LESIONS OF SKELETAL MUSCLES IN RHEUMATOID ARTHRITIS
NODULAR POLYMYOSITIS *

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Multiple nodular inflammatory lesions in peripheral nerves in cases of rheumatoid arthritis were reported for the first time in previous papers.[1,2] They were found in 3 of 5 cases. Identical findings observed in 5 more cases of this disease are to be reported in another paper. Since muscular atrophy, occasionally of rapidly progressive nature, is seen clinically in many cases of rheumatoid arthritis, an attempt was made to search for anatomopathological changes to which muscular atrophy could be related.

MATERIAL AND TECHNIC

Muscle in quantity is not easily obtainable during life. The patient is often reluctant to permit the removal of tissue for biopsy for scientific purposes alone without prospect of therapeutic benefit. Pieces of muscles taken for biopsy are usually small, rarely over 2 gm., and are taken at random from a large muscle of the arm or leg. In 4 cases of rheumatoid arthritis such specimens were taken from the gastrocnemius muscle; in 1 of these an additional specimen was taken from the deltoid muscle. In 2 cases specimens from the triceps muscle were taken for biopsy. In another case of rheumatoid arthritis a mid-thigh amputation of both legs was performed, because of immobility and marked deformity of the patient's lower extremities. The peripheral nerves of both legs were dissected. Some muscle tissue, adherent to these nerves, was obtained incidentally. In 2 cases pieces of muscle were taken at autopsy, in 1 from the pectoral muscle, in the second from the rectus abdominis, pectoral and iliopsoas muscles. The latter case was found at autopsy among our control material. Altogether, muscles from 9 cases of rheumatoid arthritis were examined.

Since pathological involvement of skeletal muscles in cases of systemic disease has been described frequently, a large number of controls was desirable. Up to the present time, 196 control cases, selected from routine autopsies and surgical operations without any previous knowledge of the history or diagnosis, have been examined. There were

* Aided by grants from The Children's Fund of Michigan and from the National Foundation of Rochester, Michigan.

Received for publication, March 12, 1945.

specimens from the recti abdominis, the pectorales, the iliopsoas, the gluteal muscles, the bicepses and tricepses.

The specimens of muscle were fixed in formalin, and blocks were cut transversely and longitudinally; after embedding in paraffin, sections were made 7 μ thick. Hematoxylin and eosin, cresyl violet, van Gieson's, and reticulin (Wilder) stains were used. Frozen sections could not be made because the small amount of muscle tissue obtained had to be embedded entirely in paraffin. Likewise there was no material available for fixation in alcohol, which excluded staining for glycogen. For similar reasons histopathological studies of striation and sarcomeres requiring special technics were not made.

No descriptions of similar findings are to be found in medical literature. The only description of pathological lesions resembling ours is in a paper by Curtis and Pollard.[3] They found increase in interstitial nuclei of the muscle fibers, small perivascular infiltrations, and atrophy of muscle fibers in specimens taken for biopsy from the calf muscles of 12 patients with rheumatoid arthritis. The purpose of their paper was to determine whether Felty's syndrome was a clinical entity or just an "expected complex of rheumatoid arthritis."

Report of Cases

Case 1

The patient (Eloise Hospital) was a white female, 54 years old, the mother of 11 children. For 19 years she had had rheumatoid arthritis involving nearly every joint. Roentgenograms revealed bony ankylosis of the left knee joint. The joint space of the right knee was lost on the lateral half, and on both sides there was some loss of joint space between the humerus and the ulna with partial bony ankylosis. The muscles of the lower extremities were markedly atrophic.

Morphological Description

The specimen was taken from the middle portion of the left gastrocnemius muscle and was 1.6 cm. long and 0.9 cm. thick in its largest transverse diameter. Grossly, it did not differ from a piece of normal muscle.

The pathological findings had to be separated into those which were inflammatory and those which were degenerative. At least five inflammatory lesions were found in each section. They were entirely separated from one another and consisted of nodular accumulations of lymphocytes and plasma cells. The plasma cells were more frequent in the peripheral portions of the nodules. The shapes of the nodules varied markedly. There were triangular, pyramidal, and spindle-shaped nodules (Fig. 1) located in the perimysium and the endomysium, separating single muscle fibers from each other. Occasionally

a small amount of adipose tissue was seen at one or both ends of the nodule (Fig. 2). In addition to the nodular accumulations, there were a few well demarcated foci composed of a smaller number of lymphocytes. There was no necrosis in the lymphocytic nodules, but occasionally there were seen a few epithelioid cells that had arisen from the cells of capillary endothelial linings or from the sarcolemma. Van Gieson's stain revealed an increase in collagenous connective tissue fibers while the reticulin stain failed to reveal an increase in reticulin fibers in the nodules.

The degenerative lesions of muscle fibers were well defined and were very irregularly distributed in close proximity to normal muscle fibers. A single degenerated fiber was never seen isolated between normal fibers; always three or more degenerated fibers were together. The degeneration of muscle fibers was marked by an increase of sarcolemmal nuclei, closely packed together; swelling or, more often, extreme shrinkage of fibers; a change of the staining reaction of the fibers from a bright red to pale red or pink (Fig. 2), and an increased coarseness in the cross striations with larger but regular interspaces between the striations. Occasionally a slightly swollen muscle fiber showed a transition to shrinkage, indicating a segmental degeneration. Extremely shrunken muscle fibers in cross section were not much larger, or were even smaller, than human red blood cells (Fig. 3). The nucleus of such a shrunken muscle fiber was located at the periphery. Occasionally an empty space like a vacuole was seen as the core of the shrunken muscle fiber, leaving at the periphery a pale, ring-shaped, membrane-like structure in which the nucleus was embedded. The nuclei were small, spindle-shaped or curved, and contained dark-staining chromatin. Occasionally a cross section through a shrunken muscle fiber revealed 8 to 15 small, dark nuclei in the center of the fiber.

In the walls of capillaries and larger blood vessels and inside perimysial nerve fiber bundles, as well as in neuromuscular spindles, no inflammatory nodules were seen. However, in perimysial locations adjacent to intramuscular nerve fiber bundles and to the adventitia of blood vessels nodular lymphocytic infiltrations were found (Figs. 4 and 5).

Case 2

The patient (Eloise Hospital), a white female, 48 years old, had had progressive rheumatoid arthritis for 19 years. She showed flexion deformities of the elbows, wrists, and fingers; complete ankylosis of the right wrist and partial ankylosis of the left; and nearly complete ankylosis of the left ankle and both knees with subluxation. Roentgenograms revealed a marked loss of joint space in the right interphalangeal joints, loss of joint space in the right elbow, and ankylosis of the right knee. The skin over the legs and on the face was glossy. There was severe muscular atrophy.

Morphological Description

The specimen for biopsy was taken from the middle portion of the left gastrocnemius muscle. It measured 2.4 cm. in length and was 0.6 cm. in its largest transverse diameter. There was no grossly visible change.

The microscopical findings again had to be separated into inflammatory and degenerative changes. The inflammatory lesions appeared in separated and remote groups. They were well circumscribed and occupied the perimysium and the endomysium of muscle bundles. Their shape was nodular but more irregular than that of the previously reported [1,2] perineuritic nodules; there were often small nests of cells connected with the nodule that in tongue-like fashion infiltrated farther into the endomysium between two muscle fibers.

The inflammatory cells were lymphocytes and plasma cells, the former being distributed very regularly throughout the nodules, the latter found in the periphery of the nodular accumulations. There was no definite inner zone of necrosis or of epithelioid cells. The nodules contained capillaries and increased collagenous connective tissue while the reticulin fiber network was scant.

Muscular degeneration was seen in very irregular distribution. Well preserved muscle fibers were seen in close proximity to severely atrophic muscle fibers (Fig. 6). There was swelling as well as shrinkage of the fibers, the swollen fibers showing discoloration, and usually a darker color. Cross striations were coarser and the interspaces larger. Instead of straight outer contours, the swollen muscle fibers showed wavy or irregularly distorted outlines. The shrunken muscle fibers were occasionally paler; nevertheless, the cross striations were often distinctly seen. The reduction in size was more than two-thirds of normal; in crosscut fibers the size of an individual fiber was often smaller than that of a red blood cell. The nuclei in these shrunken fibers were peripherally located; however, there was an occasional accumulation of 8 to 10 nuclei closely packed together. In some of the markedly shrunken muscle fibers only a nucleus and a membrane-like outer structure remained, and the inner core was represented by a vacuole. The perimysial connective tissue was increased in amount and showed more nuclei than are normally present. There were accumulations of nuclei even in the muscle fibers that did not exhibit degenerative changes. Occasionally an increased amount of adipose tissue could be seen between muscle fibers.

In the walls of capillaries and larger blood vessels and inside of perimysial nerve fiber bundles as well as in neuromuscular spindles no inflammatory nodules were seen. However, in the vicinity of two small

perimysial nerve fiber bundles, nodular infiltrations involving the perineurium and adjacent interstitial tissues were seen (Fig. 7).

Case 3

The patient (Harper Hospital) was a white male, 53 years of age, who was admitted to the hospital on May 29, 1944, complaining of painful and swollen joints. The condition had followed the removal of a tumor of the bladder 4 years previously. The joints were involved in the following order: feet, knees, hands, elbows, neck, and shoulders. Over a period of several months the joints had become swollen, stiff, and sore. The extremities were moist and cool. The condition was worse during cold or wet weather. The patient had become gradually weaker, and he noted that his muscles wasted as time went on. On two occasions he had had transitory "lumps" at his elbows. His muscles were always sore, especially those of his arms and legs. He had received fever therapy and a course of gold injections at another hospital, but he felt that his condition had not been improved.

The patient was a large man, somewhat pale, with marked deformity of all joints. There was fusiform swelling of the phalanges. The metacarpophalangeal and the carpometacarpal joints showed diffuse periarticular swelling; there was marked interosseous atrophy. The elbow joints could not be fully extended, and the arms could be raised only to an angle of 45° from his body. Motion of the feet and knees was limited. No nodules were felt. The heart was not enlarged, and no murmurs were present. The blood pressure was 140/85 mm. Hg. All reflexes were hyperactive. Sensation was normal everywhere except for some hyperesthesia of the feet.

During his stay at the hospital the patient had prostigmine, methylsalicylate, myochrysine, blood transfusions, massive doses of sodium salicylate, high vitamin-D medication, and physiotherapy. There was moderate improvement.

Laboratory Findings. Examination of the blood showed: Hemoglobin, 86 per cent; red blood cells, 4,460,000; white blood cells, 8,400, with a normal differential count. Several determinations of the sedimentation rate gave a maximum of 27 mm. and minimum of 21 mm. in 60 minutes. Blood nonprotein nitrogen was 36.6 mg.; blood calcium, 11.5 mg.; and blood phosphorus, 2.1 mg. per cent. A Kahn test of the blood was negative.

Radiological Examination. Soft tissue swelling was seen about the majority of the proximal interphalangeal joints with decrease in the joint spacing of all carpal bones and a generalized demineralization of all bones examined. No hypertrophic changes could be seen. There was roentgenographic evidence of arthritis, of a rheumatoid type, involving the left hand. Studies made of the right knee revealed thinning of the articular cartilages with considerable effusion into the bursae.

Morphological Description

Specimens were taken from the left gastrocnemius and deltoid muscles. The two pieces of tissue from the gastrocnemius muscle were 1.1 by 0.9 cm., and 0.4 by 0.2 cm. The piece from the deltoid muscle was approximately 1 by 1 cm. Grossly, there were no visible changes.

Except for an increase in sarcolemmal nuclei, no degenerative or inflammatory lesion was found in the gastrocnemius muscle. The specimen from the deltoid muscle showed two small inflammatory nodules of typical appearance, without atrophic lesions of the muscle fibers.

The inflammatory cells again were lymphocytes and a few plasma cells. Rarely, polymorphonuclear cells were seen.

In the walls of capillaries and larger blood vessels, in perimysial nerve fiber bundles, and in neuromuscular spindles no inflammatory nodules were seen.

Case 4

The patient (Harper Hospital) was a white male, 46 years old, whose chief complaint was painful, stiff, swollen joints. Six years before he had noticed occasional pain in the muscles of his left arm. This slowly progressed to the other arm, and then the knees became involved. He received treatment in many forms during this period of time, the last being 100,000 units of vitamin D daily. On this he improved slightly. At the time of entrance to the hospital he was totally disabled and could not walk. Occasionally, when the joint condition grew worse, hoarseness developed.

Past illnesses were septic sore throat in 1932; gonorrhea in 1935; malaria in 1935; and pneumonia in 1940. There was nothing remarkable in the family history, and there was nothing of importance in the physical examination except for the findings which concerned the joints. The heart was not enlarged. There were no murmurs and no arrhythmia. Blood pressure was 147/75 mm. Hg. The spleen was palpable. Examination of the joints revealed ulnar deviation with inability to extend the metacarpophalangeal joints. The elbows were slightly flexed as were the feet and knees.

Laboratory Findings. Examination of the blood showed: Hemoglobin, 80 per cent; red blood cells, 4,700,000; white blood cells, 8,750, with 60 per cent segmented forms, 34 per cent lymphocytes, and 6 per cent band forms. The sedimentation rate was 23 mm. in 60 minutes. Chemical studies showed nonprotein nitrogen of the blood to be 36.6 mg.; calcium, 11.1 mg., and sugar, 80 mg. per cent. A Kahn test upon the blood was negative.

