THE PATHOLOGY OF ISCHEMIA OF SKELETAL MUSCLE IN MAN

A Description of Early Changes in Muscles of the Extremities Following Damage to Major Peripheral Arteries on the Battlefield*

Robert E. Scully, Capt., M.C., U.S.A.R.,† and Carl W. Hughes, Lt. Col., M.C., U.S.A.‡

From the Surgical Research Team in Korea, of the Army Medical Service Graduate School and the 406th Medical General Laboratory, Tokyo, Japan

During wartime the treatment of vascular trauma is a major concern of the surgeon. Most of the progress in this field has related to the perfection of techniques for optimal restoration of blood flow. Comparatively scant attention has been paid to the striking changes that take place in devascularized tissues. Since the degree of damage to skeletal muscle is of great significance to the surgeon who must decide whether or not to amputate, or what level of amputation to select, a clinicopathologic study of ischemic skeletal muscle was undertaken in soldiers sustaining arterial trauma during and shortly after the Korean conflict.

Material and Methods

Muscle specimens taken from the extremities of 30 soldiers whose major peripheral arteries were damaged acutely form the basis of this report. The arterial injuries comprised severances, lacerations, perforations, and contusions resulting in spasm or thrombosis. In 22 cases, the injuries were due to fragmenting missiles, in 7, to bullets. One soldier sustained vascular trauma in a vehicular accident. The patients ranged in age from 19 to 40, with an average of 24 years.

Samples of skeletal muscle were obtained in three ways: (1) Biopsy. Twenty-five specimens were taken from 19 soldiers during initial débridement of a wound, at the time of fasciotomy, or coincident with revision or closure of a wound. An effort was made to secure tissue for biopsy from regions of muscle which had not been directly traumatized, so that the changes in most of the specimens were attributable to deprivation of blood supply alone. Most of the samples for biopsy were placed in saline solution for 15 to 20 minutes

* Received for publication, October 6, 1955.

† Now at Massachusetts General Hospital, Department of Pathology, Boston 14, Mass.

‡ Now at Division of Surgery, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington 12, D.C.

to reduce the incidence of artifacts and were fixed subsequently in 10 per cent formalin. (2) Surgical excision of degenerating muscle groups (3 cases). (3) Amputation (15 cases). In most instances the entire amputated specimen was received by the pathologist. A few specimens were dissected by the surgeon, and formalin-fixed samples of various muscles were forwarded to the laboratory.

The clinical aspects of the patients' injuries were analyzed. The various samples of muscle were embedded in paraffin and stained with hematoxylin and eosin. A bacterial stain and connective tissue stains were done in selected cases. In addition to routine microscopic examination, all stained sections were viewed using crossed Nicol prisms. Chemical determinations of myoglobin and hemoglobin content were done on one specimen.

Review of the Literature

Experimental Studies

Because of the complexity of the human vascular system and the great number of factors involved in clinical cases of vascular injury, most of the fundamental knowledge of muscle ischemia has been gained by carefully executed animal experiments. Attempts have been made by various investigators to characterize the changes in skeletal muscle secondary to (1) obstruction of arterial blood flow, (2) obstruction of both arterial and venous blood flow, and (3) pure venous obstruction.

Obstruction of Arterial Blood Flow

The effects of experimental obstruction of arterial blood flow on muscle depend upon the degree of obstruction, the length of time it has been allowed to exist, and the duration of the recovery period before pathologic examination is done. When the arterial flow is more or less completely interrupted, either by multiple ligations designed to eliminate collateral circulation, or by the application of a tight tourniquet, massive areas of muscle necrosis result.[1] Early in the course of such experiments the ischemic muscles may go into a temporary state of contracture, simulating rigor mortis.[2,3] Eventually, a permanent contracture not unlike Volkmann's contracture in humans may supervene.[1,2,4] In the end stage of severe arterial ischemia, the muscle is hard and is composed of yellow or greenish-yellow infarcts separated by scar tissue.

Following somewhat less than complete interruption of arterial

blood flow, smaller portions of the muscle may undergo infarction.[5,6] Early in the ischemic period the muscle may be pale and swollen with fluid.[5] In small animals such as the rabbit, this degree of ischemia may be followed by more or less complete regeneration and reconstitution of the muscle.[7]

With still less severe grades of ischemia, such as may obtain following ligation of a single main artery of a muscle, weakness[2] or paralysis,[5] from which the animal subsequently recovers, may be the only recognized effect. In some instances of single arterial ligation, the collateral circulation is so efficient that no functional or structural change in the muscle is detected.[5,6]

Harman[8] has described in detail the histologic changes in muscle which has been completely deprived of its arterial blood. The longitudinal fibrils of the fibers become vague and lose their wavy character, while the cross striations grow increasingly more prominent. Eventually, the latter are so accentuated that they appear as broad disks separated by clear spaces (Bowman's discoid degeneration). At intervals, the fibers crack apart between the disks. The fibers meanwhile have become separated from one another, appearing as long individual units. This individualization creates an appearance distinctly different from the "syncytoid" aspect of normal skeletal muscle fibers. A relatively late change is degeneration and eventual disappearance of muscle nuclei. In a later study Harman and Gwinn[9] correlated the histologic findings in ischemic muscle with its contractibility, its content of energy reserves, and its ability to recover. They found that (1) the presence and strength of contraction upon stimulation by faradic current are related directly to the number of histologically undamaged fibers; (2) muscles which are unable to contract and are depleted of their energy reserves recover functionally and resynthesize their energy reserves, provided that they contain a sufficient number of structurally intact fibers. The authors' conclusions suggest that histologic examination provides a more accurate index of viability of muscle than biochemical measurement of energy reserves or contractibility tests.

Clark and Blomfield,[6] who appear to have produced lesser degrees of ischemia than Harman,[8] described microscopic changes which are probably in part due to the retention of a small amount of arterial flow. Such incompletely devascularized muscles showed swelling of fibers with preservation and accentuation of cross striations, weak staining of fibers with eosin, edema and necrosis of the endomysium

(connective tissue framework between individual muscle fibers), exudation of neutrophils between the fibers, and scattered foci of hemorrhage. Later, histiocytes became the principal inflammatory cells as they phagocytized the necrotic muscle; fibroblasts from adjacent, relatively normal muscle grew into the endomysial exudate and formed new endomysial tubes; and muscle nuclei proliferated into the tubes in the wake of digestion of the dead fibers by the histiocytes. The new fibers acquired longitudinal fibrils early in their development; later, cross striations appeared. The initially thin new fibers gradually attained normal thickness. The ultimate result was a completely reconstituted muscle showing variable degrees of fibrosis.

The changes so far described have been those of unrelieved arterial obstruction. Several authors have commented upon striking changes which may occur following restoration of circulation. These include the appearance of tense swelling,[3,5,10] capillary engorgement,[11] edema,[10,11] hemorrhage,[5,10] acute inflammatory exudation,[11] and release of myoglobin.[12] Harman and Gwinn,[9] who produced essentially complete interruption of arterial flow by means of a tourniquet, described a sudden increase in the rate of muscle fiber damage upon release of the tourniquet. They noted the appearance of two new types of muscle degeneration which were not seen in unrelieved total ischemia. These were Zenker's degeneration (in which the fibers became swollen, homogeneous, and structureless) and granular degeneration (in which they became granular, disorganized, and deeply acidophilic). Harman[11] further presented evidence that muscle capillaries and possibly finer arterioles and venules were damaged in ischemia, and that following restoration of circulation, blood flow through them was sluggish. Such vascular damage may account, at least in part, for the severe changes occurring in ischemic muscles upon resumption of their arterial flow.

