THE PATHOGENESIS OF RHEUMATIC FEVER.

By HOMER F. SWIFT, M.D.

(From the Hospital of The Rockefeller Institute for Medical Research.)

PLATES 22 TO 27.

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The manifold clinical signs of rheumatic fever have been the cause of much confusion in our conception of the essential nature of the disease. Another reason for this confusion is the fact that so many diseases at times have joint pains as a part of their symptom-complex. Indeed, Wiesel (1) has recently stated that no less than 80 different pathological conditions have been included under the term rheumatism. Gradually, as more exact knowledge of various diseases has been acquired, one after another of these numerous conditions has been placed in its proper nosological position; and we now realize that inflammation of the joints or muscles is usually a symptom of some general disease. In fact, most specific bacterial infections may occasionally have arthritis as one of their complications.

But the disease known today as rheumatic fever was generally regarded, until recent years, as having arthritis as its principal manifestation. Indeed, the term acute articular rheumatism is sufficiently descriptive to indicate that historically, at least, attention was focused on the organs of locomotion. With the development of auscultatory methods and the application of statistical studies it became evident a century ago that chronic cardiac valvular disease was frequently preceded by acute arthritis (2–6). Endocarditis was then regarded as a complication or sequela of acute articular rheumatism; but we now realize that heart involvement is the most important part of the disease, and that the patient is often suffering from active visceral infection with little or no evidence of arthritis. This altered conception of the disease is reflected in changes in the names applied to it from time to time; *viz.*, acute articular rheumatism, or acute inflammatory rheumatism, acute rheumatic fever, or better

still, rheumatic fever; the last appellation is probably best because the infection not infrequently passes into a subacute or chronic form.

It is surprising that in spite of the great advance in the knowledge of the causation of most common infectious diseases we still must recognize our uncertainty of the etiologic agent in this infection. Certain contributing environmental factors have been suggested (7, 8), and non-hemolytic streptococci have been claimed by several authors (9–13) to be the causative microorganisms; but the failure to recover these streptococci from a majority of patients (14) and the fact that the classical disease presented by man has not been reproduced by inoculating them into the lower animals (15, 16) have caused most students to hesitate before considering the question settled.

To obtain a better understanding of rheumatic fever we are, therefore, forced back to a continued bedside study of the patient, with newer instrumental methods to aid our senses, and to an examination of the various tissues that can be obtained from the subject during life and post mortem. By the correlation of the different facts so obtained we should arrive at a more exact knowledge of the life history of the disease.

The gross clinical manifestations of rheumatic arthritis are pain, tenderness, swelling, redness, and local heat diffusely distributed about the joint; an examination of the synovial fluid reveals many exudative cells, mostly polymorphonuclear leucocytes. Remarkable features of the acute arthritis are (1) the tendency for the inflammation to to migrate—to jump—from one joint to another without any apparent involvement of the intervening tissues; (2) the failure of the process to go on to suppuration; and (3) the rapid disappearance of the symptoms and signs of inflammation after the patient has taken such antipyretic drugs as certain derivatives of salicylic acid or phenylcinchoninic acid.

Histopathology of Cardiac Lesions.

In fatal cases, the longest recognized (17) and most striking gross feature found post mortem is the appearance of rows of small bead-like excrescences along the free margins of the heart valves. On microscopic examination these verrucæ are seen to be made up of coagulated elements derived from the circulating blood, in other words, small globular thrombi deposited on the valvular endocardium

at a place where the lining endothelium has disappeared (18). In older verrucæ there is also definite evidence of a tendency to healing (19); the verrucæ are covered with endothelium and invaded by organizing connective tissues. But even in the young lesions there is seen in the substance of the heart valve under the endocardium distinct evidence of inflammation not exudative but proliferative in nature (Figs. 1 and 2).[1] It is a moot point whether the destruction of the endothelium is primary or subsequent to an injury to the underlying tissue. Of this, however, we are certain—that characteristic lesions occur in the mural subendocardial region without primary injury to the endothelium and, also, are found in the base of the valve leaflets (Figs. 3 and 4). It is not difficult to conceive, therefore, of the primary injury of the valves occurring in their substance rather than on their surface; and if this is true it would be better to consider rheumatic disease of these structures as a valvulitis rather than a simple endocarditis. If edema and swelling are present in the valves to the same extent as about the joints, it is easy to think of them as being functionally faulty and to see the possibility of the swollen covering endothelium being broken by repeated impacts against an opposing valve leaflet.

When the pericardium is extensively inflamed there is often a widespread pouring out of serofibrinous exudate with a plastering together of the two layers of the pericardial sac. Upon first glance this seems an entirely different process than is found in other tissues; but the presence in the pericardium of focal lesions similar to Aschoff bodies, which shortly will be described, indicates that the essential or primary pathological process is similar to that found elsewhere, but that the gross appearance is altered by the peculiar anatomical structure of the pericardial sac, and the manner in which such large endothelial membranes respond to injury.