Radiological Examination. Roentgenograms were made of the chest, teeth, paranasal sinuses, and gallbladder; no abnormal findings were recorded. Roentgenograms of the hands showed marked narrowing of the joint spaces with considerable demineralization of the bone, and there was some periarticular soft tissue swelling. The cartilaginous disks had almost entirely disappeared.

Clinical Diagnosis. The case was diagnosed as typical rheumatoid arthritis. The patient was discharged to his private physician with recommendations for the resumption of gold therapy, of which he had had inadequate amounts several years before.

Morphological Description

The specimen from the left triceps consisted of two pieces, one of oval shape measuring 0.5 and 0.6 cm., and a very small piece composed of but ten muscle fibers longitudinally cut. There was no grossly visible change in either of them. However, sections stained by hematoxylin and eosin showed grossly visible, dark blue dots separated from each other. The size and shape of these dots varied from round to elliptic. With a hand lens seven of these areas were counted in the larger pieces and two in the smaller. Their shape was irregular due to elongated processes of dark blue color extending from some of them.

In serial cuts these dark blue-staining spots extended through 10 to 15 consecutive sections. Since each section was 7 μ thick, the average size of such a nodule was 0.070 to 0.105 mm. in thickness, the maximum length being about 1 mm.

Microscopically, the inflammatory lesions were well circumscribed, although there were processes from the nodular mass infiltrating the perimysium and the endomysium (Fig. 8). These elongated processes were composed of the same cells as the nodules. The inflammatory cells were lymphocytes, many of them immature with vesicular nuclei. There were also rather abundant plasma cells in a more peripheral location, and mast cells outside the nodules. In larger nodules circumscribed accumulations of the epithelioid cells with nuclei poor in chromatin and definite nucleoli were seen (Figs. 9 and 10). These nuclei seemed to be related to capillary endothelial cells or sarcolemmal cells. They were grouped together, usually nearer to the periphery of the nodule. In sections stained with van Gieson's stain, the increase of collagenous fibers was marked, and the location of the inflammatory process in endomysium and perimysium could be ascertained. Many of the larger nodules showed a somewhat loose structure with spaces surrounding the lymphocytes and plasma cells. No stroma was recognized in these spaces; a reticulin stain revealed scanty reticulin fibrils. In one elongated nodule the accumulation of inflammatory cells was interrupted by a crosscut capillary, the walls of which were not infiltrated by inflammatory cells. Aside from larger nodules, small foci of lymphocytic infiltration were seen more widely spread.

Of special interest were small inflammatory foci where a muscle fiber was surrounded by endomysially located inflammatory cells, lymphocytes, and plasma cells. Here a beginning degenerative alteration of the muscle fiber was seen (Fig. 11). There was an occasional peculiar arrangement of small vacuoles in longitudinal rows parallel with the longitudinal striations of the fiber, which then did not show any cross striation (Fig. 12). These muscle fibers were much paler than the normal ones in their vicinity and toward their peripheral portions showed increased large nuclei poor in chromatin. These nuclei regularly contained two nucleoli, were elliptic or ovoid, and showed a distinctly outlined nuclear membrane; occasionally the nuclei were distributed in rows close together at the periphery of the muscle fiber (Figs. 11 and 13). Rarely, one large elongated nuclear mass containing dark-staining chromatin was seen instead of the numerous pale nuclei described before (Fig. 14). In the pale gray-staining sarcoplasm of these degenerating muscle fibers peculiarly pale-staining granular

dots of minimal size were seen. Coarser cross striation, beginning longitudinal fibrillation, and beginning vacuolization around hyperplastic muscular nuclei were seen in some of the muscle fibers (Figs. 15 and 16). Most of the muscle fibers, however, did not show beginning or advanced degeneration although there was occasional swelling.

The epimysium showed no signs of inflammation, nor did the walls of capillaries and of larger blood vessels, the perineurium of intramuscular nerves, or the neuromuscular spindles.

Case 5

The patient, a white male, 61 years old, was admitted (Harper Hospital) on August 4, 1944, because of pain in his joints. He had suffered from rheumatoid arthritis for 4 months, being troubled with pain that seemed to originate at the back of his neck. His attending physician believed that the discomfort on flexing his neck was due to "abscessed" teeth. These were removed. Following the extraction, however, the pain spread to the joints of his upper extremities, affecting chiefly the elbows and fingers. During the month prior to his admission he developed pain in both knees.

There was nothing remarkable on physical examination except a slight increase in the transverse diameter of the heart; a blowing systolic murmur was heard at the apex and transmitted toward the base, P_2 being slightly accentuated. Blood pressure was 120/60 mm. Hg. The margin of the liver was palpable; the spleen was not palpable. Except for hyperactivity in his reflexes there were no abnormal neurological findings. There was marked pain on flexion of the knee joints and slight muscular atrophy above and below the joints. In the upper extremities there was slight fusiform swelling of the first phalangeal joints and some thickening of the distal joints of his fingers. The amount of pain and stiffness was variable; at one time he was unable to lift his arm to his head. There were slight elevations of temperature during his stay in the hospital.

The patient was placed on myochrysine therapy with marked improvement.

Laboratory Findings. Examination of the blood showed: Hemoglobin, 76 per cent; red blood cells, 3,910,000; white blood cells, 9,050, with a differential count of 6 per cent band forms, 68 per cent segmented forms, 24 per cent lymphocytes, and 2 per cent eosinophils. Sedimentation rate was 20 mm. in 60 minutes. Nonprotein nitrogen of the blood was 48.6 mg. per cent. The Kahn test was negative. There was a slight trace of albumin in the urine and occasional fine granular casts.

Radiological Examination. Studies of both hands revealed some periarticular swelling of soft tissues with a very slight demineralization of the bones. Although there was no disturbance in joint spacing except slight thinning of the cartilages of the joints, particularly of the metacarpophalangeal joints, the film study showed arthritis of an early atrophic type.

Morphological Description

Two pieces were taken from the left gastrocnemius muscle. One was 0.9 and 0.4 cm. in longitudinal and transverse diameters respectively; the other was 0.7 by 0.5 cm. Grossly, there was no visible change. Microscopically, there were again lesions of two distinct types, inflammatory and degenerative. The inflammatory lesions were of a

definitely nodular type. In the entire section five nodules were seen, four in the perimysium and endomysium, and one in the epimysium. The nodules seen in crosscut muscle fiber bundles were endomysial; the muscle fibers themselves were not invaded by inflammatory cells (Fig. 17). As before, the inflammatory cells were lymphocytes and plasma cells. The nodules were small, much smaller than in the previous case; they did not contain epithelioid cells and apparently represented earlier stages of muscle involvement than in the previous case. Nevertheless, the collagenous connective tissue was increased in and around the nodules. The epimysial nodule had developed between blood vessels, but there was no involvement of the vascular walls. The inflammatory cells were spread between the adventitial layers of the blood vessels, and no inflammation was present in the adventitia, media, or intima of the vascular walls.

In spite of the smallness of the inflammatory nodules, scanty but definite signs of degeneration of muscle fibers were seen. The degenerating muscle fibers were located between normal muscle fibers, the ratio of normal to degenerating muscle fibers being 20 to 1. There was a definite color change of the degenerating fibers; some exhibited a more bluish tinge, others a bright, peculiarly refractile, yellowish color (in hematoxylin and eosin stain). The discolored fibers, when longitudinally cut, showed a marked longitudinal fibrillation. The degenerated fibers showed somewhat irregular lines of cross striations and coarser interspaces between the transverse striae. Most of the bluish muscle fibers showed an increase of large, pale nuclei with one or two large nucleoli; the nuclei were sometimes arranged in longitudinal rows. In these fibers vacuolization at the periphery of the muscle fiber or around the large nuclei was occasionally seen (Fig. 18). Again, this early lesion seemed to be segmental, occupying a short longitudinal portion of a single fiber. Neuromuscular spindles were free of inflammation.

Case 6

The patient, a white female, 29 years old, was admitted (Harper Hospital) on August 14, 1944, having been in good health until 13 months previously when she had begun to suffer with rheumatoid arthritis. Three weeks after the birth of her first child she had felt pains and stiffness in the muscles and joints. At the outset, the symptoms came and went without any evidence of swelling, but a short time later she noticed slight swelling, redness, and tenderness. At that time an "abscessed" tooth was extracted. There was no history of any other previous acute infection or chronic illness. The patient had been carefully examined in two other medical clinics: in one no diagnosis was made; in the other, because of an increased sedimentation rate, she was told that the possibility of rheumatoid arthritis had to be considered. Roentgenograms of the joints at each clinic revealed no changes suggestive of rheumatoid arthritis.

At the first examination the patient complained as much of pain in the muscles, particularly in the deltoid muscles, as of pain in the joints. She was worse at night, and when awakening found it difficult to move because of pain and stiffness.

The skin was somewhat glossy, delicate, moist, and smooth. The heart sounds were clear and of good quality. There was a slight spindle-shaped swelling of the fingers of each hand, and a very slight interosseous atrophy of the dorsum of each hand. The right great toe was stiff, but no enlargement could be determined. The reflexes of the extensor muscles of the forearm, the biceps, and the patellars were hyperactive. No clonus was elicited. During the 9 days that the patient was in the hospital her temperature rose to 101° F. on two occasions and promptly subsided. The pulse rate varied from 80 to 110. Myochrysine therapy was begun during hospitalization.

The patient presented the clinical features of early rheumatoid arthritis.

Laboratory Findings. Examination of the blood gave the following results: Hemoglobin, 78 per cent; red blood cells, 3,910,000; white blood cells, 4,150, with a normal differential count. The sedimentation rate was 24 mm. in 60 minutes. A Kahn test upon the blood was negative. Examination of the urine gave only negative findings.

Radiological Examination. Examined in dorsopalmar projections, the hands showed no evidence of abnormality. When these roentgenograms were examined 1 month later, one roentgenologist thought that some slight narrowing of the joint spaces was present, but no destructive process was discernible.

Morphological Description

Two small pieces were obtained for biopsy from the left triceps muscle. The larger was 0.4 cm. in longitudinal and transverse diameters; the smaller was a pyramidal-shaped piece with a 0.3 cm. longitudinal axis and a 0.4 cm. base. Microscopically the inflammatory nodules were smaller than those seen in the three previous cases; their morphological appearance, however, was identical. Individual degenerating muscle fibers were seen of the same type as those in case 5, but they were fewer.

Case 7

The patient (Eloise Hospital) was a white female, 27 years of age, who was admitted in January, 1942, because of swollen and painful joints. At the age of 11 she had had swelling and redness of the left knee that disappeared after rest in bed; the pain did not migrate. The patient did not recall that she had had any fever. She had been in good health until about 6 years prior to admission, when pain and stiffness appeared in the right knee, both shoulders, and in the right temporomandibular joint. Later she had swelling and severe pain in the knees. An impacted wisdom tooth was extracted, the right knee joint was aspirated, and she received vaccine and physiotherapy, but no relief was forthcoming. She was able to get about on crutches. Following the delivery of a full-term child 3 years before admission to the hospital, her condition became worse. Swelling and tenderness extended to other joints of her body, notably to the fingers of both hands. Two years before admission both legs and the left elbow joint were put in casts. No improvement followed attempts to straighten the legs and to manipulate the joints.

On admission, the skin was pale, cool, thin, and shiny, especially over the extremities. The heart was not enlarged nor were there any murmurs. All joints

of the body were involved, with marked deformity, limitation of motion, and fixation of some of them, especially the knees and ankles.

Laboratory Findings. The blood showed: Hemoglobin, 10 gm.; red blood cells, 4,200,000; white blood cells, 4,400, with 40 per cent filamented forms, 4 per cent nonfilamented forms, 39 per cent lymphocytes, 6 per cent large mononuclear cells, and 11 per cent eosinophils. The sedimentation rate was 20 mm. in 60 minutes. A Kahn test was negative. Urinary examination showed no abnormality, and the electrocardiographic tracings were considered normal.

Radiological Examination. The fingers and wrists showed osteoporosis and sharply outlined joint margins. Similar changes were seen in both elbows, knees, and feet. The right knee showed, in addition, a fused patella and apparent fusion of the tibia and fibula. In both ankles there was tibial-tarsal fusion. The proximal phalanges of both feet were dislocated; marked hallux valgus was present.

Clinical Diagnosis and Course. The diagnosis was advanced rheumatoid arthritis, trophoneurotic disturbances, and hypochromic microcytic anemia.

Treatment consisted of blood transfusions, sedatives, and physiotherapy. Kirschner wires were inserted into both tibiae and traction applied. Two months later osteotomy of the right knee was performed and a plaster dressing at 10° flexion applied. One month later roentgenograms showed fusion of the tibia and femur, and union of patella with the right femur. The ankylosis and deformity of the lower extremities gave the patient constant pain and almost total immobility. She was able to use her upper extremities somewhat. The patient and her husband demanded consideration of the fact that she could be more easily handled at home if the useless legs were removed. First the right leg was removed at the mid-thigh, and 3 weeks later the left leg at the mid-thigh. She made an uneventful recovery and was discharged.

At the time of amputation our interest was focused on the investigation of peripheral nerves. By chance, some muscle tissue adherent to the left tibial nerve and another piece of muscle adherent to the left superficial peroneal nerve were removed. The nerves showed typical nodulous rheumarthritic perineuritis.

