing similar intimal musculo-elastic hyperplastic lesions, *A*; *B*, media. Weigert-hematoxylin and eosin. × 119.

FIG. 34. Rabbit 71-09; sacrificed 10 days following last of 9 infections. Artery in left ventricle showing heavily elastified intimal musculo-elastic hyperplastic lesions, *A*; virtual obliteration of lumen; *B*, break in internal elastic lamella; *C*, media. Weigert-hematoxylin and eosin. × 364.



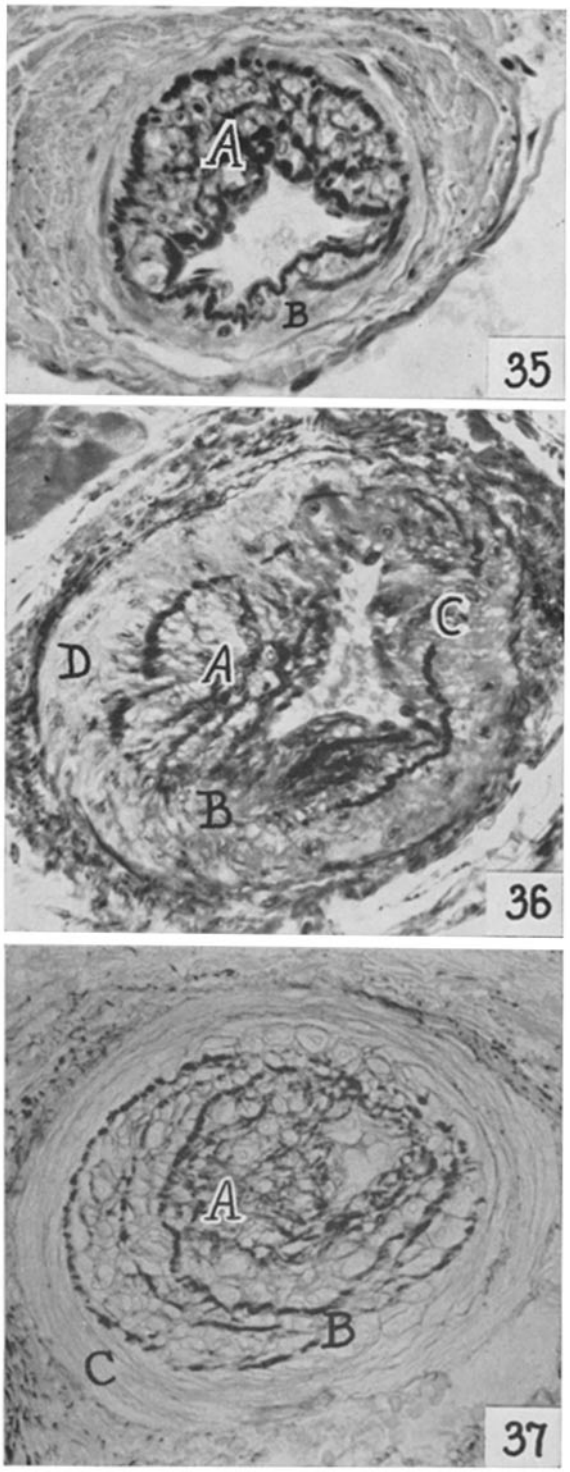
(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 34

FIG. 35. From a 34 year old woman who died after multiple attacks of rheumatic fever (autopsy 629, Rockefeller Institute Hospital). Artery in left ventricle showing intimal musculo-elastic hyperplastic lesions, *A*; narrowing of lumen; *B*, media. Weigert-hematoxylin and eosin. × 533.

FIG. 36. Rabbit 70-57; sacrificed 11 days following last of 11 infections; artery in left ventricle showing marked laminated intimal musculo-elastic hyperplastic lesions, *A*; marked narrowing of lumen; *B* and *C*, splitting of internal elastica; *D*, media. Weigert-hematoxylin and eosin. × 378.

FIG. 37. From a 28 year old man who died with active rheumatic heart disease (autopsy 411, Rockefeller Institute Hospital). Artery in auricular myoepicardial wedge showing quite comparable marked laminated intimal lesions, *A*, suggesting repeated attacks of rheumatic fever; marked narrowing of lumen; *B*, splitting of internal elastica; *C*, media. Elastic tissue stain. × 422.