The most generally recognized specific histological lesion of rheumatic fever is the so called Aschoff body (20, 21), which is a submiliary nodule located in the myocardium usually in close relationship with small blood vessels (Figs. 6 and 7.). There is practically always a small central area of necrosis surrounded by peculiar cells, having

[1] Clawson (Clawson, B. J., *Arch. Int. Med.*, 1924, xxxiii, 157) directs attention especially to the proliferative nature of the inflammatory process in the valves in 9 cases of rheumatic endocarditis recently studied by him.

vesicular nuclei and a cytoplasm that takes a granular red color when stained with methyl green pyronine; usually many cells are present with multiple nuclei, forming a particular type of giant cell, different from that seen in tuberculosis. Mixed with these Aschoff body cells are polymorphonuclear leucocytes and lymphocytes in various amounts, proportional to the acuteness of the general infection. Although the submiliary nodule is primarily in the interstitial tissue, the surrounding muscle fibers are often seen to be involved (Fig. 7). Indeed, certain pathologists claim that the giant cells arise from the muscle fibers, although the majority of observers think that the cells forming the nodules are derived from the endothelium of the perivascular spaces and from the endothelial lining of the blood vessels.

Changes in the blood vessels are common; not infrequently one encounters partial or complete closing of the lumina with thrombi that have probably been formed as a result of injury to the vessel wall (Fig. 5). The blood vessel may also be constricted in other ways: We have seen Aschoff bodies in the perivascular space compress one segment of the wall against another (Fig. 6). When two or more submiliary nodules are close together but on different sides of a vessel the edema, often present in the region of such foci, probably forms a constricting ring (Fig. 7). Endarteritis, with swelling and proliferation of the endothelium as well as of the other intimal cells, is not infrequently encountered in the smaller branches of the coronary arteries (Fig. 8). Interference with the circulation must lead immediately to disturbed nutrition of the muscle tissue and of the impulse-conducting fibers supplied by the involved blood vessels (22). Bedside study and electrocardiographic investigation in a series of our patients indicates that the myocardium or conduction system was disturbed in about 95 per cent of the cases (23). While it is conceivable that these functional disturbances may have been merely toxic in origin, it seems more rational to conclude that there is a direct relationship between the histopathological lesions demonstrable post mortem, and the disturbed myocardial function found during life. The transitory nature of many of these cardiac disturbances is no argument against their being due to actual focal lesions, for evidence is constantly increasing that focal lesions persist about inflamed joints, even though clinical manifestations of arthritis are present only a few days.

It is important, on the other hand, to realize that active disease of the heart may be the only demonstrable evidence of a continuing rheumatic fever infection. Recently, two fatal cases have been brought to our attention in which myocardial weakness was the sole clinical picture, and post mortem the only distinct lesions were Aschoff bodies widely disseminated throughout the heart muscle. In several patients suffering from chronic cardiac disease we have observed relapse after relapse with pyrexia and the general features of recurring infection in which all of the symptoms and signs were referable to myocardial and endocardial involvement. Post mortem, these cases have shown widespread rheumatic myocarditis, along with endocarditis and pericarditis. These correlated clinical, physiological, and pathological studies are giving us a clear conception of the chronic or relapsing nature of rheumatic fever.

Histopathology of Subcutaneous Nodules.

For many years English clinicians (24) have called attention to the frequent occurrence of fibroid nodules in the subcutaneous tissue of rheumatic children. Anatomically, they are found in the deep fascia over bony prominences and in tendon sheaths and tendons. The essential histological picture is similar to that seen in the Aschoff body (25). In close apposition to areas of cellular proliferation there is tissue destruction varying in size from small submiliary areas to long strands of hyaline necrosis affecting connective tissue fibers; combined with necrosis are deposits of fibrin (Fig. 9). Surrounding these destroyed foci are found numerous cells similar in appearance and staining reaction to the type of cells found in Aschoff bodies; multinuclear giant cells are also present (Figs. 10 and 13). In nodules it is not difficult to demonstrate these endothelioid cells arising from perivascular spaces as well as from the vascular endothelium (Figs. 11 and 12). In fact, the participation of the blood vessels in the general response is one of the most marked features of the subcutaneous nodules. Many capillaries are seen in which the swollen endothelium has practically obliterated the lumen; in the arterioles the proliferation of the endothelium at times takes the form of a crescent-shaped mass of cells, appreciably narrowing the vessel. Still other small arteries are seen obliterated by thrombi; in others the media is involved; and surrounding many of the smaller vessels there can often be seen collections of endothelioid cells evidently compressing the

walls. A participation of fibroblasts arising from the connective tissue is easy to demonstrate. A few polymorphonuclear cells and lymphocytes invade the diseased tissue and foci of edema are demonstrable. While, grossly, these nodules vary in size from 0.5 to 5 or 10 mm. it is evident upon microscopic examination that the larger nodules are composed of a conglomeration of submiliary nodules (Fig. 9). The pathological unity of the myocardial and subcutaneous lesions is, therefore, easily comprehensible.

These subcutaneous nodules attract attention clinically only on account of their mechanical presence. They are usually painless because they are not in close apposition to nerves. Involving only connective tissue which has no important function except that of a supporting structure, they are not a local source of danger. Their chief significance is that they indicate a similar process going on in such important organs as the heart or brain.