Morphological Description

In the muscle tissue adherent to the left tibial nerve two nodules were seen. One was the largest in this series of cases. It was seen grossly in stained sections as a deep-blue dot, 1 mm. in transverse diameter and 1.1 mm. in longitudinal axis. The other nodule was small and was seen only microscopically. The muscle tissues in the vicinity of the left superficial peroneal nerve showed three small nodules.

Again, inflammatory and degenerative lesions were distinguishable. The large nodule showed a massive accumulation of lymphocytes and plasma cells, the latter at the periphery. Epithelioid cells were not conspicuous; there were, however, remnants of degenerating muscle fibers in the center of the nodule as well as at its periphery (Figs. 19 and 20). Not far from the nodule, in the perimysium, an artery was seen with nodular inflammation of its wall, mostly in the media and adventitia (Figs. 21 and 22). A marked increase in collagenous connective tissue fibers was seen in the nodule and in its surroundings, with no increase in reticulin fibers. In the vicinity of the nodule the muscle fibers showed severe degeneration, a lack of cross striation, vacuolization, dis-

tortion of the straight longitudinal form with wave-like outer contours, and an increase in large nuclei that were poor in chromatin and contained one or two prominent nucleoli. Occasionally the muscle fibers were broken up into smaller, irregular fragments containing these large nuclei.

In the muscle in the vicinity of the left superficial peroneal nerve one perineurial nodular accumulation of lymphocytes and plasma cells was seen; the perineurium of a small intramuscular nerve fiber bundle was completely infiltrated with lymphocytes and plasma cells (Fig. 23). The other two nodules were endomysial without relationship to nerves or blood vessels. There was a severe shrinkage of muscle fibers in isolated nests as described in previous cases.

Case 8

The patient was a white male, 55 years old. When he entered Eloise Hospital in August, 1941, complaining of painful, swollen joints, he had been suffering with rheumatoid arthritis for more than 11 years. Eleven years before he had noted pain in the left hand and elbow and some swelling and reddening of the joints. Progressively, over a period of several months, the shoulders, knees, hands, and feet became involved. Treatment was of no avail, and gradually his hands and feet became deformed. Numbness and tingling of the toes occurred at various times, and cramping of the calf muscles was an occasional symptom. Some shortness of breath was experienced on exertion. For the past 3 years slight swelling of the ankles had been noticed.

On admission his temperature was 98° F.; the pulse, 90; and respiration, 20. The eyegrounds showed some arterial tortuosity; the tonsils were atrophic; and the mouth was edentulous. Signs of fluid were present in the left pleural cavity, and a few moist râles were present at each base. The heart dulness merged with the dulness at the left base. There were no murmurs and no arrhythmia, although the aortic second sound was slightly accentuated. Blood pressure was 158/90 mm. Hg. All joints of the body were involved. There was marked limitation of motion of the larger joints. The fingers were flexed and rigid. Atrophy of all muscles of the body was apparent, especially those of the hands, arms, legs, and thighs. The feet and legs were cool, the right cooler than the left. Pulsation in the dorsalis pedis was less noticeable in the right foot than in the left. The reflexes were all markedly exaggerated. Clonus, muscle spasm, and fibrillation were not present. Subcutaneous nodules were present at each elbow. A nodule was excised for biopsy.

In September, 1941, cardiac decompensation developed, but the patient recovered temporarily following appropriate therapy. In August, 1942, the right great toe became infected, and gangrene of the foot followed. Cardiac decompensation returned. A right mid-thigh amputation was performed but the patient's condition did not improve and he died of cardiac failure on October 10, 1942, 6 weeks following amputation.

Laboratory Findings. Examination of the blood showed: Hemoglobin, 9.5 gm.; red blood cells, 3,780,000; white blood cells, 9,600; blood sedimentation on admission, 20 mm. in 60 minutes. A Kahn test was negative. Examination of the urine showed albuminuria of mild degree, with a few hyaline and finely granular casts; the average specific gravity was 1,020. Electrocardiograms revealed severe myocardial damage.

Radiological Examination. There was marked contracture deformity of the left hand. All proximal phalanges were dislocated in relation to the heads of the metacarpals. The joints of the wrists were narrowed. The joint spaces of the left elbow were narrowed and the margins sclerotic and irregular. Both patellae were fixed and the joint spaces of the knees were narrowed with sclerotic margins. The same changes were present in the ankles.

Clinical Diagnosis. Advanced rheumatoid arthritis, subcutaneous nodules, generalized arteriosclerosis, arteriosclerotic heart disease, myocardial failure, bilateral hydrothorax, gangrene of the leg, and peripheral arteriosclerotic disease.

Morphological Description

The findings at autopsy were bilateral purulent empyema, bilateral chronic adhesive pleuritis, hypertensive and atherosclerotic heart disease, chronic fibrinous pericarditis with obliteration of the pericardial sac, atherosclerosis, and arteriolar sclerosis of both kidneys.

At the autopsy, three pieces of tissue were taken from the left pectoralis major muscle. In each of the three there was nodular lymphocytic inflammation, with usually three to five nodules in each section. They were located in the perimysium, more rarely in the endomysium. Small, elongated, spindle-shaped, circumscribed, inflammatory foci were seen in the endomysium (Fig. 24). An increase of collagenous connective tissue fibers and a lack of reticulin fibril production were apparent as usual. The perimysial nodules were often seen in the vicinity of blood vessels periadventitially, but never adventitially (Fig. 25). There was an occasional nodule in the perineurium of an intramuscular nerve bundle. The muscle fibers showed irregularly distributed swelling and a loss of cross striation. There were a few severely shrunken muscle fibers, usually in bundles of two or three between normal fibers. The shrinkage was seen in both crosscut and longitudinally cut fibers.

In one of the pieces of muscle tissues there was arteriolar sclerosis with atherosclerosis in the larger arteries.

Case 9

This case was found among our 196 control cases. For controls, specimens were removed routinely at autopsy from the pectoral, iliopsoas, and rectus abdominis muscles. They were fixed in formalin and brought to the laboratory without any clinical or post-mortem data.

The patient was a white male, 55 years of age, who had died in the admitting room of the hospital after 1 week of illness. No other data were available. At autopsy left lobar pneumonia (pneumococcus, type VII), fibrinous pleuritis, hyaline perisplenitis, and perihepatitis were found. In addition the patient showed ulnar deviation of both hands and bilateral hallux valgus with lateral deviation of the other toes of both feet. He had multiple subcutaneous nodules; one at the knee joint was saved for microscopical examination. The diagnosis of arthritis had been made post mortem.

Morphological Description

Pieces from the iliopsoas and pectoralis muscles showed no conspicuous lesions; however, in the piece from the rectus muscle two distinct inflammatory nodules were found. They were located in the perimysial connective tissue near a nerve and an arteriole. There was no infiltration of the endoneurium of this nerve and no perivascular arrangement. The inflammatory cells were lymphocytes and plasma cells; van Gieson's and reticulin stains revealed the same characteristics seen in the nodules in the muscles of the previously described cases. Definite degenerative changes of the muscle fibers were not found.

The subcutaneous nodule was composed of a large central zone of necrosis in which cells and connective tissue had completely disappeared, being replaced by necrotic structureless masses. Peripheral to the necrotic zone, rows of radially arranged proliferating cells of fibroblastic origin were seen. The necrotic center was sharply demarcated by the palisading arrangement of these fibroblasts. In the peripheral zones of the nodule marked infiltration with lymphocytes and plasma cells was present, usually in perivascular arrangement. There were three smaller nodules of miliary size in the vicinity of the large nodule. In these smaller nodules the central necrotic zone was in the beginning stage, showing numerous fibroblasts resembling epithelioid cells, and both fine and thick, bright-staining, collagenous connective tissue bundles in a somewhat radiating arrangement.

Discussion

The muscular lesions reported herein were of an inflammatory nature. There were also degenerative changes in muscle fibers. The inflammation was of a nodular type, lymphocytes and plasma cells were abundant, mast cells occasional, and polymorphonuclear cells and eosinophils rare or absent. The size of the nodules varied from those seen grossly in stained sections to very small ones. The shape was round or oval, triangular or spindle-shaped, often elongated, with processes of inflammatory cells infiltrating the endomysium between two or more muscle fibers. There were also smaller foci composed of twenty or less lymphocytes. The inflammatory nodules were located in the endomysium and the perimysium, rarely in the epimysium. In the larger nodules cells of an epithelioid type were seen, usually not in the center of the nodule but at the periphery. The origin of these cells could not be established definitely. They were derived either from capillary endothelial cells or from muscular nuclei, for there was a

definite resemblance between these nuclei and those of degenerating muscle fibers. The inflammatory nodules were found in each of the nine cases of rheumatoid arthritis examined. Striking features of the nodules were an increase in bundles of collagenous connective tissue fibers and a lack of reticulin network. Even in larger nodules a loose structure was evident with spaces around the inflammatory lymphocytes and plasma cells.

There were various stages of degeneration of muscle fibers. In late cases of rheumatoid arthritis, such as our cases 1 and 2, both of 19 years' duration, the degenerative changes were advanced and were represented by a marked atrophy, fatty metamorphosis, and severe distortion of the outer contours of the fibers. The early stages of muscle degeneration were seen in our cases 4, 5, and 6 (of 6 years', of 4 months', and of 13 months' duration respectively). They were distinct from the late stages, in which shrinkage was the most prominent feature. In the early stages of involvement there was a change in color to a bluish tinge or, more rarely, to a peculiar bright yellow. The cross striations were not straight but somewhat wavy, and the interspaces between them were coarser than normally. There were pale muscle fibers and peculiar vacuolization of these fibers. The bluish discoloration was somewhat similar to that reported in the basophilic granular degeneration of muscle fibers in trichinosis. The muscular nuclei were more numerous, and an alteration of position and shape was seen. Instead of being just beneath the sarcolemmal sheath the nuclei were located more toward the interior of the fibers or in the central longitudinal axis. The nuclear shape changed from rod-like to oval or round, and the nuclei became twice as large as normal. The perinuclear cytoplasm was not distinct; there was, however, perinuclear vacuolization. Densification of perinuclear sarcoplasm was seen also, the sarcoplasm exhibiting a darker color and a distinctly granular appearance. The nuclear chromatin was poor; the nucleolus was large, and there were often two nucleoli, which took the acid stain. Amitotic divisions and incomplete segmentation between nuclei were also found. Rarely an elongated giant nucleus was observed, its longitudinal axis being three times as long as the axis of one of the swollen nuclei. The proliferated nuclei appeared in longitudinal rows parallel with the longitudinal axis of the muscle fiber. Such rows contained as many as twenty nuclei.

In three cases the perineurium of intramuscular nerves showed nodular inflammation, and occasionally periadventitial and mural nodular inflammation of blood vessel walls was seen in the perimysium and the

epimysium. However, the early stages of the disease showed nodular inflammation in the endomysium and the perimysium without relationship to intramuscular nerve fiber bundles, blood vessels, or neuromuscular spindles.

Classification

The anatomopathological lesion in the muscular tissues must be designated as nodular polymyositis with secondary muscular atrophy. The name, polymyositis, has been selected because of the multiplicity of the inflammatory lesions and their wide distribution over the entire skeletal muscular system (gastrocnemius, other unidentified muscles of legs (case 7), deltoid, triceps, pectoral, and rectus abdominis muscles). The term "nodular" has been chosen in spite of occasional, more diffuse, inflammatory changes in the vicinity of the nodules because in most of the sections the muscular nodules appear as well demarcated lesions.

Perimysium and endomysium as well as muscle fiber and nuclei are of mesodermal origin. Since connective tissue, in general, and perimysium and endomysium, in particular, have a low grade of differentiation, the histological response to various infections and to other stimuli is limited. Among the infectious diseases a number of characteristic histological reactions of connective tissue can be recognized, for instance: tuberculous caseous necrosis, gummatous reticular fibrosis, fibrinoid necrosis with cellular palisading in subcutaneous nodules of rheumatic fever and rheumatoid arthritis, and Aschoff bodies in the myocardium. All of these more or less specific granulomatous reactions are characterized by the appearance of circumscribed nodules of varying sizes, composed of special tissue elements in special arrangements. Hence these processes are distinguishable from diffuse inflammatory infiltrations. The character of the infiltrating inflammatory cells is another factor determining the classification of inflammatory changes. Granulomas, in general, exhibit the subacute or chronic picture of lymphocytic cellular infiltration. Besides the characteristic appearance in nodules, there is often a lymphocytic accumulation in ring-like fashion at the periphery of the lesion. This lymphocytic ring is typical in nodular perineuritis of rheumatoid arthritis; the inner zone is occupied by epithelioid cells or fibroblasts. In the small nodular granulomas in the muscles of our patients, lymphocytes and plasma cells were evenly distributed throughout the entire granuloma; epithelioid cells were seen only in the larger nodules. Lymphocytes and plasma cells predominated; eosinophils and polymorphonuclear cells were rare. In rheumarthritic perineuritis the nerve fibers themselves did not ap-

pear to be damaged while in rheumatoid polymyositis a severe degeneration of muscle fibers accompanied the inflammatory process.

The muscular lesion found in our cases of rheumatoid arthritis may be classified as nodular polymyositis.