Obstruction of Both Arterial and Venous Blood Flow

Because of clinical claims made during World War I that simultaneous ligation of veins reduced the incidence of gangrene in limbs requiring arterial ligation,[13,14] several workers have approached the problem of ligation of veins using experimental animals. The results have been conflicting. Brooks, Johnson, and Kirtley[4] concluded that simultaneous ligation lessens the incidence of gangrene and muscle contracture, while Wilson[2] detected no difference in the distribution or extent of muscle necrosis, or in the incidence of contracture.

Pure Venous Obstruction

Brooks[5] and Middleton[15] investigated the effects of obstruction of the entire venous outflow of a muscle whose arterial supply was intact. The muscle became swollen, dark blue, and bloody. Microscopically, there was hemorrhage, necrosis of fibers, and marked neutrophilic infiltration. Later, proliferation of fibroblasts took place between individual muscle fibers. The hemorrhage, inflammation, and fibrosis spread into the surrounding tissue. The end result was a muscle with extensive fibrosis; occasionally, individual muscle fibers were no longer detectable. Contracture was produced constantly. Working with entire limbs instead of isolated muscles, Fontaine and de Sousa-Pereira[16] showed that complete ligation of the venous system was necessary before gangrene could be produced.

It must be kept in mind, in interpreting the results of many of the experiments described, that units of the vascular system other than the ones specifically obstructed can undergo significant secondary changes, and that these may be difficult to recognize and evaluate unless elaborate methods of investigation are used. The stasis which occurs in capillaries secondary to arterial obstruction has already been mentioned. Barnes and Trueta[10] presented evidence that a severe and persistent arterial spasm could be produced in legs by the application of a tight wire tourniquet. This spasm affected main arteries and collaterals as well as, on occasion, the main artery of the opposite uninjured limb. Harman,[11] conducting experiments similar to those of Barnes and Trueta, failed to observe evidence of arterial spasm, and attributed the positive findings of these investigators to the use of a highly irritating radio-opaque medium for determining vessel caliber. On the other hand, the observations of Laufman, Martin, and Tuell[17] supported the concept of the existence of secondary vasospasm in vascular occlusion. These workers measured vessel caliber micrometrically in a series of experimental procedures on the mesenteric vascular tree. They found that: (1) Vasospasm generally accompanies main stem vascular occlusions. (2) In venous occlusion there is a marked arterial spasm and a venous dilatation. (3) Following release of venous occlusion, the artery remains in a state of moderate spasm for a considerable period of time. (4) In arterial occlusion, there is a marked arterial spasm and a concomitant venous spasm. (5) Following release of arterial occlusions, grossly visible reactive hyperemia occurs, but during this state, the precapillary arteriole remains in spasm.

STUDIES IN HUMANS

Very little is recorded of the pathology of skeletal muscle ischemia in man. Military surgeons[18,19] have characterized muscle hours after arterial injury as hard, tense, and swollen. Foisie[20] described the typical appearance of the biceps muscle early in the course of Volkmann's ischemic contracture as swollen, gray, and lifeless.

A major contribution to the *late* pathology of human muscle ischemia is that of Griffiths,[1] who identified the pathologic lesion of Volkmann's contracture as being muscle infarction. The affected muscles are composed of hard, homogeneous yellowish cores, surrounded by scar tissue. Microscopically, masses of necrotic muscle are enclosed successively by zones of histiocytes and fibroblasts, and dense collagen. Griffiths presented convincing evidence confirming Volkmann's concept that the muscle infarction characteristic of his contracture is due to a deprivation of arterial blood. This may occur secondary to embolism as well as to arterial trauma.

Bowden and Gutmann[21] studied muscle specimens obtained for biopsy from 14 patients at intervals of 40 to 800 days after trauma. They attributed three types of pathologic change to ischemia: massive necrosis, diffuse interstitial fibrosis, and focal necrosis with interstitial fibrosis. In all patients with massive muscle necrosis there was evidence of past damage to the main artery of the limb or to the artery supplying the affected muscle or muscles. In patients whose muscles showed the other types of pathologic change there was no uniformity in the nature of the vascular disturbance; in several instances the accumulation of blood in a rigidly bound muscle compartment was implicated; in others, the pathogenesis of the muscle damage was not clear.

Whether pure venous obstruction ever produces serious muscle degeneration in man is disputable. Rare cases of muscle fibrosis and contracture have been reported[15,21,22] wherein the histologic picture has been similar to that of experimental pure venous obstruction.

The significance of venous obstruction when superimposed on arterial blockage in humans is equally controversial. Some surgeons have claimed that a degree of venous obstruction is beneficial in arterial insufficiency.[13,14] On the other hand, DeBakey and Simeone,[19] in reviewing Makins' cases of arterial injury in World War I and the American cases in World War II, concluded that there is no evidence from human experience that venous ligation furnishes protection against the development of gangrene.

RESULTS

MUSCLE CHANGES DURING THE FIRST 2 DAYS AFTER ARTERIAL INJURY

Thirteen samples of muscle were taken from 11 soldiers at intervals of 6½ to 27 hours after arterial injury.

Clinical Appearance of Muscles

Four soldiers had muscle contractures resembling rigor mortis. The involved muscles were described as being hard, tight, and fixed. In 4 individuals, 2 of whom had contractures, the muscles were considered by the surgeon to be severely ischemic and probably irreversibly damaged. These muscles exhibited one or more of the following: a soft or mushy consistency, a pale or bluish gray color, a failure to bleed or delayed bleeding on incision, and an inability to contract on pinching. The muscles in the remaining 5 cases appeared normal.

Microscopic Appearance of Muscles

Many of the specimens exhibited artifacts or changes more properly attributable to trauma than to ischemia. The more common of these were blurring and patchy fragmentation of cross striations, retraction of fibers from their sarcolemmas and separation from one another, swelling and loss of structure of sarcoplasm, and nuclear shrinkage or swelling. Certain of these changes were considered artifactitious only when they appeared in relation to the cut edges of the specimens.

Findings of questionable etiology, probably related to ischemia in some of the specimens, were congestion of small blood vessels and petechiae. Excluding the presence of these changes, the five samples of muscle considered normal by the surgeon were unremarkable microscopically. Specimens from the three muscles which were in contracture, but which did not appear otherwise abnormal at operation, were likewise unremarkable microscopically.

Of the five specimens of muscle regarded as severely ischemic by the surgeon, two showed a subtle but definite exaggeration of cross striations as the only significant change (Fig. 2). Some of the striations, in addition to appearing coarser than usual, were smoothly curved instead of straight. One "severely ischemic" muscle was remarkable only for the presence of intense neutrophilic infiltration in the walls of its veins. Finally, two muscles placed in the severely damaged category by the surgeon showed marked changes histologically. These comprised, in addition to exaggeration and curving of cross striations, separation and individualization of fibers, and striking

engorgement (thrombosis?) of small vessels with erythrocytes (Fig. 3). The specimen of one "severely damaged" muscle further exhibited focal necrosis of several medium-sized arteries. The necrotic lesions were characterized by fibrinoid degeneration, slight neutrophilic infiltration, and marked edema of the vessel walls; and an infiltration of round cells into the perivascular connective tissue. These changes resembled strongly those seen in polyarteritis nodosa.

MUSCLE CHANGES DURING THE FIRST 2 DAYS AFTER SURGICAL REPAIR OF ARTERIAL INJURY

Five specimens were obtained for biopsy from 5 soldiers at intervals of 24 to 56 hours after arterial injury (and 12 to 48 hours following surgical repair).

Clinical Appearance of Muscles

In 4 of the 5 soldiers a striking clinical feature was the onset of muscle swelling some hours after vascular repair. When fasciotomies were done to relieve the tension within the muscle compartments, the swollen muscles bulged through the incisions. In some instances, blood-tinged fluid exuded. In addition to swelling, all four muscles exhibited changes suggestive of severe ischemia. In one case the muscle was not swollen and appeared normal at operation.