Histopathology of Joint Lesions.

The inflammation of the joints, a most outstanding feature from the patient's view-point, has been the least studied by histopathological methods. The transient nature of the arthritis, and the fact that patients rarely succumb to the acute disease easily explains the apparent gap in our knowledge. Heart failure is practically always accountable for the death of these patients at a time when the arthritis has disappeared, and hence the chief attention of the pathologist has been directed to this organ.

Nevertheless, Fahr (26) has found changes in the capsule of the knee of patients succumbing to rheumatic fever which he states are in every way comparable to the myocardial lesions. Coombs (27) makes a similar statement concerning the shoulder joint of one patient. Lately, we have examined portions of the capsule of the knee or ankle at the acute stages of rheumatic arthritis, and found focal lesions of the synovia, focal necrosis of the capsule, thrombosis of the smaller arteries, and endothelial and perivascular reactions comparable with changes found in the heart and in subcutaneous nodules (Figs. 14 to 16). The presence of many small nerves in the joint capsule and surrounding ligaments easily explains the great pain in rheumatic arthritis. The finding of distinct histological lesions in the joint capsule of a patient fully under the influence of neocinchophen, and from whom all clinical signs of arthritis had dis-

appeared, indicates that the essential rheumatic process may go on in spite of these antiphlogistic drugs.

Histopathology of Chorea Minor.

The relation of St. Vitus' dance, or chorea minor, to rheumatic fever has been discussed for many years. It has been known that valvular heart disease and chorea were frequently concomitant; also that arthritis and chorea occurred together. The relatively few studies of the brains of chorea patients reported in literature indicate that the chief lesion is vascular in origin (28). Thrombi, endothelial proliferation, and perivascular collections of round cells together with small focal changes in the nervous tissue contiguous to these vessel lesions have been described. The very small amount of connective tissue in the parenchyma of the brain, and the fact that the response of the central nervous system to injury is normally a neuroglia proliferation, would naturally cause a different histological picture in the brain than would be seen elsewhere. The finding, however, of typical Aschoff bodies in the hearts of patients dying from chorea, and the demonstration of subcutaneous fibroid nodules in others who have recovered, all support the view-point that the lesions in the various organs are all evidence of tissue response to a common causative agent—the infective agent, or virus, of rheumatic fever.

Correlation of Symptoms and Histopathological Lesions of Rheumatic Fever.

With this conception of the essential pathology of rheumatic fever, *viz.* disseminated focal submiliary nodules with edema in the contiguous tissues during the acute stages, combined with lesions of blood vessels, it is not difficult to reconcile the manifold and apparently unrelated manifestations of the disease. It is apparent that the type of response is an effort on the part of the body to limit the activity of the infective agent, a type that in many ways reminds us of the focal lesions of tuberculosis or syphilis. The edema, redness, and local heat seen about the joints with acute arthritis are evidence of an intense tissue reponse, and give the impression that exudation is the most marked feature. These gross clinical signs, however, disappear quickly, both spontaneously and following the exhibition of certain drugs. But small disseminated lesions of a focal character are

evidently present in the periarticular tissue and synovia much the same as in other organs, and are doubtless slower in undergoing complete resolution than the rapid recession of clinical symptoms would indicate. The pain and tenderness of the acute arthritis are probably due to the implication of numerous nerves in the acute exudative process. With the disappearance of extensive edema these symptoms usually disappear; but not infrequently one encounters patients in whom slight pain, stiffness, and tenderness persist in certain joints for weeks or months. These continuing symptoms might easily result from a persistence of focal lesions of a subacute or chronic character. The intensity of the response about the joints is probably an important factor in the complete healing of arthritic lesions. The synovia and perisynovial tissues are rich in blood vessels and hence are in a condition to respond quickly and intensely to numerous small focal injuries.

In subcutaneous nodules, on the other hand, the tissue involved is less vascular; acute exudation is less marked than about joints; perivascular cellular proliferation is very prominent; and the more subacute type of response is made evident by a slower disappearance of the evidence of injury. As already mentioned, the absence of nerves in the tissues implicated by subcutaneous nodules easily explains the lack of pain or tenderness about them.

With an understanding of what happens about joints and in subcutaneous nodules it is not difficult to construct a picture of the various cardiac lesions. The Aschoff body closely reproduces the changes seen about a single vessel in a subcutaneous nodule. In the heart there is a relatively smaller amount of connective tissue than is present about subcutaneous nodules, and in addition as the submiliary nodules usually occur about small arteries, their microscopic size is easily understood. Again a low degree of vascularity compared with the articular tissues explains the comparatively small amount of exudation; but transitory exudation is suggested by the rapidity with which electrocardiographic signs of myocardial involvement appear and disappear during the acute stages of rheumatic fever. Partial or complete occlusion of the arterioles would also result in a compromising of the nutrition of the portion of the heart supplied by them. There is also actual destruction of muscle fibers to explain

certain symptoms of myocardial disease. It is therefore, probably not overstressing the point to contend that in rheumatic fever disturbance of cardiac function points to the presence of focal lesions in the myocardium or cardiac blood vessels.