Nodulous rheumarthritic perineuritis as reported in previous papers [1,2] and nodular polymyositis described herein are essential findings in rheumatoid arthritis. Both lesions are of an inflammatory nature, are found in perineurial, and in perimysial and endomysial locations, and are alike in their histological patterns. Therefore, the findings in peripheral nerves and muscles may be classified in a single phrase as nodular neuromyositis of rheumatoid arthritis.

Specificity of Muscular Lesions

The histological observations reported herein are thought to be of specific character.

1. *Nodular Appearance and Distribution.* One of the main characteristics of the muscular lesions is their nodular appearance. Our material was not extensive enough to supply data on the distribution and preferred location of these nodular lesions in the entire mass of one skeletal muscle, to say nothing about the distribution in the entire skeletal muscular system or about the predilection of one or more individual muscles. Up to the present time the muscles examined are the gastrocnemius, deltoid, triceps, rectus abdominis, and pectoralis major. Our controls were the musculus pectoralis major, m. rectus, and m. iliopsoas. Our control material of 196 cases was not sufficient for a completely adequate comparison. Further, our control muscles showed other pathological lesions (atherosclerotic and arteriolar lesions, cartilaginous metaplasia in perimysial adipose tissue, post-traumatic abscess formation, trichinosis) in addition to those found in the cases of rheumatoid arthritis. Only in one control case were small lymphocytic infiltrations found in the endomysium and perimysium; these, however, were without secondary muscular atrophy. This was in a case of subacute bacterial endocarditis superimposed on old rheumatic heart disease. Another control case (reported herein as case 9) proved to be a case of rheumatoid arthritis.

Characteristic of the muscular change was the irregular distribution of the inflammatory lesions throughout the muscle tissues; in one section one to five nodules were seen, and the remaining perimysial spaces were without inflammatory lesions, or the lesions were very mild compared with the nodular accumulations. In serial sections these nodular inflammatory lesions did not extend through more than 10 to 15 sections, each 7 μ in thickness. Occasionally nodules were found in the

perineurium of small intramuscular nerves and in the walls of small arteries and veins. The intramural vascular inflammation was less often seen than the periadventitial arrangement. The neuromuscular spindles were never involved. An interesting histological detail was noted; namely, the increase of collagenous connective tissue and the decrease of reticulin fibers in the nodules.

2. Constancy of Occurrence and Uniformity in Appearance. Differential Diagnosis. Of a total of 10 muscle specimens from 9 cases, 7 were obtained for biopsy (2 from one case), and 3 through amputation of legs or at autopsy. Nine of these specimens showed definite and identical pathological lesions. The muscle tissues of each case were positive. In case 3 the specimen from the deltoid muscle was positive but not that from the gastrocnemius muscle. Although the amount of muscle tissue examined in each individual case was very small compared with the total quantity in the body, the high incidence of positive findings in various muscles is an indication of the wide distribution of nodular polymyositis throughout the skeletal muscular system in rheumatoid arthritis.*

Identical findings of nodular polymyositis in all 9 cases suggest the specific nature of this lesion. The control muscles did not show any lesions comparable to those found in rheumatoid arthritis. The controls were muscles taken from routine autopsies (196 cases) and 7 cases in which pathological lesions in muscles could be expected; namely, 1 case each of congenital myatonia, of myasthenia gravis, of amyotrophic lateral sclerosis, of progressive muscular dystrophy, of dermatomyositis, of lupus erythematodes, and of trichinosis. In addition to the previously mentioned pathological findings in our control material from routine autopsies, muscular degeneration without inflammatory lesions was found in cases of amyotrophic lateral sclerosis, of congenital myatonia, and of progressive muscular dystrophy. The inflammatory lesions in dermatomyositis and trichinosis were easily distinguished from those seen in the muscles of cases of rheumatoid arthritis. In dermatomyositis the inflammatory changes were diffusely spread and did not occur in nodular fashion as they did in the muscles of rheumatoid arthritis. In trichinosis, inflammation was close to encysted trichinae, with a definite capsule and numerous eosinophilic cells. There are a number of other diseases with definite muscular involvement; for example, glanders and Chagas' disease, that could not be examined for lack of material. On the other hand, in at least 7 of

* Five additional muscle specimens from 5 other cases of typical rheumatoid arthritis have shown identical lesions.

the 9 cases of rheumatoid arthritis from which muscle tissues were taken, there was not the slightest possibility of any other disease; they were typical cases of rheumatoid arthritis without any complication.

3. Morphological Similarity to Other Lesions Seen in Rheumatoid Arthritis. There is a striking resemblance between the muscular lesions in rheumatoid arthritis and those in peripheral nerves; the nodular arrangement is seen in muscles and peripheral nerves alike. Both lesions have the same type of cellular infiltration, lymphocytes and plasma cells. The location in the perimysium corresponds to that in the perineurium. The nodular perineurial inflammation in small intramuscular nerves is identical with that seen in nodulous rheumarthritic perineuritis. The general pattern of the lesions found in the muscles is quite similar also to that of lesions in the synovia, in subcutaneous nodules, and in scleromalacia perforans. An inflammatory nodular character prevails everywhere. In one of our cases (case 9) multiple subcutaneous nodules were present, one of which was examined microscopically. It presented the typical histological picture of a subcutaneous nodule in rheumatoid arthritis.

4. Histological Comparison with "Fibrositis." In favor of the specificity of the muscular lesions in rheumatoid arthritis is the entirely different histological picture in "fibrositis," which occasionally is characterized by the appearance of gross fibrous nodules. Hench,[4] declaring the fibrositic nodules as the "signposts of the disease," emphasized the disappointing results following biopsy. He found little or no histological abnormality. Other observers (Collins,[5] Slocumb,[6] Buckley[7]) agreed that the structural changes in fibrositic lesions are meager. The pathological findings in "fibrositis" as first described by Stockman;[8] namely, numerous fibroblasts, serous or serofibrinous exudate, and thickening of walls of the small blood vessels and nerve sheaths, were considered by Collins as unimportant. Collins emphasized the absence of cellular infiltration as the only important fact of Stockman's investigation. At any rate, there is not the slightest similarity between the muscular lesions in rheumatoid arthritis and the findings in "fibrositis," a strong point favoring the specificity of polymyositis in rheumatoid arthritis.

5. Comparison of the Skeletal Muscular Lesions in Rheumatoid Arthritis with Those in Rheumatic Fever. Klinge[9, 10] showed photomicrographs of granulomas in the musculus constrictor pharyngis and in the diaphragm of a patient with a second attack of rheumatic fever and rheumatic endocarditis. He considered these rheumatic nodules in the striated muscles more or less characteristic. They were often found

in the vicinity of joints but were also independent of the joints, for example, in the diaphragm and the pharynx. Graeff [11] also found typical granulomas in the voluntary muscles in rheumatic fever.

An interesting finding, heretofore not reported, is the involvement of the blood vessel walls in the muscles of rheumatoid arthritis. Definite nodular arteritis and periarteritis could be seen in small muscular branches in some of our cases. Von Glahn and Pappenheimer [12] described specific lesions of the small peripheral arterioles and capillaries in 10 of 47 cases of rheumatic cardiac disease, but skeletal muscles were not included in their routine autopsy material. As Collins [5] stated, polyarteritis has been observed frequently in rheumatic fever, but in rheumatoid arthritis the vascular lesions seem to be confined to the joints or subcutaneous nodes. This statement is no longer valid.

Pathogenetic Relationship between the Various Local Manifestations in Rheumatoid Arthritis

Rheumatoid arthritis is a systemic disease with many local manifestations such as inflammation in the synovia, in joint capsules, and in periarticular soft tissues; subcutaneous nodules; and inflammatory nodules in peripheral nerves and skeletal muscles.

1. Relationship between Lesions of Joints, Periarticular Lesions, and Lesions in the Muscles. In a previous paper,[2] emphasis was laid on the fact that the perineuritic nodules were not in contact with synovial or periarticular lesions. This independence applies also to the muscular changes, since specimens were taken for biopsy from gastrocnemius or triceps muscles far from any joint or periarticular tissues. In one of our cases the rectus abdominis showed nodular inflammation. There was no relationship of the muscular lesions to subcutaneous nodules, since, with two exceptions (cases 8 and 9), no subcutaneous nodules were present in the cases from which the specimens were taken.

2. Relationship between Perineuritis and Polymyositis. Theoretically it might be assumed that the muscular lesion results from damage done to the peripheral nerves in nodulous perineuritis. In our previous paper [2] reasons were presented why clinically manifested muscular atrophy seemed to us not at all related to perineuritic lesions. Also we were not able to disclose degenerative changes in axis cylinders or myelin sheaths of peripheral nerve fibers. Hence there is little foundation for the assumption that muscular lesions are secondary to perineuritis. Furthermore, the irregular distribution and the nodular type of lesion speak in favor of the autochthonous origin of the muscular lesions. There is often a perineurial inflammation of small intra-

muscular nerves, to be sure, but serial sections show this change to be discontinuous. The process certainly does not ascend from the intramuscular nerve twigs into the larger bundles of the nerve trunk. It also does not descend from a perineuritic lesion in the peripheral trunk into smaller intramuscular ramifications of nerve fiber bundles. There is no pathogenetic interdependence between the lesions in the trunks of peripheral nerves and the muscular lesions.

3. Relationship between Polymyositis and Muscle Degeneration. While perineuritis did not produce grossly or microscopically visible damage in adjacent nerve fibers, there seemed to be a close relationship between polymyositis and muscular degeneration. The myositis is certainly not a consequence of a primary muscle degeneration, for, in our control material of purely degenerative diseases affecting the skeletal muscular system, marked inflammatory changes were absent. In degenerative lesions of the muscle Hassin [13] has observed scanty infiltrations in the perimysium, but these are not nodular as they are in polymyositis of rheumatoid arthritis, and they are accompanied neither by perineuritis of the small intramuscular nerve fiber bundles nor by arteritis of intramuscular arterioles. In our cases of rheumatoid arthritis *early* stages of muscular degeneration were seen only when there was a severe endomysial inflammation; without inflammation no beginning muscle fiber degeneration was found. Thus, muscular degeneration in rheumatoid arthritis does not give rise to inflammation; rather, muscular degeneration is a consequence of the inflammatory nodular lesions because of the close spatial relationship of damaged muscle fibers to inflammatory foci. The irregular distribution of degenerated muscle fibers in close relationship to inflammatory lesions, the appearance of débris of muscle fibers in the nodules, and the absorptive phenomena of muscular tissue in intimate connection with the nodular inflammation are proof that muscular degeneration and atrophy are a consequence of the nodular inflammatory polymyositic process.

It may be asked why a similar secondary degeneration of the nerve fibers in peripheral nerve bundles was not found accompanying the perineuritic nodular inflammation in our previously reported cases. Endomysium, perimysium, and muscle fibers are all of mesodermal origin. Consequently an inflammatory process encroaching on the muscle fibers by way of the perimysium and endomysium does not encounter such a complete barrier as it does in the perineurium at the border between mesodermal and ectodermal tissues of the peripheral nerves. As a result of this barrier endoneurial inflammatory lesions were not seen or were extremely rare while endomysial inflammation was com-

mon. With perineuritic inflammation no degenerated nerve fibers or endoneurial inflammation could be seen, while endomysial and perimysial nodular inflammation with damage to the muscle fibers was prominent in the same section. The occurrence of both types of inflammation in the same section indicates that the inflammatory processes are identical and that the resistance of nerve fibers is due to histological and physiological dynamics by which the nerve fiber is much better protected than the muscle fiber.

In summary, the inflammatory lesions in the synovia, joints, and capsular and pericapsular tissues; the subcutaneous nodules; the nodular lesions in peripheral nerve trunks; and the nodular polymyositic inflammation with arteritis and perineuritis in skeletal muscles are concomitant lesions due to the same unknown cause but entirely independent of one another. They are coordinate, not subordinate. However, muscular degeneration is a consequence of the inflammatory lesion in the perimysium and endomysium.

Clinical Significance of Nodular Polymyositis in Rheumatoid Arthritis

Clinically, rheumatoid arthritis has to be treated as a chronic inflammatory process, for the similar character of the muscular lesions and the lesions in other structures (synovia, subcutaneous tissue, and perineurium) is strong evidence of a generalized inflammatory process, possibly of infectious origin. Since the infectious agent is unknown, only general principles of treatment can be applied. That gold (myochrysine) treatment is not entirely satisfactory is evident from the fact that muscle specimens taken from cases 3, 5, and 6, thus treated, revealed inflammatory nodules identical with those seen in our cases in which no gold treatment had been given recently or in which inadequate amounts of myochrysine had been administered several years before (case 4).

Polymyositic nodules are specific for rheumatoid arthritis. In the future the clinical diagnosis in early or doubtful cases of rheumatoid arthritis may be supported by biopsy of affected muscles. Further, it is possible that the value of therapeutic procedures may be controlled by such means.

The findings in rheumatoid arthritis are more closely related to those of rheumatic fever than to those of any other disease. Whether there is an etiological relationship between these two diseases cannot be established by morphological investigation. However, when both have been recognized in the same patient, rheumatic fever has always preceded rheumatoid arthritis.