Microscopic Appearance of Muscles

The sample of the grossly normal muscle was unremarkable. The specimens of the four swollen, "severely ischemic" muscles, on the other hand, exhibited diverse and striking changes. In one there was advanced necrosis characterized by disruption and loss of structure of fibers, and extensive neutrophilic infiltration. These changes were far out of proportion to, and different in kind from, those ordinarily observed in purely ischemic muscle, and were interpreted as being secondary to contusion. In the second case, the muscle of the anterior tibial compartment gradually swelled after repair of a lacerated superficial femoral artery. A fasciotomy, done 34 hours postoperatively, revealed swollen muscle which appeared severely ischemic. The specimen taken for biopsy showed changes consistent with early ischemia: exaggeration of cross striations, congested small vessels, and numerous hemorrhages. In the third case, pulsations became palpable in the foot following relief of spasm of the common femoral artery; later they disappeared as the calf muscles began to swell. At the time of fasciotomy, 23 hours after restoration of circulation, the gastrocnemius muscle was swollen and was considered "probably

non-viable." Microscopically (Fig. 4), most of the fibers were closely approximated. Over half of them showed degenerative changes. These included waxy swelling characterized by deep staining of sarcoplasm, nuclear pyknosis, and focal rupture of fibers (Zenker's degeneration); vacuolar degeneration; exaggeration of cross striations; and weak staining with eosin. Many fibers, nevertheless, were normal in appearance. In the last case, the flexor muscles of the arm had been in contracture prior to operation; although warmth was restored to the arm by anastomosis of the severed brachial artery and evacuation of its thrombus, the contracture increased thereafter, and the muscles of both flexor and extensor compartments began to swell. A small specimen of flexor compartment muscle showed slight separation of many fibers, exaggeration and slight curving of cross striations, and small foci of waxy swelling of fibers.

LATER MUSCLE CHANGES (4 TO 26 DAYS AFTER ARTERIAL INJURY)

The pathologic material, obtained from 20 soldiers 4 to 26 days after injury, included five specimens taken for biopsy, three specimens composed of fragments from muscle compartment excisions, six samples taken from amputated limbs, eleven entire amputated limbs, and one amputation stump.

Clinical Appearance of Muscles

Adequately detailed data were unfortunately not available on the clinical appearance of most of the cases. Although, in some instances, the surgeon's observations must have been similar to the gross observations of the pathologist, it is obvious that such properties as color and consistency may often have differed at operation and at the dissecting table. Therefore, the following gross pathologic findings described cannot be regarded as coinciding in every respect with the findings of the surgeon.

Gross and Microscopic Pathology of Muscles

A wide range of pathologic changes characterized the later stages of muscle ischemia. Essentially four types of muscle were seen. Categorized in order of decreasing damage, these were: (1) more or less completely necrotic muscle with little or no evidence of inflammation or repair; (2) muscle showing patchy, and usually extensive necrosis, accompanied by inflammatory and reparative responses; (3) severely damaged muscle with small foci of complete necrosis, but notable for widespread survival of stroma and muscle regeneration; (4) essen-

tially normal or minimally damaged muscle. Although borderline forms existed among these four categories, and although one portion of a given muscle might fit into one category and another portion into a second, by and large an entire muscle or a large part of it was uniform in its pathologic appearance.

1. Complete necrosis was encountered most often in the long slender muscles of the leg. On dissection of the amputated limb these muscles appeared to be of normal color or somewhat pale. Their consistency was normal or slightly flabby. They were at times swollen and bulged slightly when their fasciae were incised. Microscopically, there was extensive necrosis involving both fibers and interstitial tissue. The fibers were closely approximated in some instances (Fig. 5) and widely separated in others (Fig. 6). Although some fibers had structureless sarcoplasm and appeared slightly swollen, the predominant change was one of discoid necrosis. Many of the disks were curved and there was periodic transverse cracking of the fibers between them (Fig. 6). The sarcoplasm often stained feebly with eosin. The nuclei showed increasing degrees of shrinkage and disappeared in time. In the areas of most advanced damage the fibers were split longitudinally and transversely or were fused into coarsely granular amorphous masses (Fig. 5). The interstitial tissue showed necrosis as evidenced by its weak staining and shrinkage of its nuclei. The small vessels were collapsed and their contents were no longer recognizable as blood. There was no congestion; at most, an exceedingly thin peripheral band of neutrophils was the sole evidence of an inflammatory response.

A frequent finding in this type of muscle, if it lay in proximity to a wound or infected incision, was invasion by bacteria, sometimes in massive numbers. Some of these bacteria were morphologically recognizable as Clostridia species. They appeared in the perimysium, endomysium, and within the sarcolemmas. In this small series, gas, edema, or other recognizable lesions attributable to the presence of Clostridia were not seen.

2. Patchy, usually extensive necrosis accompanied by inflammation and repair was observed most often in the soleus muscle; other muscles occasionally showed this change. Grossly, muscle of this type was brownish yellow, or so light yellow that it was easily mistaken for fat. A common appearance was a geographic pattern of pale brown patches of necrosis separated by yellow or white bands of inflammatory exudate. Gross areas of hemorrhage often were visible. Although the consistency generally was about normal, it sometimes was mushy or semi-liquid. Microscopically, there was extensive patchy death of

both fibers and interstitial tissue. The fibers sometimes showed a more or less pure picture of discoid necrosis (Fig. 7); more often, however, there was a considerable admixture of discoid fibers with swollen fibers having blurred or absent striations (Fig. 8). It also was not uncommon to find dead fibers which had retained exceedingly delicate cross striations. The fibers generally were separated from one another, sometimes by empty spaces, at other times by edema fluid and disintegrating neutrophilic exudate (Figs. 7 and 8). When the muscle was liquefied, fragments of disintegrating fibers penetrated by neutrophils might be seen lying in seas of exudate or hemorrhage. The interstitial tissue in the dead areas stained weakly and exhibited pyknosis of its nuclei. The small vessels were either collapsed and necrotic or were distended by closely packed erythrocytes. The larger vessels in and near the zones of necrosis commonly showed inflammation or necrosis of their walls. Often the veins, and less frequently the arteries, were distended by thrombi (Figs. 8 and 9) which eventually underwent organization.

In the muscle peripheral to the areas which had undergone complete necrosis, a variety of changes was seen. Early, bands of disintegrating neutrophils characterized this zone (Figs. 9 and 10). Later, histiocytic invasion of sarcolemmic tubes, with digestion of degenerating sarcoplasm, and the appearance of chronic inflammatory cells were prominent features. Proliferation of capillaries and of fibroblasts laying down collagen and an intense but limited muscle cell regenera-

TABLE I

Pigment Content of Muscle *

	Normal muscle		Yellow muscle	
	First determination	Second determination	First determination	Second determination
Myoglobin	5.12	5.09	2.57	2.52
Hemoglobin	0.27	0.26	0.53	0.50

* Given as per cent of dry weight (12 hours at 120°C.). Modification of method of Björck.[30]

tion were still later activities. We have observed no more than minimal penetration of fibroblasts, capillaries, and regenerating muscle fibers into the areas of completely necrotic muscle.

In one case the myoglobin content of a pale yellow muscle belonging in this category was analyzed, and was found to be half its normal value (Table I).

3. Severely damaged but live muscle showing widespread regen-

erative activity was encountered in 2 cases—in the triceps muscle 8 days after wounding, and in the gastrocnemius muscle 10 days after wounding.