Focal lesions of the pericardium, if small, may result in a localized pericarditis, and, on the other hand, if widespread, may be followed by extensive exudation. In fact, outpouring of a serofibrinous exudate is the usual mode of response to extensive injury of large endothelial lined cavities like the pericardium and pleura, even though the character of lesions produced by the causative organisms in other tissues is usually focal in nature; for example, tuberculosis of the pleura or pericardium is ordinarily accompanied by a serofibrinous exudate. The organization of this exudate with the secondary changes incident to such organization is merely the logical outcome of a widespread pericarditis.

The peculiar character of rheumatic valvular endocarditis is more difficult to reconcile with the other focal lesions of this disease. As already mentioned, if we conceive of edema of the valve occurring as an exudative response about focal rheumatic lesions in the valve substance it is not difficult to see how the endothelium at the line of closure would be injured and small thrombi deposited on the valves at this site of injury. The healing of these thrombi must be necessarily accompanied by formation of new blood vessels and fibrous tissue; and with this process there is not only the scarring of the valves leading to a disturbance of their function, but also the production of a *locus minoris resistentiæ* in or about which subsequent relapses of rheumatic fever are liable to set up new foci of inflammation (Fig. 2). It is only fair to state that we are still uninformed of the exact mechanism by which chronic inflammation of the valves leads to progressive narrowing or funnel-shaped deformities.

The manner in which multiple vascular and perivascular lesions in the brain set up the symptoms of chorea is not entirely clear. In chorea, however, there is usually evidence of a widespread encephalitis. Sometimes practically all of the voluntary movements of the body are rendered incoordinate; at other times the symptoms point to a less extensive distribution of the pathological process. Nevertheless, we scarcely ever encounter evidence of large, single lesions in the central

nervous system, such as we see in syphilis. The symptoms of implication of the central nervous system by the virus of rheumatic fever, therefore, point to the existence of many small foci, probably in the corpus striatum, but also in the cerebral cortex; we may regard these foci as similar in nature to those found in other tissues of the body.

Doubtless comparable lesions in other organs or tissues are not infrequently present (26, 29), but are not detected either because they fail to give rise to symptoms or because the usual well marked manifestations of the disease outweigh them in prominence.

SUMMARY.

It is evident that there are two distinct types of response on the part of the body to the infectious agent of rheumatic fever; *viz.*, proliferative and exudative. The perivascular proliferative type of lesion, resembling an infectious granuloma, explains the subacute and chronic character of the clinical symptoms in many patients with this disease. Marked exudation of serum into the periarticular tissues and of serum and cells into the joint cavities are concomitants of the acute arthritis occurring with high fever and general intoxication; these acute exudations disappear following the administration of certain drugs. But their disappearance does not mean necessarily that all lesions of the proliferative type have resolved. In fact, we know that these last mentioned lesions, when present in the subcutaneous tissues, often continue for months; and from analogy we may conclude that they have a similar persistent character in other tissues of the body invaded by the causative agent of rheumatic fever.

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EXPLANATION OF PLATES.

PLATE 22.

FIG. 1. Rheumatic valvular endocarditis and valvulitis. Verruca composed of thrombotic elements derived from the blood stream; there is a proliferative type of tissue response in the valve under the thrombus. × 118.

FIG. 2. Rheumatic cardiac valvulitis. Marked perivascular reaction about the vessels near the free edge of the aortic valve which was thickened because of a long standing rheumatic valvulitis. From the same heart as Fig. 1. × 312.

PLATE 23.

FIG. 3. Rheumatic carditis. Typical Aschoff bodies occurring in the subendocardial region in the wall of the left ventricle. *A*, Aschoff bodies; *E*, mural endocardium; and *M*, myocardium. × 68.

FIG. 4. Rheumatic cardiac valvulitis. Aschoff bodies found at the base of the mitral valve at a considerable distance from the myocardium. × 218.

FIG. 5. Rheumatic carditis. Small organizing thrombus occluding a blood vessel in the heart of a patient with rheumatic fever. × 112.

FIG. 6. Rheumatic myocarditis. Lumen of a small coronary blood vessel narrowed by the presence of an Aschoff body in the perivascular space. × 112.

PLATE 24.

FIG. 7. Rheumatic myocarditis. Aschoff bodies and edema compressing a branch of the coronary artery. *A*, Aschoff bodies; *E*, area of edema; *V*, compressed blood vessel; and *M*, broken and necrotic muscle fibers. × 140.

FIG. 8. Rheumatic myocarditis and endarteritis. *C*, artery with swollen intima and desquamating endothelium; and *A*, Aschoff body in the perivascular space. × 330.

PLATE 25.

FIG. 9. Subcutaneous rheumatic nodule. Multiple foci of perivascular proliferative reaction and (*S*) long strands of hyaline necrosis and deposits of fibrin. × 39.

FIG. 10. Subcutaneous rheumatic nodule showing a type of cell reaction similar to that seen in the myocardial submiliary nodule. *E*, endothelioid cells; and *G*, giant cells. × 445.

FIG. 11. Subcutaneous rheumatic nodule; marked perivascular proliferation of endothelioid cells and fibroblasts. *V*, small blood vessels with swollen lining endothelium. × 210.