Rheumatoid arthritis, even in its late stage, is not a disease that has terminated in scar formation but is a smoldering, active, distinctive entity as shown by the presence of inflammatory foci in the muscles and in the perineurium. The seemingly "burnt-out" clinical picture in old cases of rheumatoid arthritis without pains but with extreme stiffness in joints and with bony deformities is deceptive, since active inflammatory processes are found in the muscles and the peripheral nerves.

Stiffness and bony contractures are responsible for some limitation of muscular activity. However, we wish to emphasize our conclusion that the anatomopathological lesions herein described, rather than disuse, are responsible for the clinical picture of muscular atrophy in rheumatoid arthritis.

The multiplicity of the inflammatory lesions in the synovia and other articular and periarticular structures, in the peripheral nerves, and in subcutaneous tissues indicates a wide spread of the causal agent in cases of rheumatoid arthritis. With the recognition of nodular polymyositis a new link in this nosological chain has been found. Simultaneously, the primary inflammatory character of this disease is made more evident.

Summary

1. The pathological findings reported in this paper comprise "nodular polymyositis." Together with previously reported perineuritis, it constitutes an essential lesion in rheumatoid arthritis, to be called nodular neuromyositis.

2. The muscular lesions are specific for rheumatoid arthritis, since they were seen in every one of the 9 cases of rheumatoid arthritis and since they were absent in control material from 196 routine autopsies of cases of other diseases and 7 selected cases in which pathological lesions in muscles could be expected.

3. The distribution of the lesions in small amounts of various muscles (gastrocnemius, other unidentified muscles of the legs (case 7), triceps, deltoid, pectoralis major, and rectus abdominis) taken at random, and the high incidence of the lesions in a minimal percentage of the entire skeletal muscular system indicate the wide spread of nodular polymyositis throughout the skeletal muscular system.

4. The muscular lesions fit into the general pattern of other lesions known in rheumatoid arthritis, such as those seen in the synovia and other tissues of the joints, in subcutaneous nodules, and in the perineurium of peripheral nerve trunks. They are all alike in their inflammatory and granulomatous nature. The muscular lesions differ from those seen in other diseases (myatonia congenita, muscle dystrophy,

myasthenia gravis, dermatomyositis, "fibrositis," trichinosis). Besides the endomysial location of the lesions, perivascular and perineuritic nodular arrangements are seen in the perimysium.

5. The muscular lesions are not related spatially to lesions of the synovia, the periarticular tissues, the subcutaneous nodules, or of the peripheral nerves. They are concomitant but independent tissue reactions to the same unknown agent. Our material is not complete enough to establish a chronological order for these various manifestations. However, it seems evident to us that the muscular involvement begins early, perhaps at the same time that lesions of the joints become manifest (see case 5).

6. There is a definite pathogenetic relationship between nodular polymyositis and degeneration and atrophy of the muscle fibers. While inflammation can occur without degeneration of muscle fibers, early muscle fiber degeneration is always combined with inflammatory lesions in the endomysium of the same fibers. Hence an irregular distribution of degenerated muscle fibers is the consequence of irregular spread of nodular inflammation. The absorption phenomenon of degenerating muscle in intimate relation with the nodular inflammatory foci is further evidence of the primary nature of the inflammation and the secondary nature of muscle fiber degeneration.

7. Various stages of muscle fiber degeneration are recognizable from the early change in staining quality; through invasion of the contractile substance by peculiar nuclei and the appearance of vacuolization, irregular outer contour, and irregular cross striation; to extreme shrinkage of the muscle fibers. This sequence seems to be related to the duration of the disease or to the time of the involvement of the particular muscle examined.

8. From a clinical standpoint our pathological findings are important as evidence of the wide distribution of the inflammatory and probably infectious process throughout the body in rheumatoid arthritis. The finding of nodular polymyositis in cases treated with gold compounds leads to the conclusion that our present treatment is not sufficiently effective. The presence of polymyositic nodules in old clinically "burnt-out" cases is evidence of a permanent and active disease process. In the future, biopsy of muscle may be an aid in diagnosis, particularly in early cases, and in the control of chemotherapeutic action.

We wish to express our gratitude to Drs. Charley J. Smyth and S. E. Gould of Eloise Hospital, Eloise, Michigan, and to Dr. Plinn Morse of the Department of Pathology at Harper Hospital, Detroit, Michigan, for granting the use of material.

REFERENCES

1. Freund, H. A., Steiner, G., Leichtentritt, B., and Price, A. E. Peripheral nerves in chronic atrophic arthritis. *J. Lab. & Clin. Med.*, 1942, **27**, 1256–1258.
2. Freund, H. A., Steiner, G., Leichtentritt, B., and Price, A. E. Peripheral nerves in chronic atrophic arthritis. *Am. J. Path.*, 1942, **18**, 865–893.
3. Curtis, A. C., and Pollard, H. M. Felty's syndrome; its several features, including tissue changes, compared with other forms of rheumatoid arthritis. *Ann. Int. Med.*, 1940, **13**, 2265–2284.
4. Hench, P. S. Acute and Chronic Arthritis. In: Nelson Loose Leaf Surgery. Thomas Nelson & Sons, London, 1936, **3**, 104–175H.
5. Collins, D. H. Fibrositis and infection. *Ann. Rheumatic Dis.*, 1940, **2**, 114–125.
6. Slocumb, C. H. Differential diagnosis of periarticular fibrositis and arthritis. *Ann. Rheumatic Dis.*, 1940, **2**, 108–113.
7. Buckley, C. W. Fibrositis, some old and new points of view. *Ann. Rheumatic Dis.*, 1940, **2**, 83–88.
8. Stockman, R. Rheumatism and Arthritis. W. Green & Son, Edinburgh, 1920.
9. Klinge, F. Das Gewebsbild des fieberhaften Rheumatismus. II. Das subakut-chronische Stadium des Zellknötchens. *Virchows Arch. f. path. Anat.*, 1931, **279**, 1–15.
10. Klinge, F. Das Gewebsbild des fieberhaften Rheumatismus. XII. Zusammenfassende kritische Betrachtung zur Frage der geweblichen Sonderstellung des rheumatischen Gewebsschadens. *Virchows Arch. f. path. Anat.*, 1932, **286**, 344–388.
11. Graeff, S. Rheumatismus und rheumatische Erkrankungen. Urban & Schwarzenberg, Berlin, 1936.
12. Von Glahn, W. C., and Pappenheimer, A. M. Specific lesions of peripheral blood vessels in rheumatism. *Am. J. Path.*, 1926, **2**, 235–249.
13. Hassin, G. B. Histopathology of progressive muscular dystrophy. *J. Neuropath. & Exper. Neurol.*, 1943, **2**, 315–325.

[*Illustrations follow*]

DESCRIPTION OF PLATES

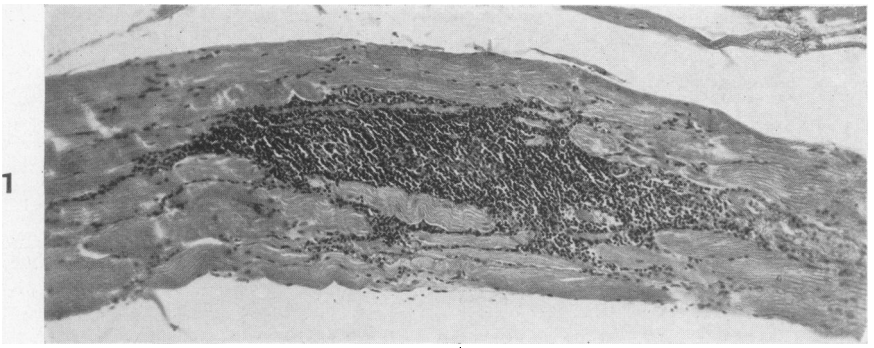
PLATE 22

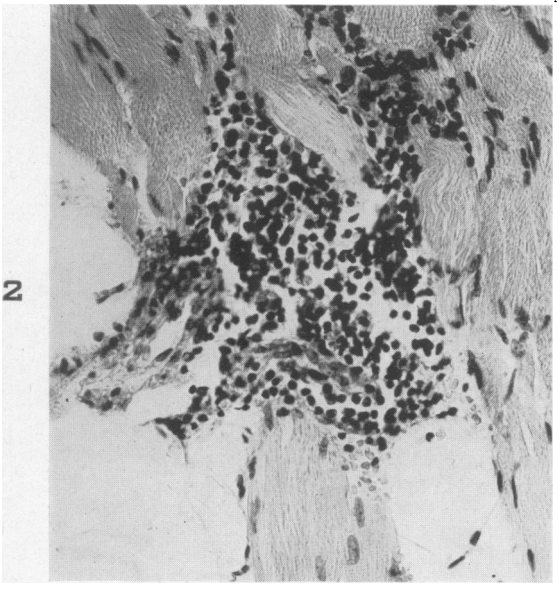
FIG. 1. Case 1. Specimen removed for biopsy from the gastrocnemius muscle. Spindle-shaped inflammatory nodule in endomysium. Hematoxylin and eosin stain. × 100.

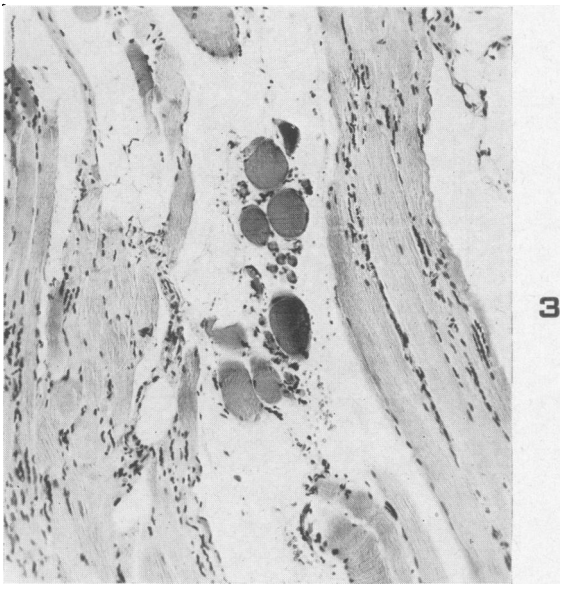
FIG. 2. Case 1. Specimen removed for biopsy from the gastrocnemius muscle. Smaller, triangular shaped, inflammatory nodule. Small amount of adipose tissue between two muscle fibers at the right lower angle of the nodule. At the upper end a pale muscle fiber is seen. Hematoxylin and eosin stain. × 300.

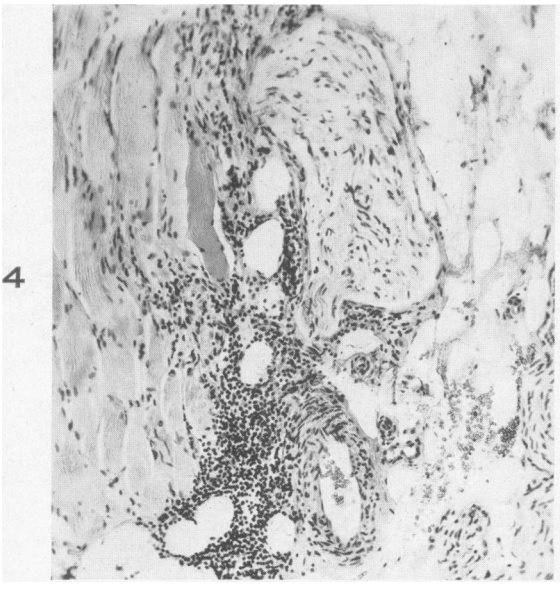
FIG. 3. Case 1. Specimen removed for biopsy from the gastrocnemius muscle. General increase in sarcolemmal nuclei. Large muscle fibers, partially crosscut, are seen in the center of the field. Between them there are a number of extremely shrunken fibers. Hematoxylin and eosin stain. × 100.

FIGS. 4 and 5. Case 1. Specimens removed for biopsy from the gastrocnemius muscle. Inflammatory nodules in a perimysial location adjacent to intramuscular nerves and to the adventitia of blood vessels. Hematoxylin and eosin stain. × 100.









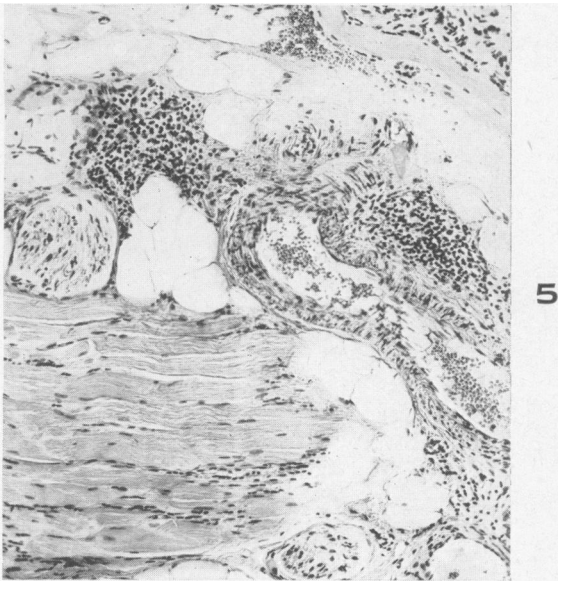


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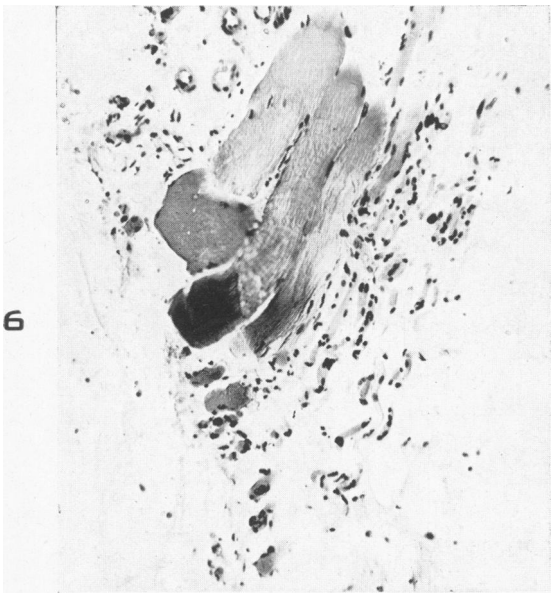
PLATE 23

FIG. 6. Case 2. Specimen removed for biopsy from the gastrocnemius muscle. Longitudinally cut, markedly atrophic muscle fibers are shown to the right and below three swollen, discolored, and slightly vacuolated fibers. Hematoxylin and eosin stain. × 150.