The triceps was cream-colored with focal patches of hemorrhage. The gastrocnemius presented, in large part, a color somewhat paler than that of fat. Both muscles were of more or less normal consistency. Microscopically, there were severe degenerative changes within the fibers, but the interstitial tissues and many muscle nuclei survived. The degenerating sarcoplasm was either discoid, or structureless, or fragmented. The fibers were closely approximated or were separated by an edematous endomysium containing scattered histiocytes and round cells (Figs. 11 and 12). The perimysium was edematous and contained inflammatory cells in small numbers. Within the sarcolemmic tubes were focal collections of histiocytes in the process of digesting the degenerating sarcoplasm (Fig. 11). Along the edges of the fibers, nuclei were missing here and there. Elsewhere, however, were rows of elongated cells with scant cytoplasm (Figs. 12 and 13). Some of these were recognizable as regenerating muscle cells with basophilic cytoplasm; others as the endothelial cells of elongated tubular capillaries (Fig. 13).

What appeared to be later phases of the same process microscopically were observed in two additional specimens 12 and 18 days after wounding. These muscles showed large numbers of thin regenerating fibers arrayed in orderly fashion in very edematous viable collagenous tissue (Figs. 14 and 15). The degenerated fibers were no longer recognizable, and the evidence of previous damage was the presence of variable numbers of lymphocytes, plasma cells, and histiocytes among the new fibers. The latter had longitudinal fibrils; in a few of them cross striations could be identified.

4. Essentially normal muscle. Of the muscles examined microscopically, the gastrocnemius or large portions of it most commonly fell into the category of essentially normal. Muscle of this type sometimes exhibited focal damage to fibers in the form of waxy swelling or vacuolar degeneration. Small areas of inflammation, regeneration, and repair also were seen.

A striking finding in the amputated legs was the relatively better condition of the gastrocnemius than of the soleus muscle after a major artery of supply had been damaged. Thus, of 10 cases in which damage occurred to either the femoral or popliteal artery, and in which sections of both gastrocnemius and soleus muscles were available for study, the former showed a lesser degree of ischemic change in 8 cases. In some instances the gastrocnemius appeared

relatively normal when the soleus was either necrotic or regenerating; in others, the former was regenerating when the latter was necrotic; while in still others, the former, though extensively damaged, exhibited less complete necrosis than the latter. In 2 cases there was little difference in microscopic appearance between the two muscles.

The use of special connective tissue staining afforded additional data on the microscopic characteristics of ischemic muscle. With phosphotungstic acid hematoxylin and Masson's trichrome stains (using aniline blue for the latter), degenerating and necrotic muscle fibers often failed to show normal staining properties. These damaged cells were weakly colored or exhibited atypical colors, such as blue (with Masson's) or buff (with the phosphotungstic acid hematoxylin stain, Fig. 7). Waxy fibers, swollen necrotic fibers, discoid fibers, and the degenerating sarcoplasm of the muscles of category 3 commonly showed weak or atypical staining. Regenerating muscle cells stained normally with the connective tissue stains in our small experience.

Using crossed Nicol prisms, it was found that muscle fibers commonly retained their birefringence in advanced stages of necrosis. Indeed, swollen fibers and fibers showing discoid necrosis were often brightly refractile even after their nuclei had completely disappeared. Refractility was lost in some fibers showing advanced discoid or structureless necrosis and in fibers exhibiting granular disintegration. It reappeared in early regenerating fibers.

Discussion

Since most of our basic knowledge of ischemia of skeletal muscle has come as a result of animal experimentation, a comparison of clinical and pathologic observations in humans with experimental findings is in order.

Contracture

An inconstant early manifestation of muscle ischemia in humans is contracture. This phenomenon is not to be identified with the permanent Volkmann's contracture, although it is possible that the former represents an initial, reversible stage in the development of the latter. In this series, no instances of permanent contracture were encountered. No structural basis for early ischemic contracture was discovered in the human specimens. In the earlier cases, in which the muscles involved appeared otherwise normal at operation, microscopic examination of the samples was unremarkable. In later cases, in which the muscles exhibited other evidences of ischemia at surgery, the specimens taken for biopsy showed changes similar to those seen

in ischemia without accompanying contracture. Early ischemic contracture has been produced experimentally in muscles in which the arterial blood supply has been more or less completely interrupted[2,3]; however, its nature has not been investigated further.

Histopathologic Features

The earlier structural manifestations of muscle ischemia in humans were similar to those described by Harman[8] in experimental animals (loss of wavy arrangement of longitudinal fibrils, exaggeration of cross striations, and separation and individualization of fibers). Straightening of the longitudinal fibrils, however, was not a reliable sign of early ischemia in man, for, although it appeared in all of the "severely ischemic" specimens, it was seen in several samples of otherwise normal muscle as well. This discrepancy may be due to the fact that the uniform fixation and staining possible in experimental material was not attained in our specimens. The vascular engorgement (thrombosis?) observed in two of the human "severely ischemic" muscles may have been the structural counterpart of the physiologic damage to small vessels demonstrated by Harman[11] in experimental muscle ischemia. The unusual vascular changes seen in two of the human specimens, i.e., the neutrophilic infiltration of the vein walls, and the necrotic arterial lesions resembling those of polyarteritis, were unique and have not, to our knowledge, been described in experimental ischemia. Interpretation of their relationship to ischemia must remain conjectural at the present time.

Swelling

Swelling of ischemic muscles occurs in humans with arterial injury as well as in experimental animals. In humans it may take place in instances of unrelieved ischemia; however, it is more frequent and more severe following surgical restoration of circulation. In experimental animals, ischemic swelling may appear as a result of less than complete interruption of arterial blood[5] or may follow release of arterial obstruction.[3,5,10] Neither animal investigation nor biopsy examination of human swollen muscle has revealed the pathogenesis of ischemic swelling. It seems possible that five factors, alone or in combination, may contribute: (1) lymphatic stasis, (2) vascular congestion, (3) enlargement of individual fibers, (4) interfibrillar edema, and (5) edema of the perimysium (connective tissue between bundles of fibers). Our specimens taken for biopsy did not permit evaluation

of the first and fifth factors; and none of the other factors was encountered with regularity. The presence of Zenker's degeneration in two human specimens of muscle swollen hours after restoration of circulation is most interesting in view of the fact that Harman and Gwinn[9] found this change under similar circumstances in their experimental animals. In the small biopsy specimen of one human muscle, the change was present in only a few foci; in the other, it was widespread. Interpretation of the lesion in the latter case, however, was complicated by the fact that the soldier had been exposed to cold. Since fiber degeneration similar to Zenker's has been reported in experimental hypothermia[23] as well as in relieved ischemia, cold injury cannot be ruled out entirely as the etiologic factor here. If, however, these unusual changes in the two human cases are due to restoration of circulation, Harman's observations on the increase in muscle fiber damage wrought by a return of circulating blood may have a direct application to vascular repair in humans.

Regeneration

Wide varieties of pathologic changes, ranging from minimal damage to massive necrosis, characterize the later stages of muscle ischemia, both clinical and experimental. For the most part, the findings in man and animal have been similar. Two aspects in which clinical and experimental observations are somewhat at variance, namely, regeneration and depigmentation, deserve special attention.

Clark[7] described extensive muscle regeneration and reconstitution in small experimental animals even when the degree of arterial ischemia had been so great that necrosis of the interstitial tissue had taken place. The same author, however, is cited[24] as saying that a similar degree of regeneration would appear unlikely in man because of the bulk of human muscles. We have seen only abortive attempts at regeneration when severe necrosis involving the interstitial tissue as well as fibers has occurred. However, several of our specimens in which the sarcoplasm had undergone widespread degenerative changes, but in which the stroma had survived, showed such striking early regeneration that a considerable amount of eventual reconstitution seemed possible. The pathologic changes in such muscles were more akin to those of Zenker's degeneration of typhoid fever and pneumonia[25] than they were to those of the more severe degrees of ischemia. More extensive experience with human cases of ischemia is needed to confirm and expand these observations.