PLATE 26.

FIG. 12. Subcutaneous rheumatic nodule. *S*, Swelling of the endothelium lining arterioles; and *P* small collection of endothelioid cells and a few lymphocytes in the perivascular space. × 495.

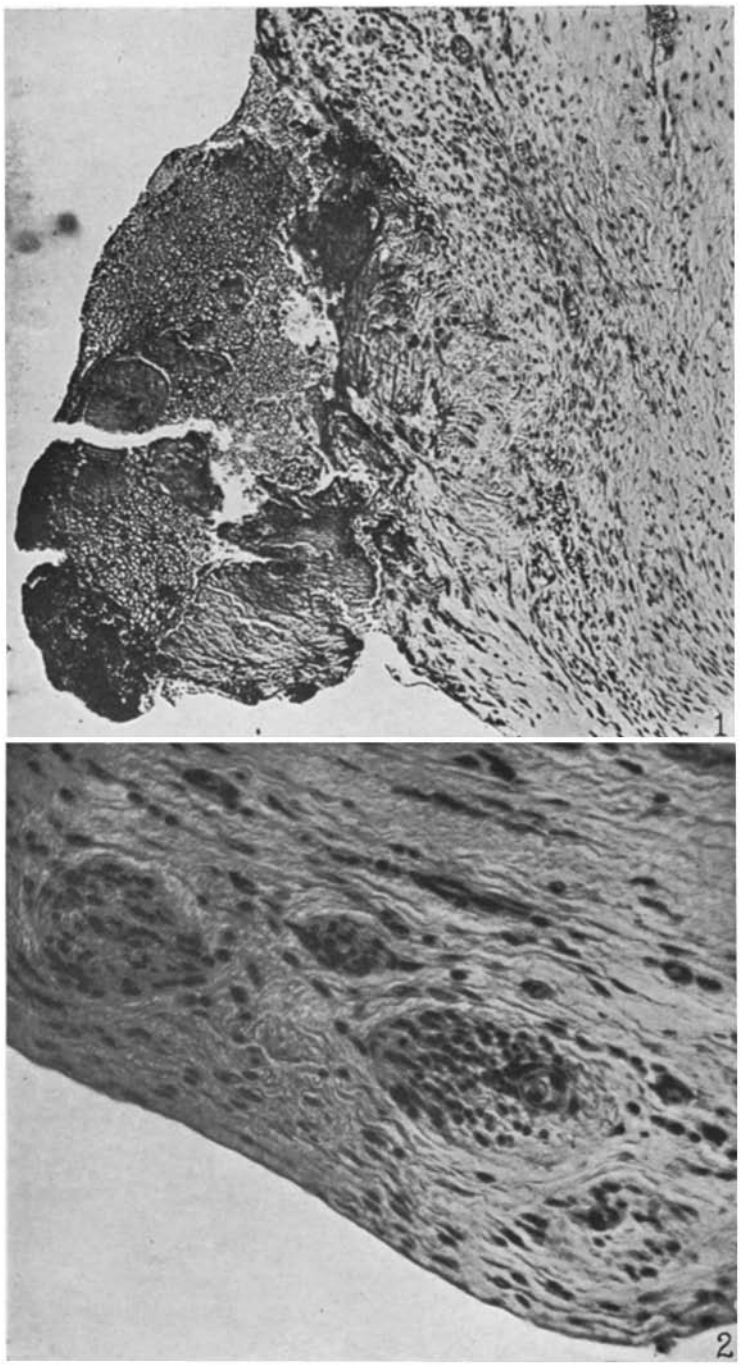
FIG. 13. Subcutaneous rheumatic nodule. *E*, endothelioid cells; *P*, polymorphonuclear leucocyte; *F*, area of focal edema; and *N*, area in which cells are undergoing degeneration. Compare with Fig. 14 showing a similar reaction in the synovia. × 234.

FIG. 14. Acute rheumatic polyarthritis. Synovia from the knee. *V*, blood vessels with swollen endothelium; *C*, swollen and actively proliferating synovia cells; and *N*, area in which cells are undergoing degeneration. × 234.

PLATE 27.

FIG. 15. Acute rheumatic polyarthritis. *N*, necrosis in the fibrous capsule of the knee with (*F*) active proliferation of fibroblasts. × 200.

FIG. 16. Acute rheumatic polyarthritis. Capsule of the knee. *E*, area of focal edema; *N*, nerve surrounded by edema; *V*, small vein with swollen endothelium; and *A*, arteriole with thickened wall compressing the lumen. × 170.