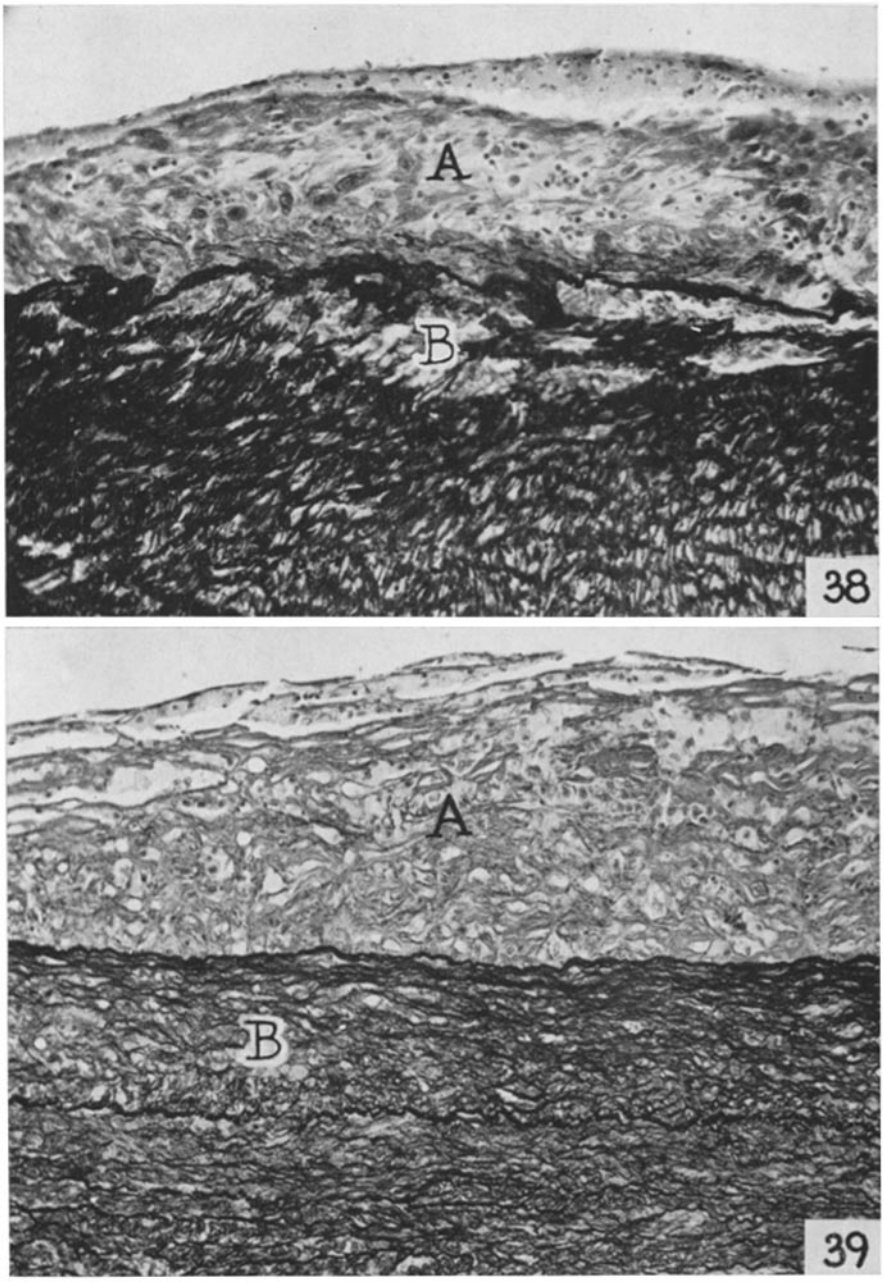


(Murphy and Swift: Induction of rheumatic-like cardiac lesions)

PLATE 35

FIG. 38. Aorta of rabbit referred to in Figs. 1, 2, 4, 6, 10, 15, 23, 29, and 31. *A*, intimal plaque composed of loose stroma of swollen collagen in which are dispersed large mono- and multinucleated cells and small mononuclears; *B*, marked splitting of elastic fibers in subjacent media. Weigert-hematoxylin and eosin. × 177.

FIG. 39. Rheumatic aortitis in human case referred to in Fig. 3. *A*, intimal plaque composed of loose stroma of swollen collagen in which are dispersed large mono- and multinucleated cells and small mononuclears; *B*, splitting of elastic fibers in media. Weigert-hematoxylin and eosin. × 146.



(Murphy and Swift: Induction of rheumatic-like cardiac lesions)