Depigmentation

Although Montagnani and Simeone[12] demonstrated liberation of myoglobin from muscles upon release of ischemia, visible depigmentation as a phenomenon of experimental muscle ischemia has not, to our knowledge, been described. Our studies have shown that in humans severe and widespread loss of pigment may occur not only in muscles which show large areas of necrosis, but also in those exhibiting regenerative changes. Thus, the appearance of a fish-flesh, cream, or pale yellow color in a muscle does not necessarily indicate that it is irreversibly degenerated. In our brief experience, muscle which is more or less completely deprived of its blood supply does not undergo depigmentation, perhaps for the reason that no circulatory system exists in the muscle to furnish enzymes necessary for the release of the myoglobin and to provide for transportation of this pigment from the muscle.

Pathogenesis of Ischemia

Whereas it is difficult to determine in experimental animals what pathogenic factors are responsible for producing the various forms and degrees of ischemic degeneration of muscle, this is an even greater problem when dealing with human cases. Here the variables are multiplied many fold and investigative methods are necessarily limited. Thus, in our series, often only a biopsy specimen was available for study. This may not always have been representative of an entire muscle, nor did it afford information about the state of the blood vessels supplying the muscle. In cases in which an entire amputated limb was forwarded for examination, usually the key obstructed vessel remained in the patient above the amputation site. Spasm of arteries or veins and the degree of obliteration of collateral vessels were most difficult, if not impossible, to evaluate. Many of the soldiers had had tourniquets applied; although in most cases information was given as to the duration and periods of release, it was not possible to determine how effectively the arterial flow had been obstructed. The degree of shock, exposure to excessive cold or heat, the state of fatigue of the muscle at the time of onset of ischemia, and individual variations in vascular supply were some of the other factors which did not lend themselves to accurate determination.

In view of the foregoing, we are unable to state the precise rôles of arterial, venous, and capillary obstruction in producing the muscle changes observed. In addition to arterial damage, large veins were injured directly or were ligated in many of our cases. Moreover,

major and intramuscular veins, and capillaries were often extensively thrombosed in the pathologic specimens. In some instances the thrombi formed in vessels damaged by the same ischemic infarction which injured the muscles they drained.

There is a remarkable similarity between the pathologic changes of muscle ischemia secondary to arterial trauma and those of the crush syndrome. In the latter condition, muscle swelling, discoid necrosis, atypical staining of fibers with connective tissue stains, and regeneration have all been described.[26] Moreover, gross depigmentation of muscle similar to that of the crush syndrome and even renal failure may be seen in cases of arterial injury without crushing.[27] The striking pathologic resemblance of the two conditions supports other evidence that the muscle changes of the crush syndrome are due to arterial spasm.[27,28]

A final observation that merits brief discussion is the usually better outcome for the gastrocnemius than for the soleus muscle in injuries of the femoral or popliteal arteries. The reason for this finding is not apparent from this study, nor from the literature. Blomfield,[29] who has investigated the blood supply of the leg muscles by injection techniques at necropsy, has stated that the gastrocnemius is served by a single artery; the soleus, on the other hand, has at least five arteries of supply. He stated further, that in local wounds of the calf, the gastrocnemius is more apt to undergo necrosis and secondary clostridial infection because of its less rich blood supply. The disparity between the outcome of the two muscles following local vascular damage and following injury to a major artery of the extremity deserves investigation. Possibly the artery supplying the gastrocnemius communicates by collateral channels with vessels arising above the level of obstruction of the femoral or popliteal artery. Again, the comparative tightness of the sheaths or fascial envelopes of the two muscles, or a difference in their metabolic requirements may play a decisive rôle in their responses to ischemia. A practical corollary of the observation regarding the gastrocnemius and soleus is that the condition of the former muscle cannot be used as a guide to that of other muscles of the leg.

Summary and Conclusions

The early pathologic changes in skeletal muscle following damage to major arteries of limbs were studied in 30 soldiers, most of whom had sustained injuries on the Korean battlefields. The material consisted of biopsy specimens, surgically excised necrotic muscles, and

amputated limbs. The specimens were obtained from 6½ hours to 26 days after injury.

The pathologic lesions observed paralleled those described in experimental muscle ischemia and appeared to be the logical forerunners of later changes reported in humans.

Swelling of ischemic muscles following restoration of circulation occurred in several cases. The nature and pathogenesis of this swelling was not evident from study of human or experimental data.

After the acute phase of ischemia had passed, the muscles studied fell into one of four pathologic categories: (1) more or less complete necrosis; (2) patchy, but extensive necrosis with inflammation and repair; (3) severe damage of fibers, but survival of stroma and widespread muscle regeneration; and (4) normal structure.

A pale yellow or cream color, probably attributable to loss of myoglobin, was an outstanding feature of several muscles in category 3 as well as in category 2. Therefore, depigmentation is not a reliable criterion of irreversible damage in ischemic muscle.

The gastrocnemius muscle fared better than the soleus in the great majority of cases of obstruction of a major artery of the leg. This result was the opposite of that reported in local wounds involving the immediate arteries of supply of the muscles. The vascular anatomical background for this disparity was not clear. Because of the difference in outcome of the two muscles, it is apparent that the condition of the gastrocnemius cannot be used as a guide to that of other muscles of the leg.

We wish to express our gratitude to 1st Lt. Gordon D. LaZerte, M.C., who participated in the early phases of the pathologic study; to Lt. Col. Tomas C. Jefferis, M.S.C., U.S.A., and Cpl. Donald D. Maheu, who performed the myoglobin and hemoglobin assays; and to Sfc. Kaye Ihara, who took the photomicrographs.

REFERENCES

1. Griffiths, D. L. Volkmann's ischaemic contracture. *Brit. J. Surg.*, 1940–41, **28**, 239–260.
2. Wilson, W. C. Occlusion of the main artery and main vein of a limb. *Brit. J. Surg.*, 1933, **20**, 393–411.
3. Miller, H. H., and Welch, C. S. Quantitative studies on the time factor in arterial injuries. *Ann. Surg.*, 1949, **130**, 428–438.
4. Brooks, B.; Johnson, G. S., and Kirtley, J. A., Jr. Simultaneous vein ligation. An experimental study of the effect of ligation of the concomitant vein on the incidence of gangrene following arterial obstruction. *Surg., Gynec. & Obst.*, 1934, **59**, 496–500.
5. Brooks, B. Pathologic changes in muscle as a result of disturbances of circulation. An experimental study of Volkmann's ischemic paralysis. *Arch. Surg.*, 1922, **5**, 188–216.