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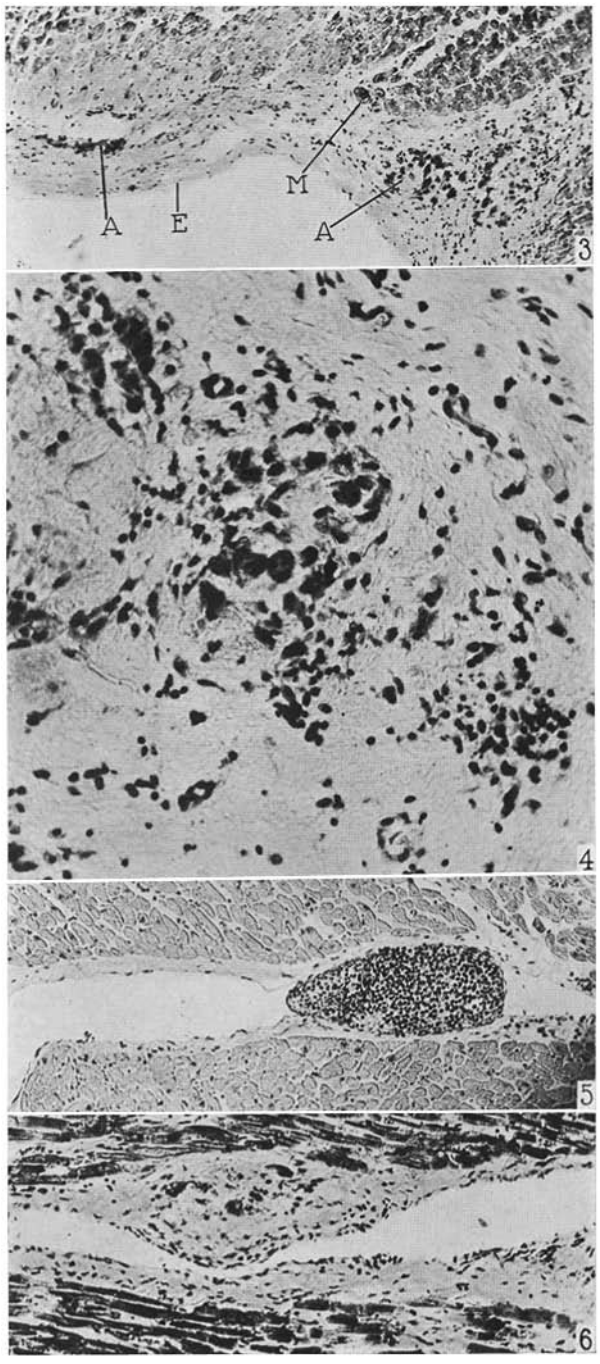

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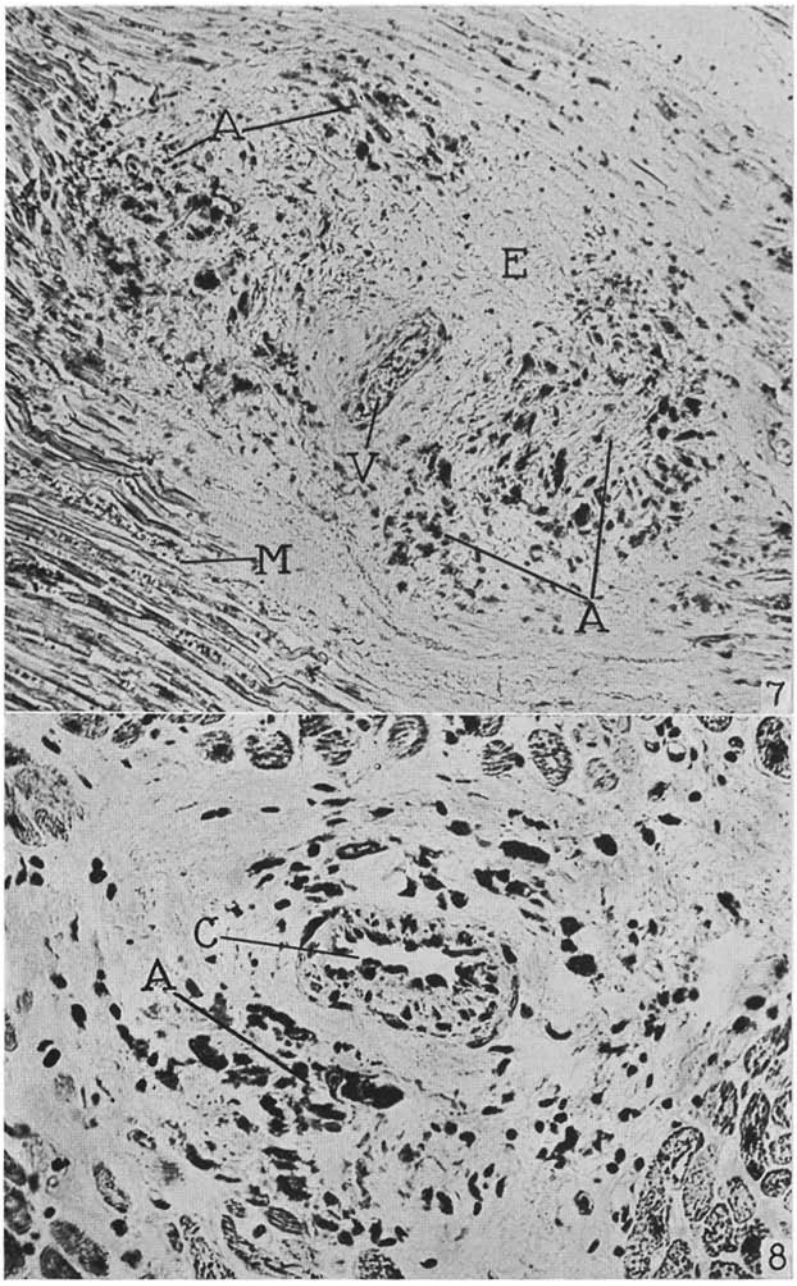