FIG. 7. Case 2. Specimen removed for biopsy from the gastrocnemius muscle. Inflammatory nodule in perimysial location between two small intramuscular nerves. Hematoxylin and eosin stain. × 150.

FIG. 8. Case 4. Specimen removed for biopsy from the triceps muscle. Well circumscribed, endomysial, nodular inflammation with extensions of infiltrating cells from the body of the nodule. Hematoxylin and eosin stain. × 150.

FIG. 9. Case 4. Specimen for biopsy from the triceps muscle. A large inflammatory nodule with accumulations of epithelioid cells near its periphery. Cresyl violet stain. × 150.



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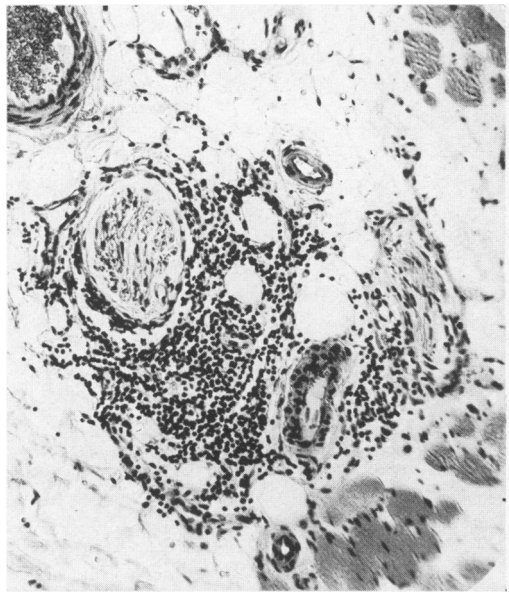

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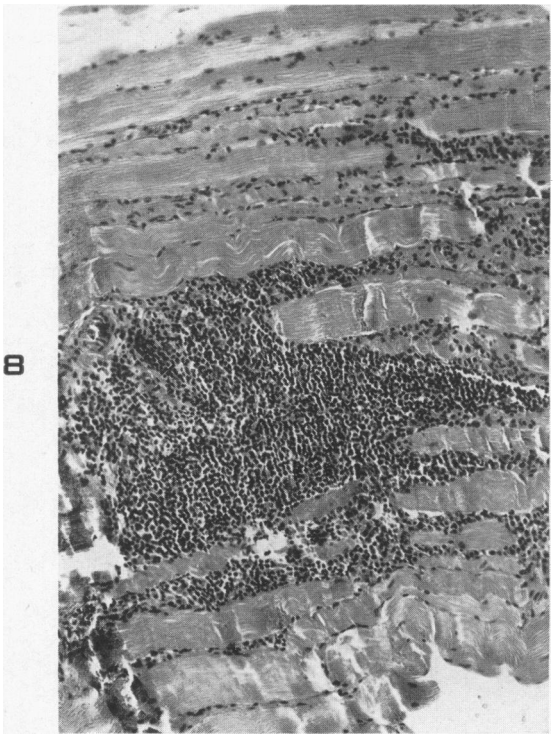

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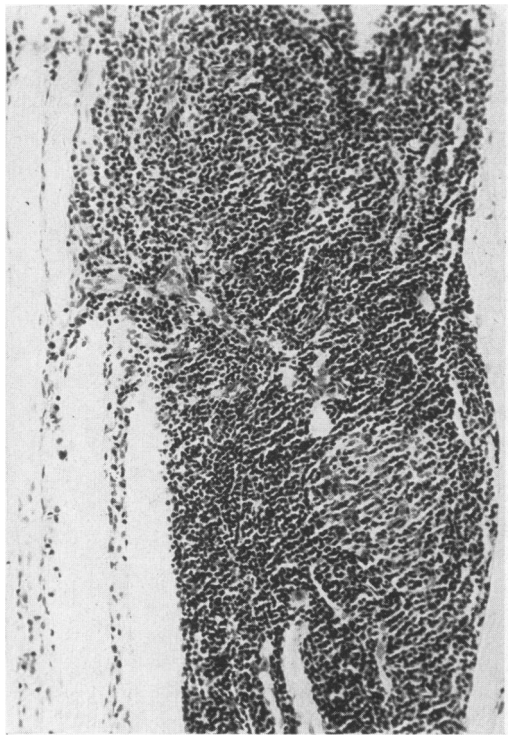

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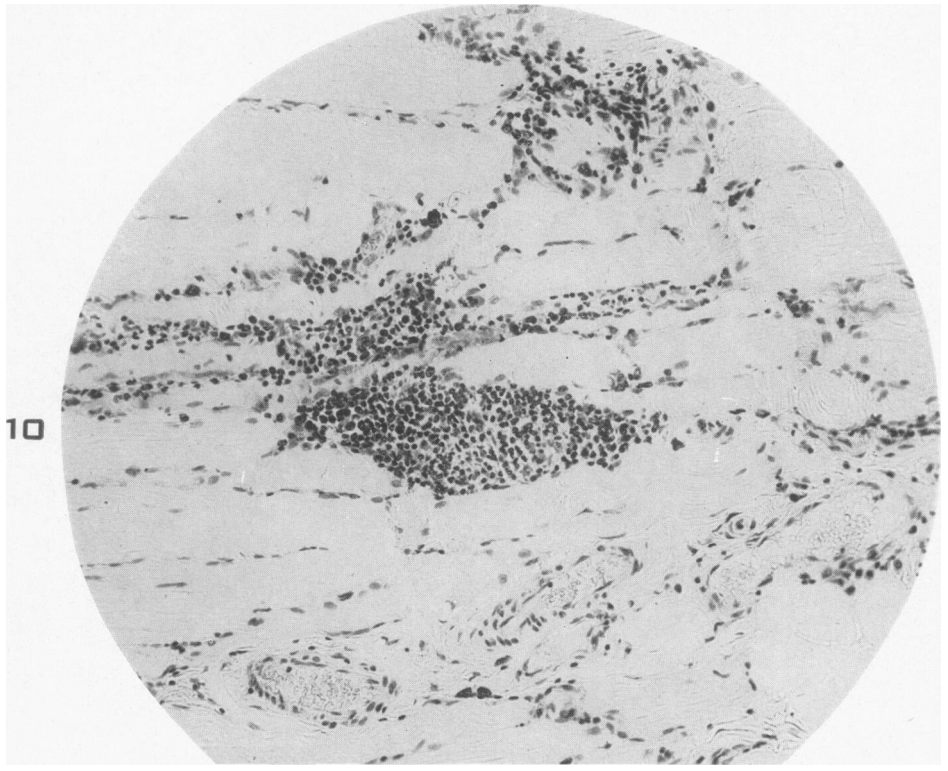
PLATE 24

FIG. 10. Case 4. A smaller inflammatory nodule from a specimen from the triceps muscle. There are many scattered mast cells. Cresyl violet stain. × 150.

FIG. 11. Case 4. Specimen removed for biopsy from the triceps muscle. Beginning degeneration of a muscle fiber, marked by lighter staining, and central position of muscle nuclei of larger size and having two nucleoli. The perinuclear sarcoplasm is granular and shows beginning vacuolization. The endomysium near this muscle fiber shows infiltration with lymphocytes and plasma cells. Van Gieson's stain. × 675.



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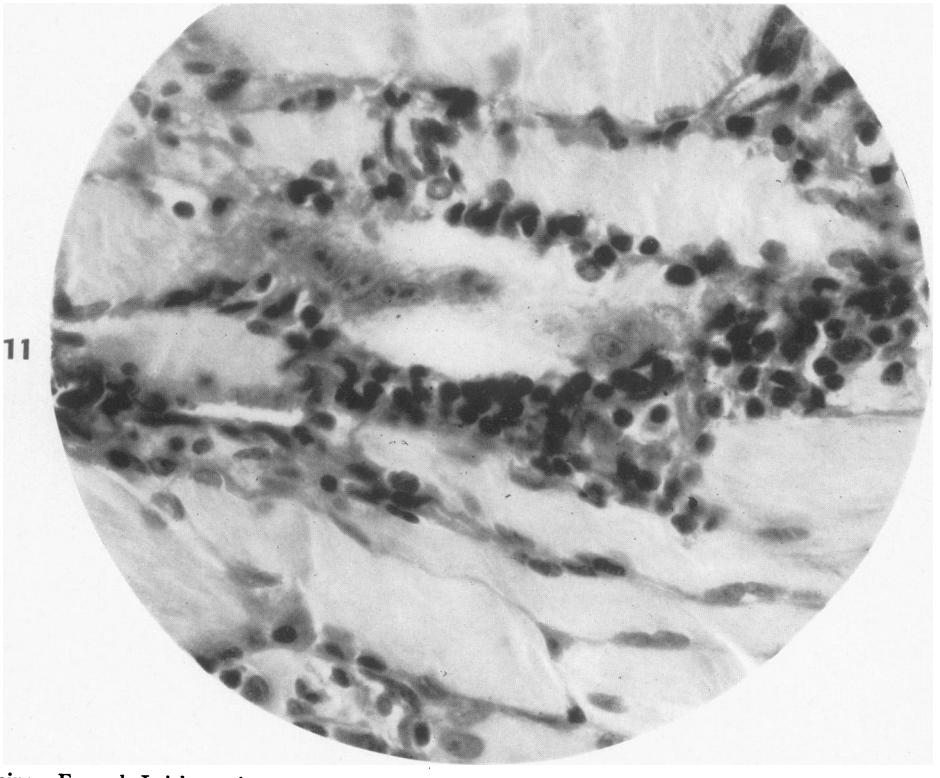

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PLATE 25

FIG. 12. Case 4. Specimen removed for biopsy from the triceps muscle. Two muscle fibers, showing degeneration, have a nodular inflammatory reaction around them, and there is a longitudinal arrangement of small vacuoles in the smaller of the two fibers. There are, also, loss of cross striation, and a pale-staining quality. Van Gieson's stain. × 675.

FIG. 13. Case 4. Specimen removed for biopsy from the triceps muscle. Abnormal nuclei at the periphery of a degenerating muscle fiber which is surrounded by lymphocytes and plasma cells. Van Gieson's stain. × 675.

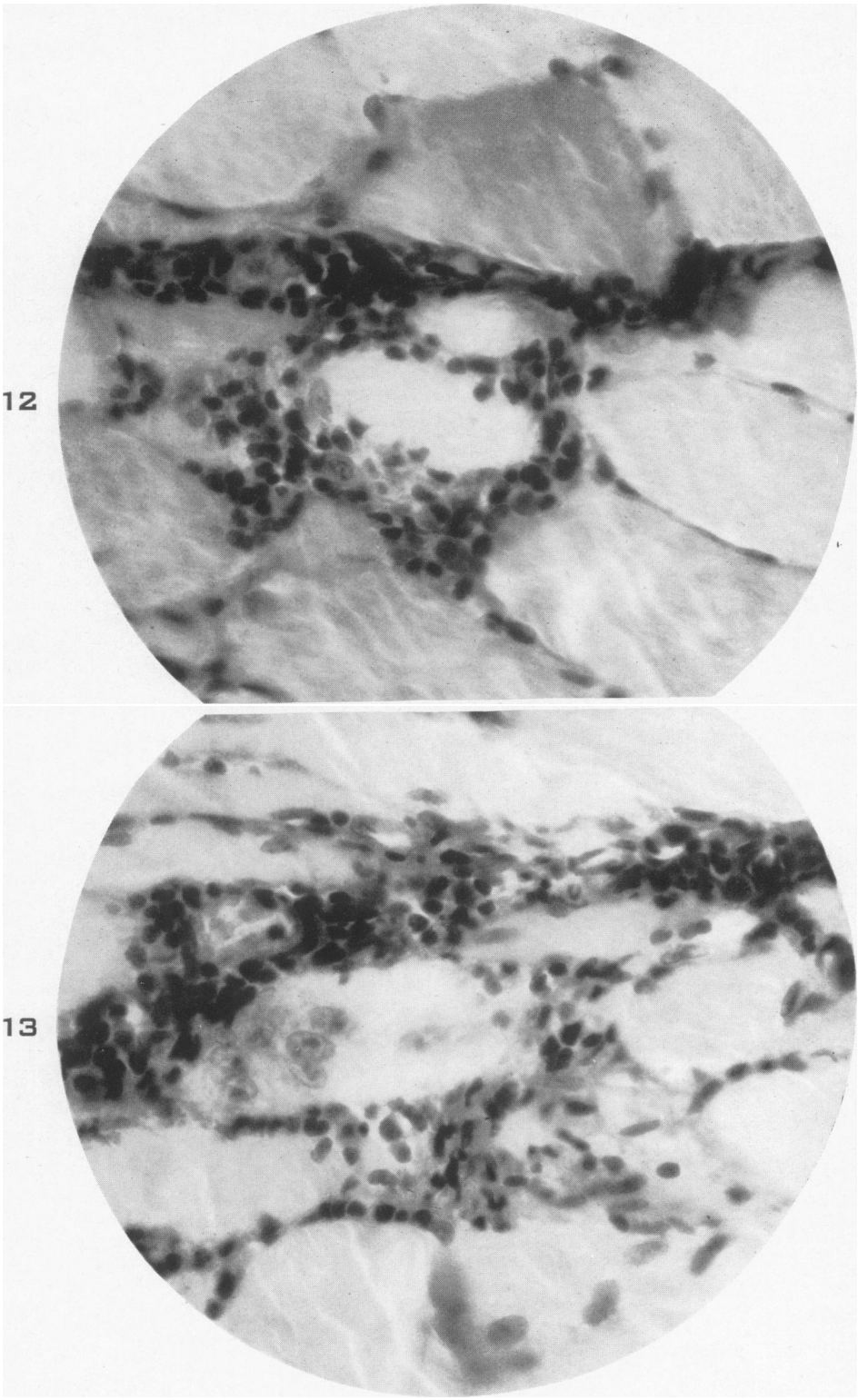

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PLATE 26

FIG. 14. Case 4. Specimen removed for biopsy from the triceps muscle. Two degenerating muscle fibers surrounded by an area of endomysial inflammation. There is a large, dark-staining nucleus in one of the fibers. Van Gieson's stain. × 600.