6. Clark, W. E. L., and Blomfield, L. B. The efficiency of intramuscular anastomoses, with observations on the regeneration of devascularized muscle. *J. Anat.*, 1945, **79**, 15–32.
7. Clark, W. E. L. An experimental study of the regeneration of mammalian striped muscle. *J. Anat.*, 1946, **80**, 24–36.
8. Harman, J. W. A histological study of skeletal muscle in acute ischemia. *Am. J. Path.*, 1947, **23**, 551–565.
9. Harman, J. W., and Gwinn, R. P. The recovery of skeletal muscle fibers from acute ischemia as determined by histologic and chemical methods. *Am. J. Path.*, 1949, **25**, 741–755.
10. Barnes, J. M., and Trueta, J. Arterial spasm. An experimental study. *Brit. J. Surg.*, 1942–43, **30**, 74–79.
11. Harman, J. W. The significance of local vascular phenomena in the production of ischemic necrosis in skeletal muscle. *Am. J. Path.*, 1948, **24**, 625–641.
12. Montagnani, C. A., and Simeone, F. A. Observations on the liberation and elimination of myohemoglobin and of hemoglobin after release of muscle ischemia. *Surgery*, 1953, **34**, 169–185.
13. Sehrt, E. Über die künstliche Blutleere von Gliedmassen und unterer Körperhälfte, sowie über die Ursache der Gangrän des Gliedes nach Unterbindung der Arterie allein. *Med. Klin.*, 1916, **12**, 1338–1341. (Cited by Simeone, F. A.; Grillo, H. C., and Rundle, F. On the question of ligation of the concomitant vein when a major artery is interrupted. *Surgery*, 1951, **29**, 932–951.)
14. Makins, G. H. On Gunshot Injuries to the Blood-Vessels. John Wright & Sons, Ltd., Bristol, 1919, 251 pp. (Cited by Simeone, F. A.; Grillo, H. C., and Rundle, F. On the question of ligation of the concomitant vein when a major artery is interrupted. *Surgery*, 1951, **29**, 932–951.)
15. Middleton, D. S. The pathology of congenital torticollis. *Brit. J. Surg.*, 1930–31, **18**, 188–204.
16. Fontaine, R., and de Sousa-Pereira, A. Oblitérations et résections veineuses expérimentales; contribution à l'étude de la circulation collatérale veineuse. *Rev. de chir., Paris*, 1937, **75**, 161–200. (Cited by Osius, E. A. Acute massive venous occlusion. *A. M. A. Arch. Surg.*, 1952, **65**, 19–30.)
17. Laufman, H.; Martin, W. B., and Tuell, S. W. The pattern of vasospasm following acute arterial and venous occlusions. A micrometric study. *Surg., Gynec. & Obst.*, 1948, **87**, 641–651.
18. Hampton, O. P., Jr. Wounds of the Extremities in Military Surgery. C. V. Mosby Co., St. Louis, 1951, p. 121.
19. DeBakey, M. E., and Simeone, F. A. Battle injuries of the arteries in World War II. An analysis of 2,471 cases. *Ann. Surg.*, 1946, **123**, 534–579.
20. Foisie, P. S. Volkmann's ischemic contracture. An analysis of its proximate mechanism. *New England J. Med.*, 1942, **226**, 671–679.
21. Bowden, R. E. M., and Gutmann, E. The fate of voluntary muscle after vascular injury in man. *J. Bone & Joint Surg.*, 1949, **31B**, 356–368.
22. Hill, R. L., and Brooks, B. Volkmann's ischemic contracture in hemophilia. *Ann. Surg.*, 1936, **103**, 444–449.
23. Lewis, R. B. Pathogenesis of muscle necrosis due to experimental local cold injury. *Am. J. M. Sc.*, 1951, **222**, 300–307.
24. Clark, W. E. L. Personal communication. (Cited by Hughes, J. R. Ischaemic necrosis of the anterior tibial muscle due to fatigue. *J. Bone & Joint Surg.*, 1948, **30B**, 581–594.)

25. Forbus, W. D. Pathologic changes in voluntary muscle. I. Degeneration and regeneration of the rectus abdominis in pneumonia. *Arch. Path.*, 1926, **2**, 318–339.

26. [Mallory, T. B.] The Crush Syndrome in Battle Casualties. In: The Physiologic Effects of Wounds, by the Board for the Study of the Severely Wounded. North African-Mediterranean Theater of Operations. Office of the Surgeon General, Department of the Army, Washington, D.C., 1952, p. 272.

27. Bywaters, E. G. L. Ischemic muscle necrosis. Crushing injury, traumatic edema, the crush syndrome, traumatic anuria, compression syndrome: a type of injury seen in air raid casualties following burial beneath débris. *J. A. M. A.*, 1944, **124**, 1103–1109.

28. Belsey, R. Discussion on the effects on the kidney of trauma to parts other than the urinary tract, including crush syndrome. *Proc. Roy. Soc. Med.*, 1941–42, **35**, 328–333.

29. Blomfield, L. B. Intramuscular vascular patterns in man. *Proc. Roy. Soc. Med.*, 1944–45, **38**, 617–618.

30. Biörck, G. On myoglobin and its occurrence in man. *Acta med. Scandinav.*, 1949, Suppl. 226, p. 67.

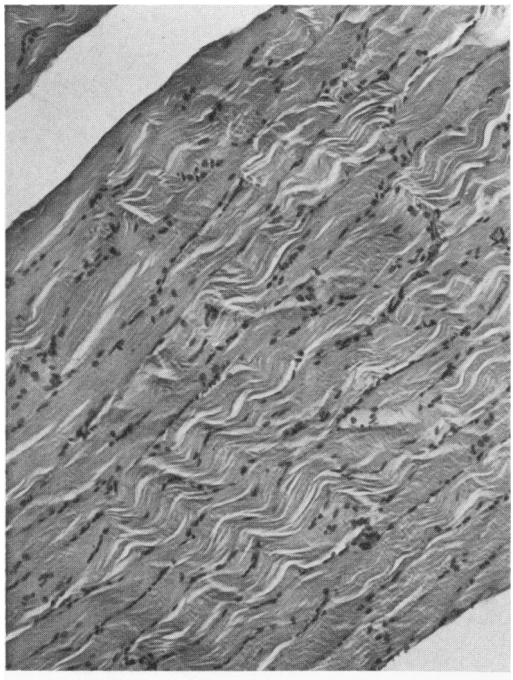
LEGENDS FOR FIGURES

FIG. 1. Histologically normal muscle. The close approximation of fibers and the wavy character of longitudinal fibrils may be noted. Hematoxylin and eosin stain. × 100.

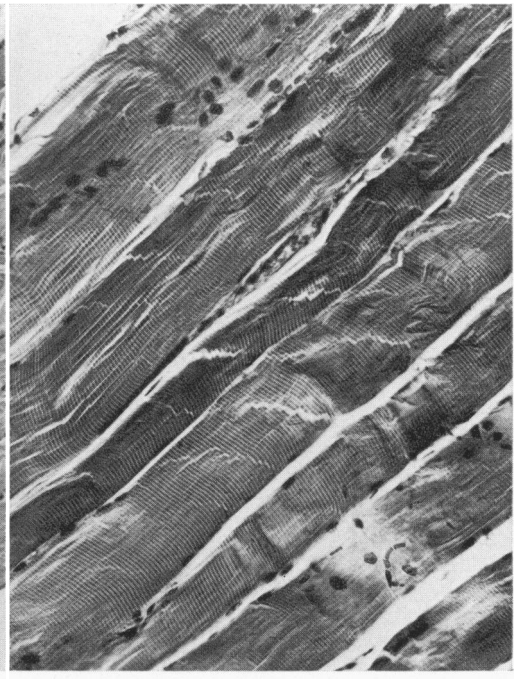
FIG. 2. Exaggeration of cross striations. (For pictorial purposes, a filter was used to emphasize the striations.) Hematoxylin and eosin stain. × 200.

FIG. 3. Separation and individualization of fibers; engorgement (thrombosis?) of small vessel. Hematoxylin and eosin stain. × 100.

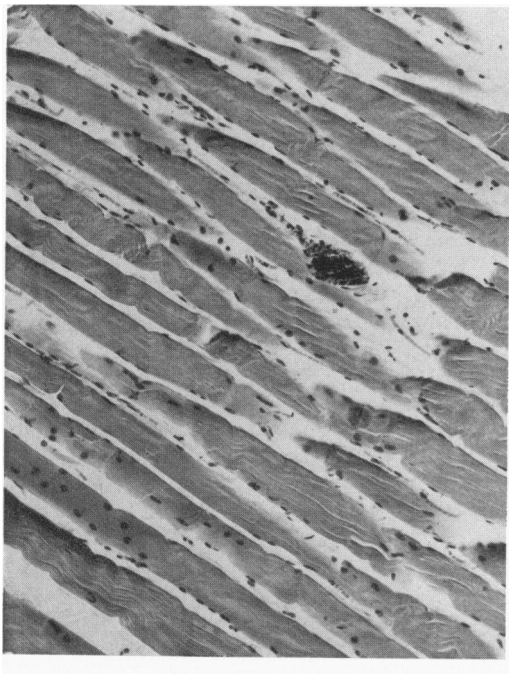
FIG. 4. Focal waxy and vacuolar degeneration of gastrocnemius muscle. Many of the fibers appear normal. Hematoxylin and eosin stain. × 100.