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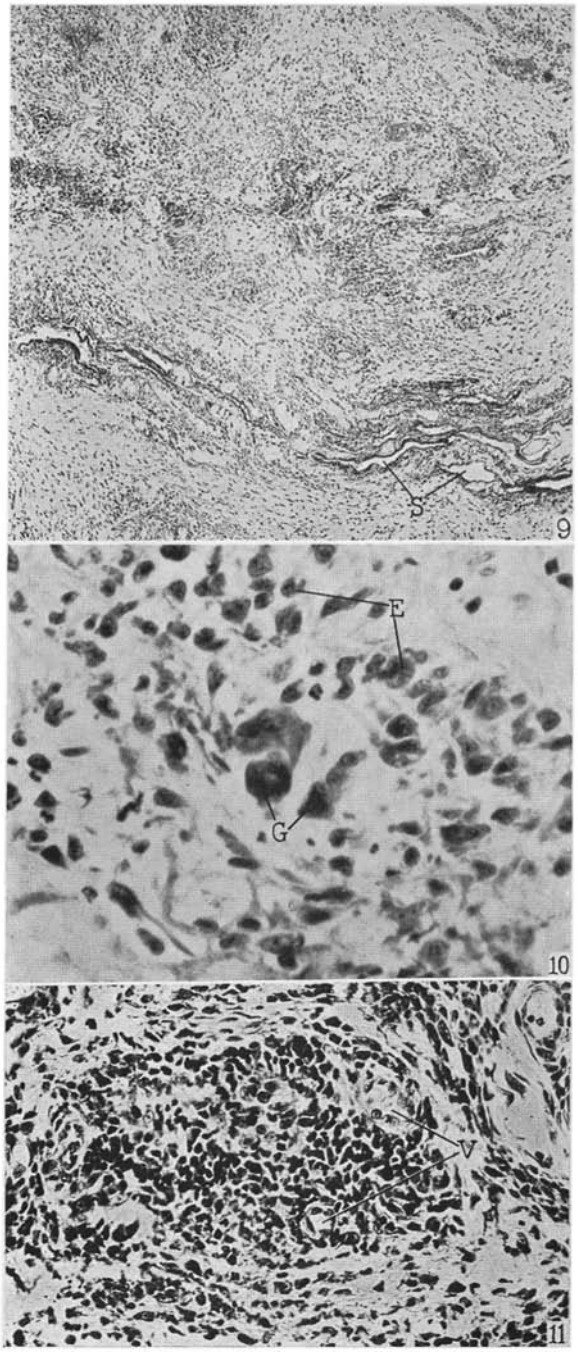

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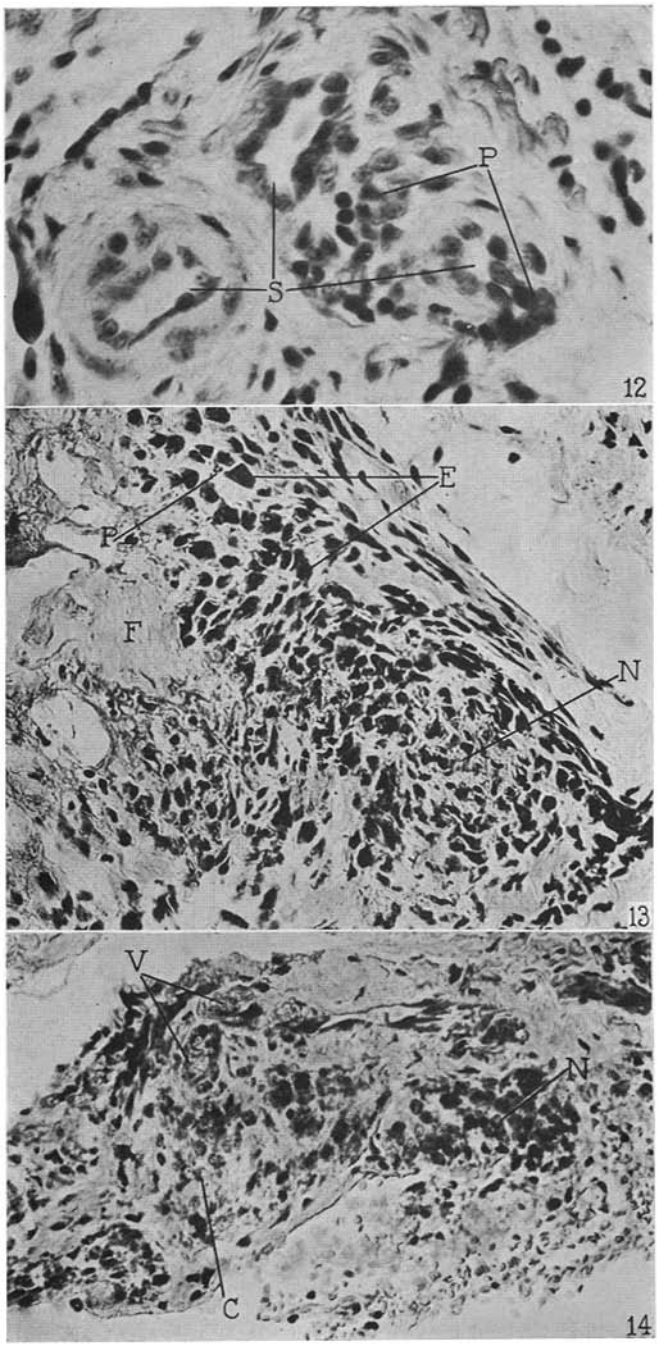