FIG. 15. Case 4. Specimen for biopsy from the triceps muscle. Crossing the field there is a degenerating muscle fiber with coarse cross striations. Below this, a second fiber shows beginning longitudinal fibrillation. This preparation was stained with cresyl violet, which gives injured muscle fibers a deeper blue color than that taken by normal fibers. × 675.

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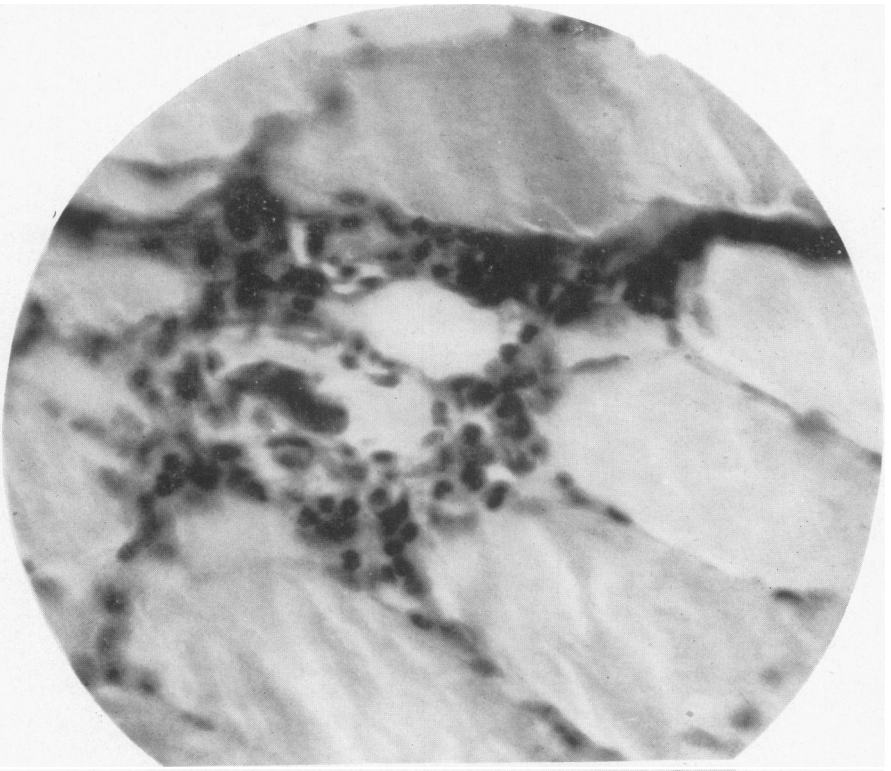

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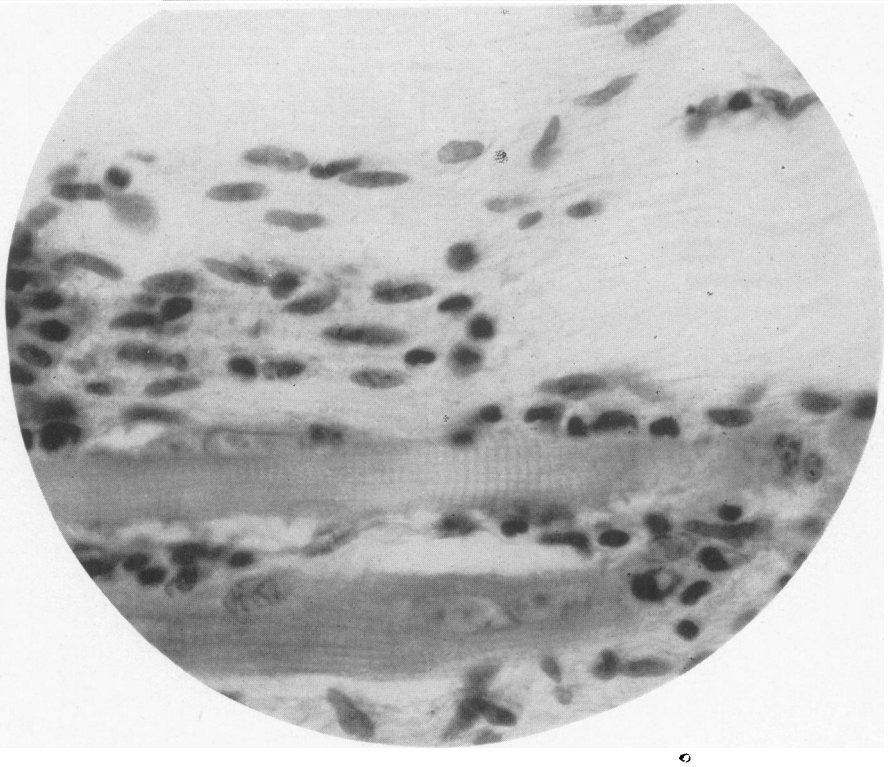

PLATE 27

FIG. 16. Case 4. Coarse, wavy cross striation of a muscle fiber. Infiltration of lymphocytes and plasma cells. Cresyl violet stain. × 675.

FIG. 17. Case 5. Specimen removed for biopsy from the gastrocnemius muscle. Small nodular inflammatory focus in an endomysial location. This shows the extent of infiltration in a transverse plane. Hematoxylin and eosin stain. × 100.

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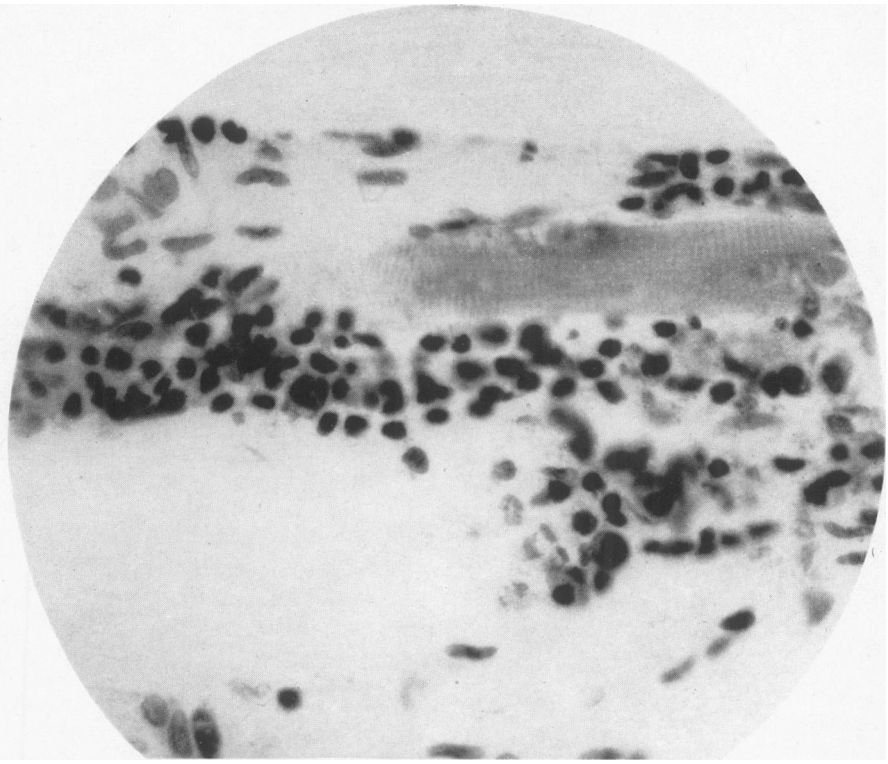

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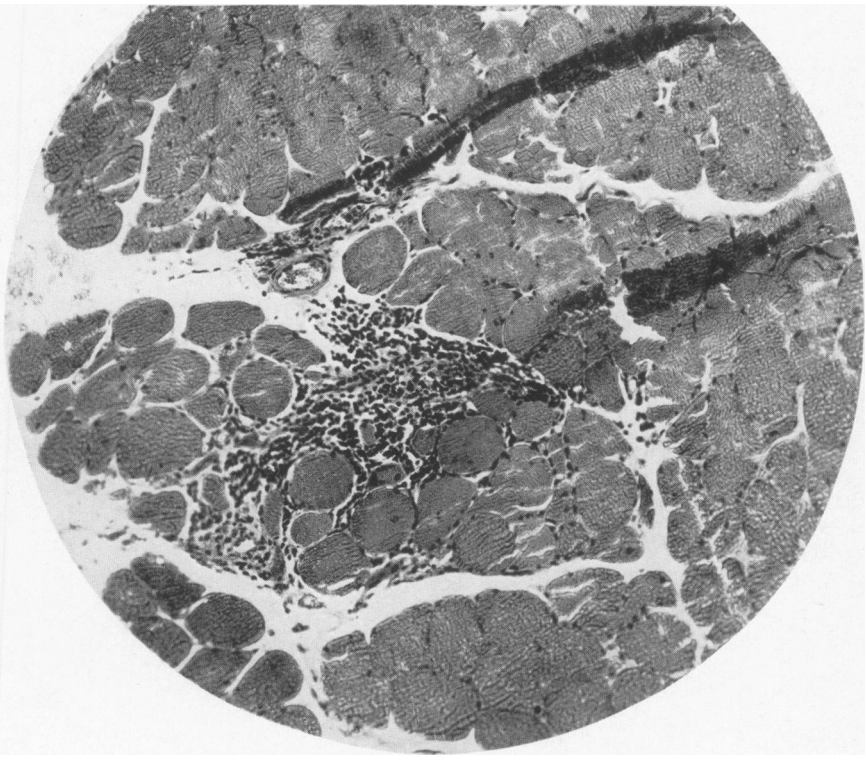

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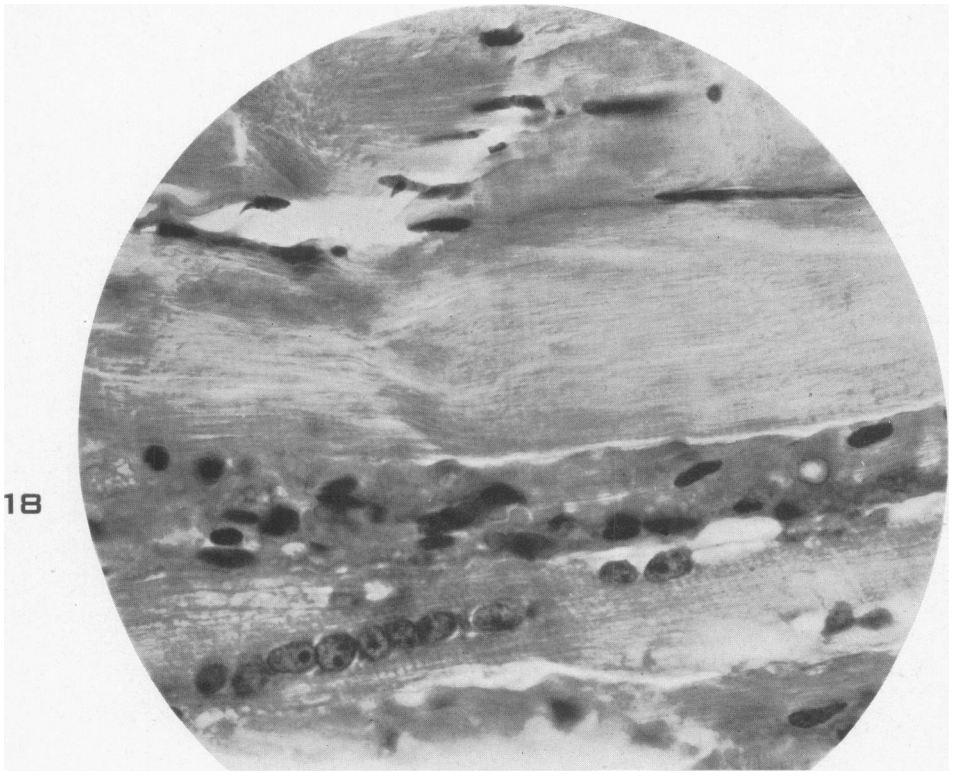
PLATE 28

FIG. 18. Case 5. Specimen removed for biopsy from the gastrocnemius muscle. A degenerating muscle fiber, with a more centrally placed row of muscular nuclei and vacuolization at the periphery and around the large nuclei, crosses the lower center of the field. Hematoxylin and eosin stain. × 675.