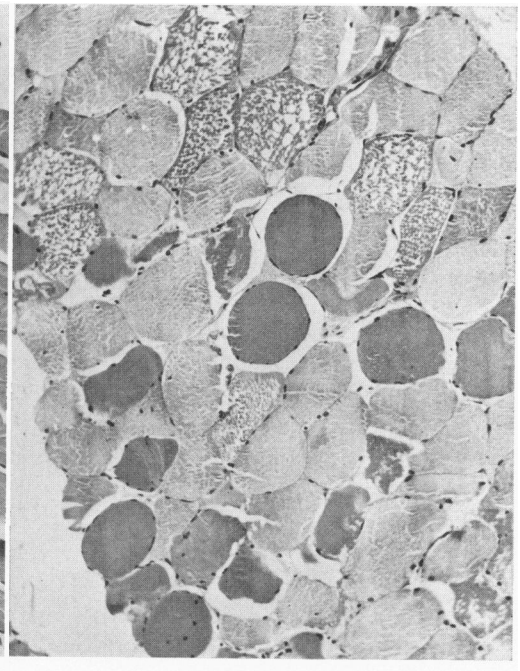
1



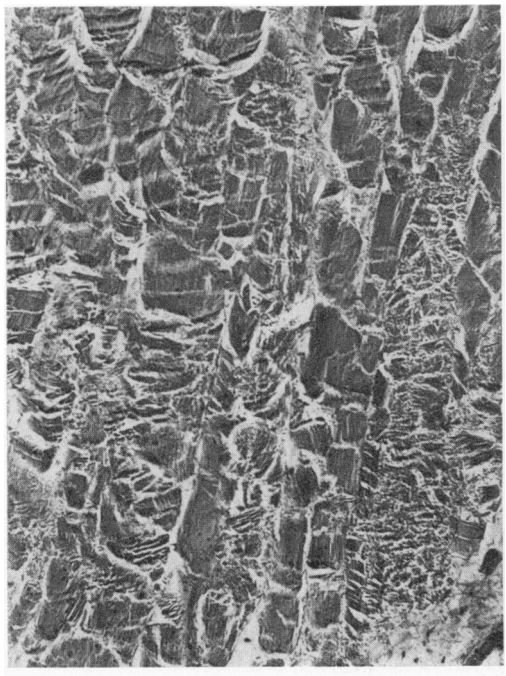
2



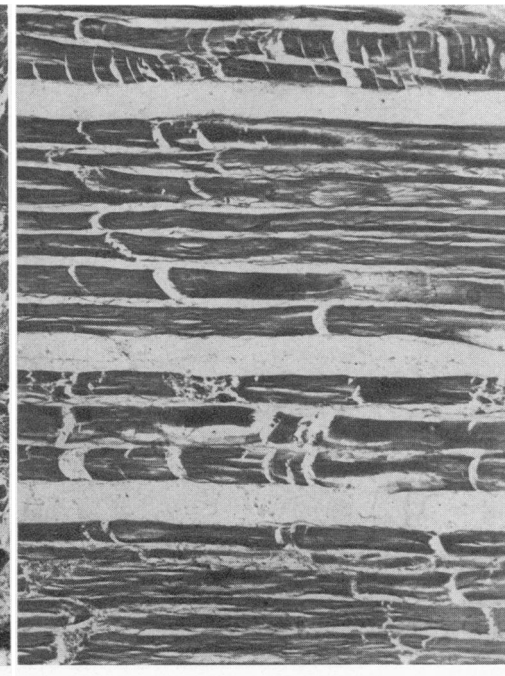
3



4



5



6

FIG. 5. Flexor hallucis longus muscle. Fragmentation and granular disintegration of fibers with minimal separation. Hematoxylin and eosin stain. × 100.

FIG. 6. Extensor hallucis longus muscle. Discoid degeneration with curving of disks and cracking between them. Nuclei have disappeared. Fibers have separated. Hematoxylin and eosin stain. × 100.

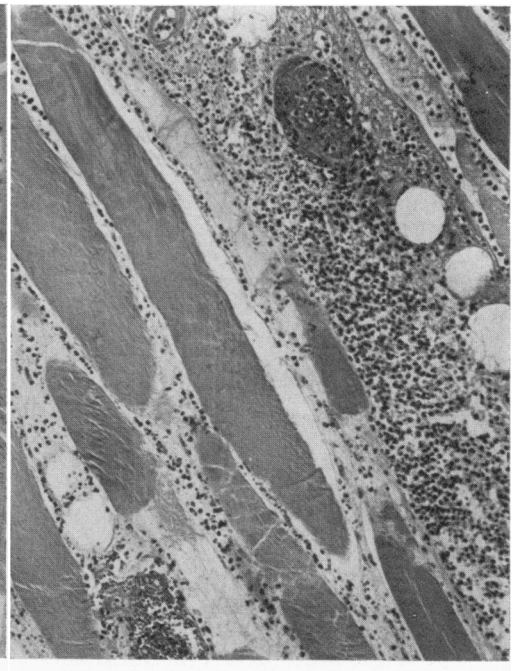
FIG. 7. Discoid necrosis of muscle of flexor compartment of arm. Many of the fibers are pale (actually buff) instead of having the normal dark tone (blue). The fibers are individualized and show curving of the disks and cracking between them. Phosphotungstic acid hematoxylin stain. × 100.

FIG. 8. Soleus muscle. Swollen, structureless, anuclear, necrotic fibers are separated by dense neutrophilic exudate. Of note is a thrombosed vein. Hematoxylin and eosin stain. × 100.

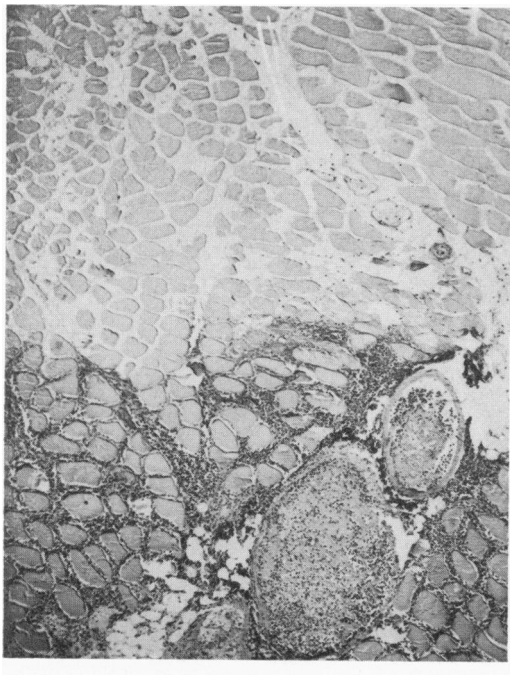
FIG. 9. Soleus muscle, with dead muscle above. Below there is extensive neutrophilic infiltration of dead muscle. A large thrombosed vein is visible at the lower right of the center. Hematoxylin and eosin stain. × 35.

FIG. 10. Lateral head of gastrocnemius muscle, corresponding to an opaque brownish yellow area grossly. Of note are discoid necrosis and separation of fibers, and a broad zone of neutrophilic infiltration in the perimysium. Hematoxylin and eosin stain. × 100.