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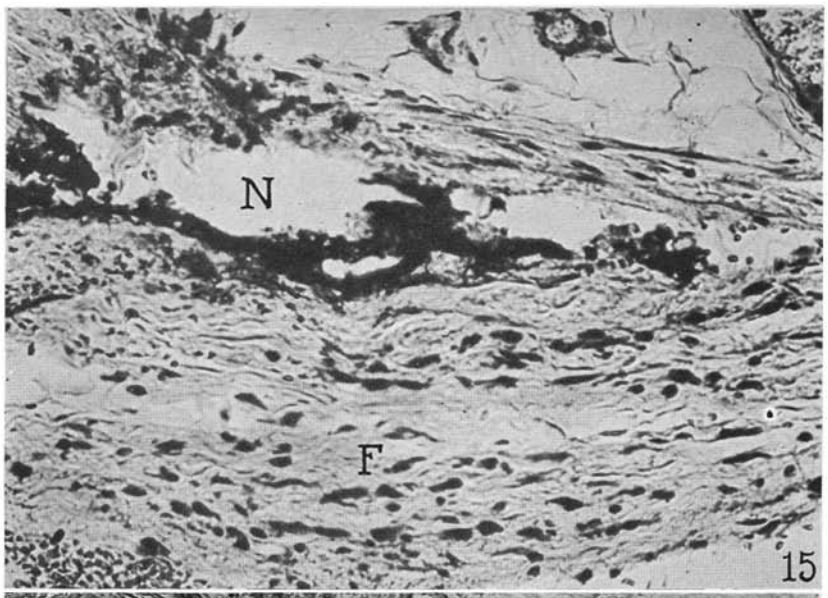

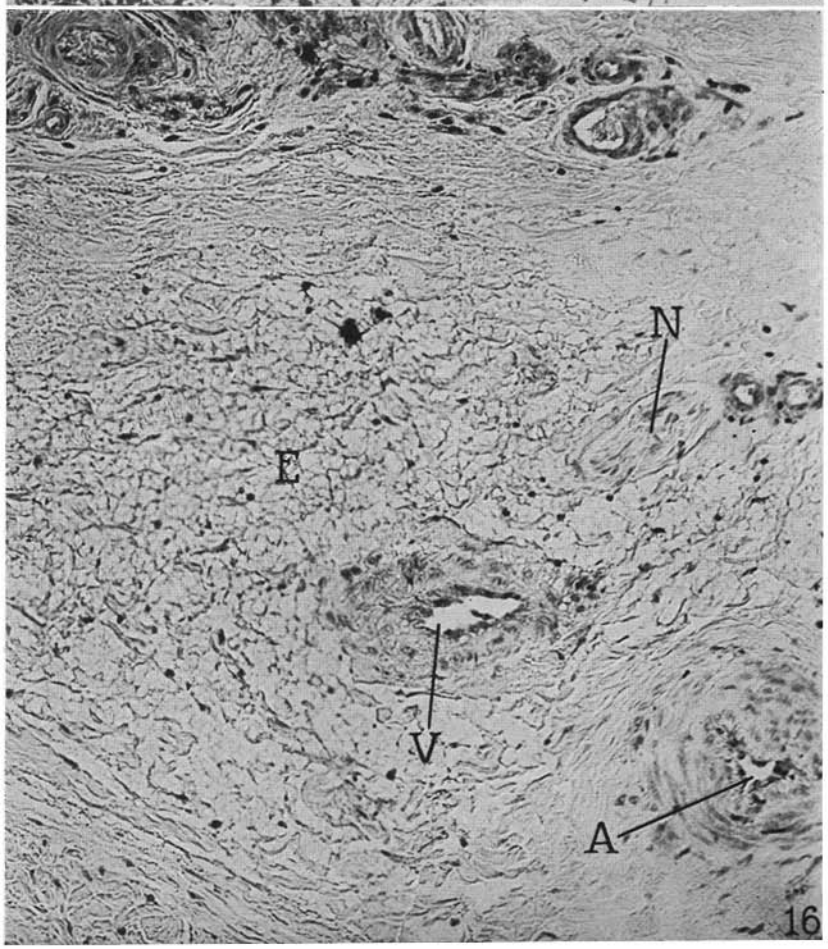

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