FIG. 19. Case 7. Specimen obtained following amputation of both legs. Muscle tissue near the tibial nerve with a massive inflammatory nodule and severe degeneration and atrophy of muscle fibers. The inflammatory cells are lymphocytes and plasma cells. Hematoxylin and eosin stain. × 100.

FIG. 20. High-power photomicrograph of a portion of the field of Figure 19, showing remnants of degenerating muscle fibers between lymphocytes and plasma cells. Hematoxylin and eosin stain. × 450.



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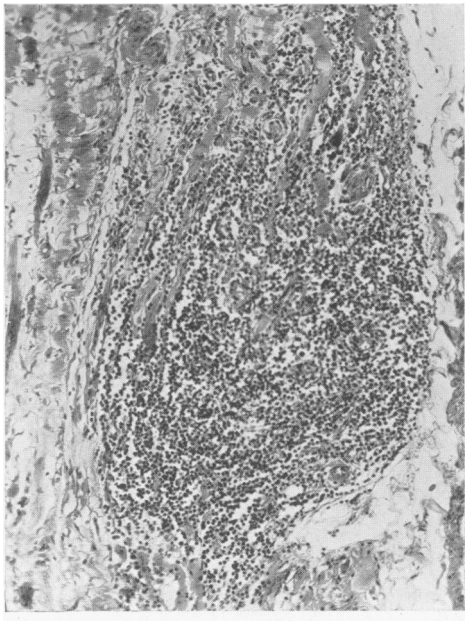

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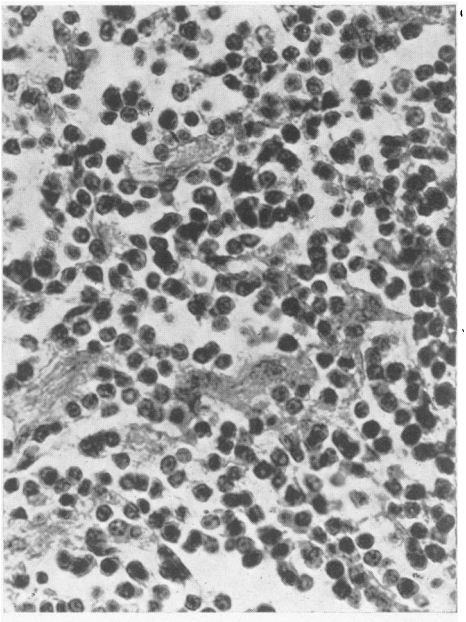

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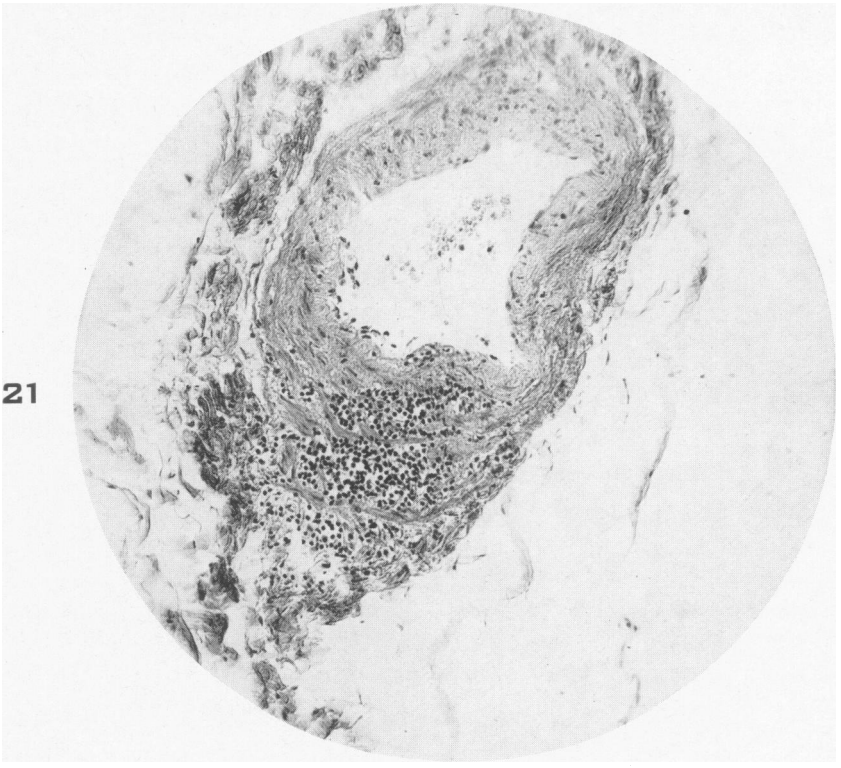
PLATE 29

FIG. 21. Case 7. Specimen obtained following amputation of both legs. Nodular lymphocytic inflammation in the wall of an artery (media and adventitia), located in perimysium. Hematoxylin and eosin stain. × 150.

FIG. 22. Case 7. A higher power photomicrograph of a portion of the field shown in Figure 21. Hematoxylin and eosin stain. × 450.

FIG. 23. Case 7. Muscle tissue found in the vicinity of the left superficial peroneal nerve. Nearly complete lymphocytic infiltration of the perineurium of a small intramuscular nerve. Hematoxylin and eosin stain. × 150.



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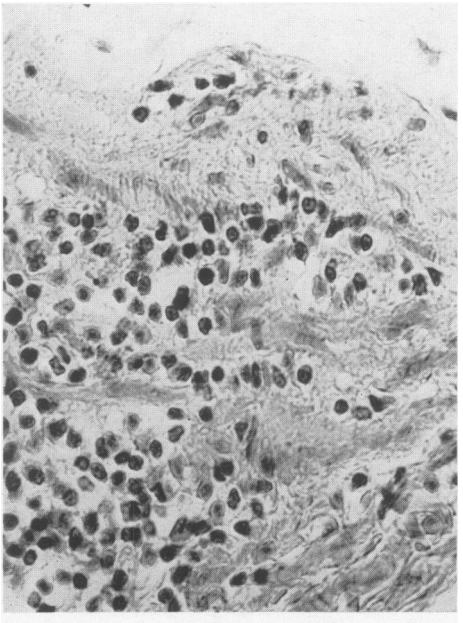

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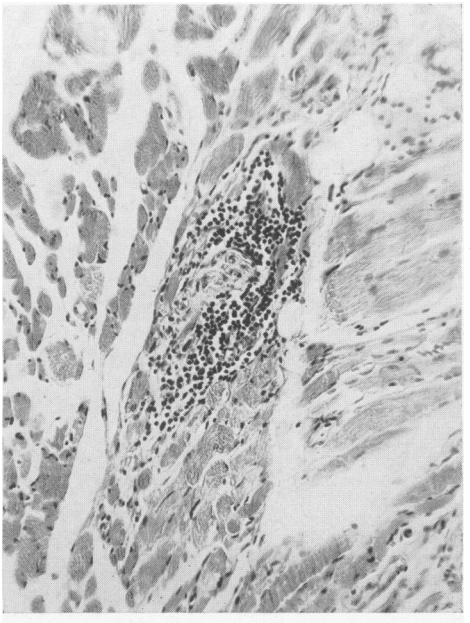

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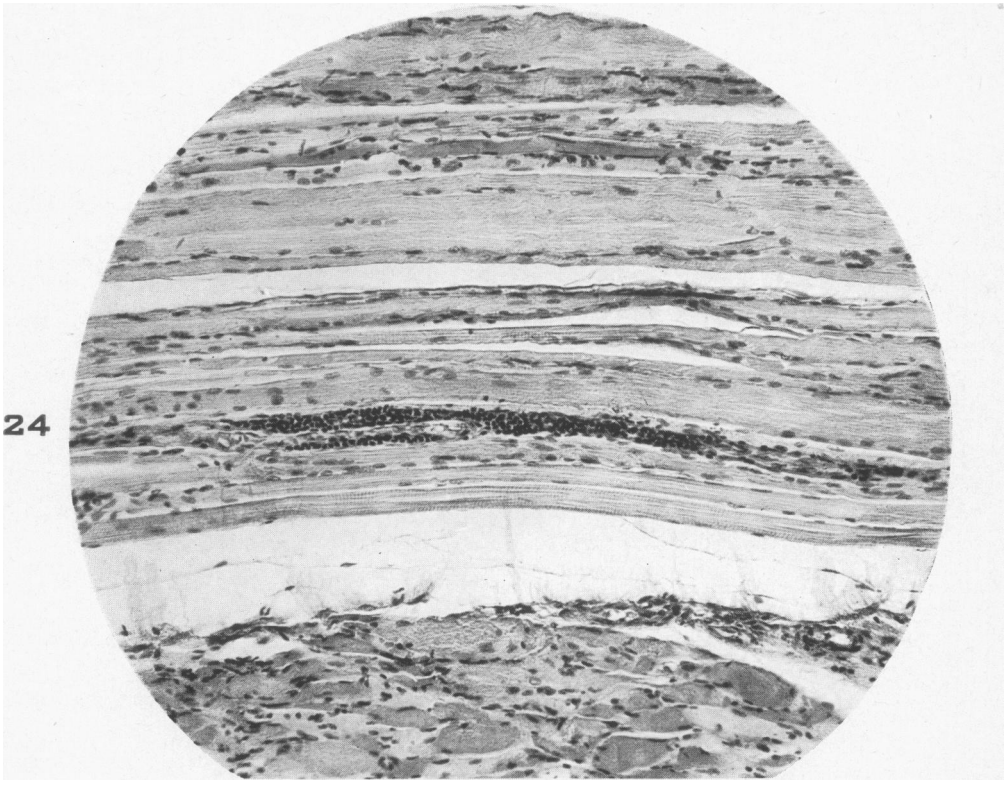
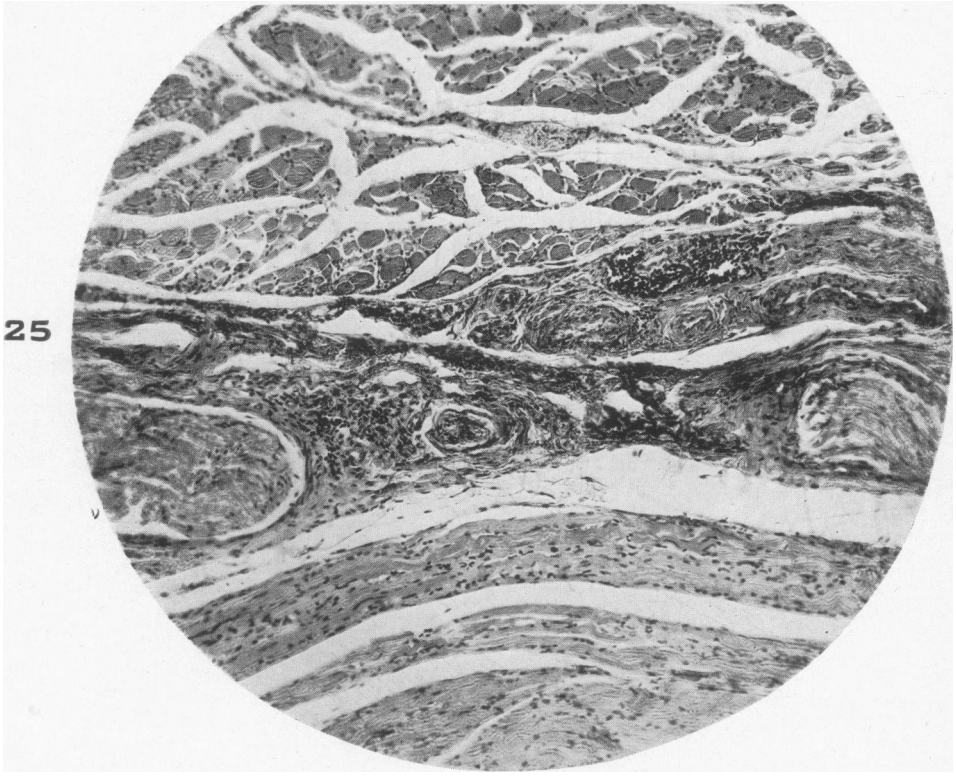
PLATE 30

FIG. 24. Case 8. Necropsy specimen from pectoralis major muscle. Small, elongated, spindle-shaped, circumscribed, lymphocytic inflammatory focus in the endomysium. Hematoxylin and eosin stain. × 150.

FIG. 25. Case 8. Necropsy specimen from the pectoralis major muscle. Two perimysial inflammatory nodules in periadventitial and perineurial locations. Hematoxylin and eosin stain. × 125.





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