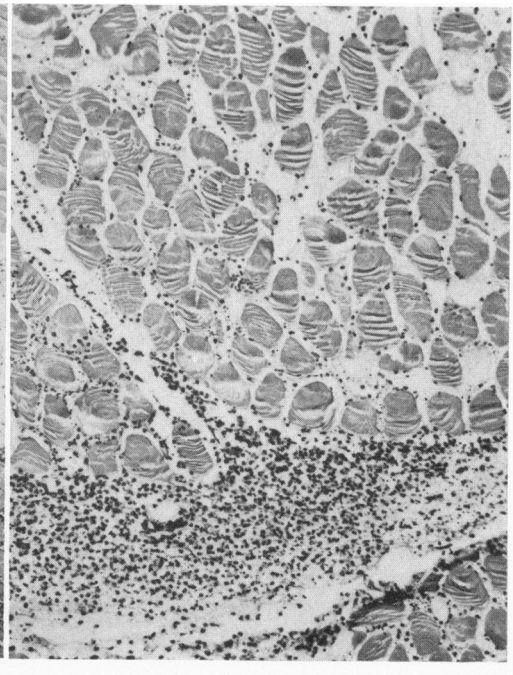
7



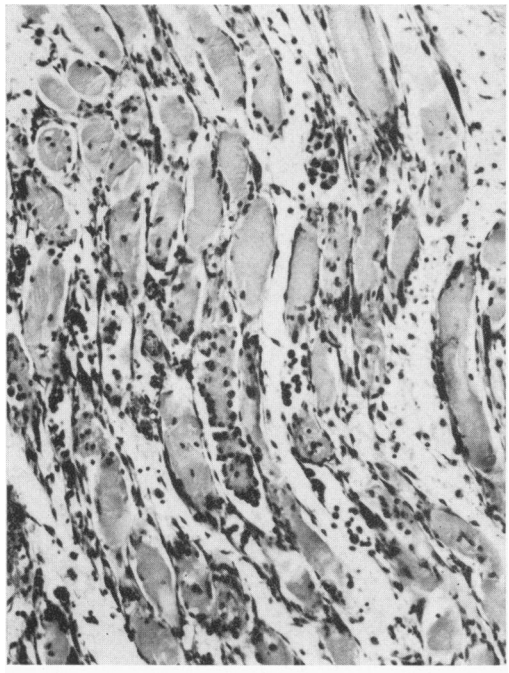
8



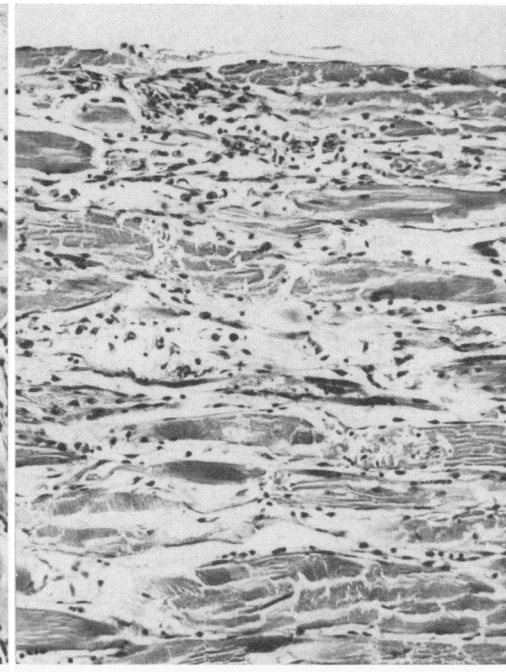
9



10



11



12

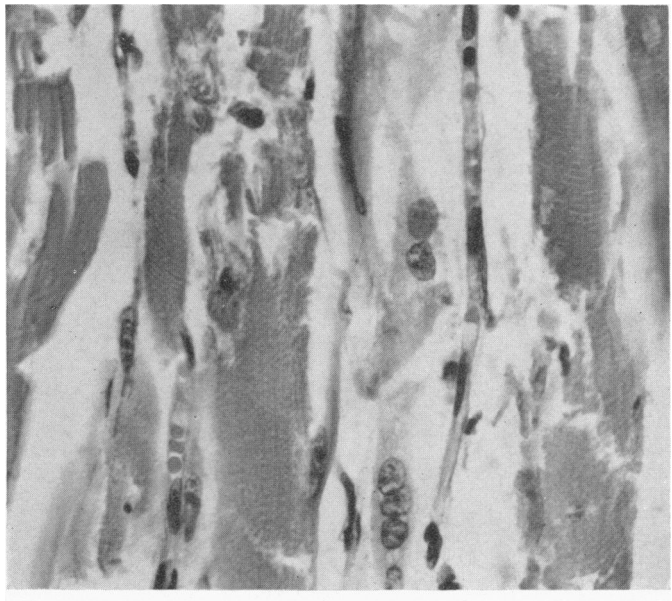
FIG. 11. Triceps muscle. Fibers show degenerating sarcoplasm. Some sarcolemmic tubes contain large numbers of histiocytes. Most of the fibers are surrounded by necklaces of elongated cells. Hematoxylin and eosin stain. × 100.

FIG. 12. Lateral head of gastrocnemius muscle, corresponding to a pale yellow area grossly. There are elongated bands of regenerating cells among degenerating fibers. Hematoxylin and eosin stain. × 100.

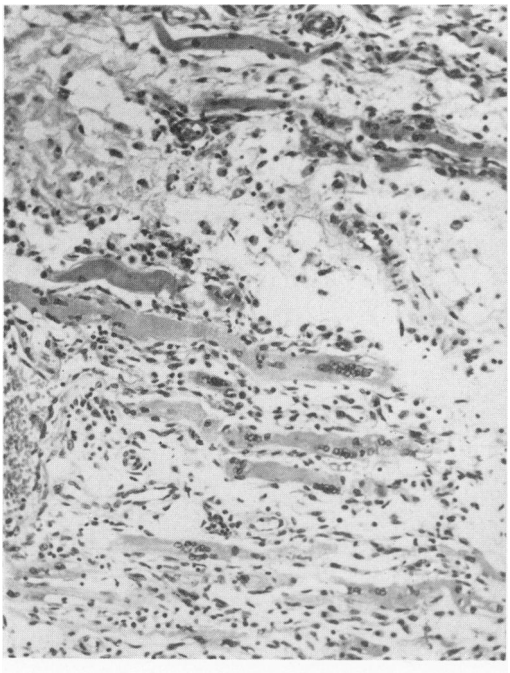
FIG. 13. Lateral head of gastrocnemius muscle. Disintegrating sarcoplasm and elongated capillary tubes are shown. A regenerating multinucleated muscle cell is present near the lower margin. Hematoxylin and eosin stain. × 400.

FIG. 14. Gastrocnemius muscle. Elongated regenerating fibers with multiple clusters of nuclei are separated by histiocytes, chronic inflammatory cells, and edema fluid. Hematoxylin and eosin stain. × 100.

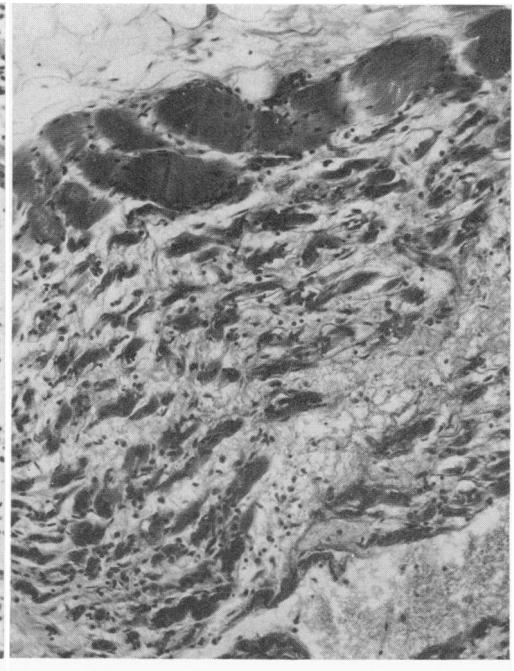
FIG. 15. Soleus muscle. Above are some remaining normal fibers. Below are numerous small regenerating fibers arrayed in an orderly fashion in edematous connective tissue. Small numbers of chronic inflammatory cells lie among the small fibers. Hematoxylin and eosin stain. × 100.



13



14



15