LESIONS OF SKELETAL MUSCLE IN LEPTOSPIROSIS

REVIEW OF REPORTS AND AN EXPERIMENTAL STUDY *

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In recent years, physicians and veterinarians have become increasingly aware of the high incidence of leptospiral infection of man and animals in this country. Several excellent reviews[1-5] and a monograph[6] have been published and repetition is not in order. In an extensive search of the literature, mention of pathologic changes in skeletal muscle was found in only 10 instances of leptospirosis.[7-16] Most of these were human infections. This is in striking contrast to the numerous reports stressing the clinical importance of myalgia and, frequently, of muscle tenderness in leptospiral diseases. These symptoms and signs commonly involve the calf and lower lumbar muscles in *Leptospira icterohaemorrhagiae* and *Lept. canicola* infections. A similar distribution is noted in leptospiral diseases which have more recently attracted attention in the United States: *Lept. pomona* (aseptic meningitis, swineherd's disease)[17-20]; *Lept. grippo-typhosa* (field fever)[21]; and *Lept. autumnalis* (mud fever, Fort Bragg fever).[22,23] A standard textbook[24] states that the muscle lesion of Weil's disease is specific, and is caused by lodgment of the organisms within muscle fibers. From the character and distribution of the lesions, this pathogenetic concept is a logical assumption, but it has not been proved. In experimental studies,[25-28] histologic examination was infrequent and did not include skeletal muscle. Consequently, a study of natural and experimental leptospirosis in small animals was undertaken with particular reference to skeletal muscle. To attain this end, dog and rat tissues were examined histologically and isolation of a virulent Leptospira attempted. Hamsters and guinea-pigs were studied culturally and histologically at various times after injection of a strain of *Lept. canicola*‡ lethal for hamsters in 3 to 5 days.

MATERIALS AND METHODS

Before beginning this study, I examined a strain of *Lept. icterohaemorrhagiae*§ in whole blood and in organ-Ringer's emulsion to

* Received for publication, August 14, 1954.

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§ Supplied by the American Type Culture Collection, Washington, D.C.

become familiar with the characteristics of the organisms under conditions anticipating those encountered in this investigation. Confusion with the so-called pseudo-spirochaetes[29] is hardly possible when one has seen real organisms. Dark-field preparations of kidney emulsion and blood were examined from all animals. Serologic studies were not done. All cultures were placed on Chang's semisolid medium[30] prepared with fresh horse serum, and on 12 per cent unbuffered fresh rabbit serum in distilled water with 6 cc. of 2 per cent agar per 100 ml. of medium. Enough whole rabbit blood was added to impart a faint pink color. The media were fractionally sterilized at 56° C. for 2 hours on 3 successive days and checked for sterility before use. The final pH was 7.6 in each medium.

Dogs and Rats

Four dogs which died of clinically typical leptospirosis were studied in addition to a control dog which died of high intestinal obstruction. All had received intensive antibiotic therapy, chiefly penicillin and aureomycin. Cultures were taken from contaminated kidney tissue and blood. Kidney emulsion from 2 dogs was injected intraperitoneally into young hamsters.

Eleven wild city rats were killed with chloroform and necropsied immediately. The thoraco-abdominal hair was shaven, the skin thoroughly washed with soap and water, and then swabbed with iodine-alcohol. Cultures of liver and kidney emulsion were planted on separate tubes of each medium using aseptic precautions. Pooled kidney emulsion of 2 rats obtained on the same day was injected intraperitoneally into young hamsters.

Hamsters and Guinea-Pigs

Control and experimental animals were fed a routine laboratory diet and given only leafy green vegetables as a source of water. The group cages were separated by a distance of ten feet.

A group of 18 hamsters, 3 to 4 weeks old, were injected intraperitoneally with 0.5 ml. of infected hamster kidney-Ringer's emulsion containing 5 to 10 *Lept. canicola* per oil immersion dark-field. One animal each was chloroformed at 1, 2, 60, and 72 hours after injection. At 3, 6, 12, 24, and 48 hours, animals were sacrificed 2 at a time. Three hamsters were found dead and necropsied at 96 hours. One died and was necropsied at 120 hours. At necropsy, cultures were taken from intracardial blood and from kidney using the technique outlined. Pooled skeletal muscle from a group of dead or moribund

hamsters used in maintaining the strain was examined for the presence of muscle lesions. The control group consisted of 3 untreated hamsters and 7 injected intraperitoneally with 0.5 cc. of kidney-Ringer's emulsion from a normal hamster. One control animal each was sacrificed at 3, 24, and 48 hours after injection and 2 each at 6 and 12 hours.

A program similar to that used in the hamsters was carried out with 12 guinea-pigs, varying from 3 days to 3 weeks old. Three normal controls and 12 injection controls were used.

At necropsy, portions of liver, kidney, heart, lungs, pectoralis major, and of longissimus dorsi and gastrocnemius muscles were routinely fixed in 10 per cent neutral formalin. These were blocked in paraffin, cut at 6 μ, and stained with hematoxylin and eosin. Selected blocks of kidney, liver, skeletal muscle, and myocardium were cut at 10 μ and stained by Dieterle's[31] and Steiner's[32] methods. Levaditi stains also were employed on some of the tissue. All silver stains were controlled using dog kidney known to contain leptospirae (Fig. 1). This tissue was initially controlled with liver from a case of congenital syphilis. When the control was negative, that lot of slides was discarded. In kidney the possibility of confusing elastic fibers, cytoplasmic membranes, and other artifacts with leptospirae is minimal. Therefore, that organ was used exclusively for diagnostic purposes. The following criteria were met before accepting a kidney as positive for leptospirae: intact cell walls and nuclear membranes; suspected structure to be of uniform diameter and entirely within the cytoplasm, without touching cell boundaries or nuclear membrane; at least three such structures to be observed in one section.

Results

In spite of aseptic precautions, over three fourths of the organ cultures were contaminated. In such instances neither Chang's nor the rabbit serum medium succeeded in supporting leptospiral growth, although simultaneous blood cultures from the same animals frequently were positive for both. As detailed in the discussion, the muscle reactions are indicated numerically by histologic type. Briefly, these are as follows:

I. Focal damage to isolated fibers
II. Diffuse or focal interstitial inflammation
III. Diffuse Zenker's degeneration
IV. Diffuse vacuolar degeneration
V. Diffuse atrophy

Dogs and Rats

Two dogs had gross changes typical of the uremic form of leptospirosis, with bulging, yellow, renal cortices and relative sparing of the medulla. There were multiple, focal, pulmonary hemorrhages, gastrointestinal hemorrhage, and varying degrees of parenchymal hemorrhage into other organs. The other two were markedly icteric and showed a narrow yellow line at the corticomedullary junction. Hemorrhagic phenomena, though present, were less striking than in the renal form. The livers of all dogs were severely congested but otherwise grossly normal. The extrahepatic bile ducts and skeletal muscles also were grossly normal in all. All dark-field preparations and cultures were negative. The injected hamsters remained healthy. The control dog also showed a yellow corticomedullary junction in the kidneys, but no hemorrhagic phenomena.

Microscopically, interstitial nephritis and tubular degeneration corresponded in degree to the gross appearance. Figure 2 illustrates the severe renal form. The icteric dogs had less severe renal changes resembling those found in rats. Organisms were seen in the kidneys of an icteric and a non-icteric dog. Very rare foci of necrosis were seen in the livers of 3 animals. The icteric dog with proved leptospirosis showed a characteristic type 1 muscle reaction (Fig. 3) which was obviously quite similar to the lesion illustrated in Figure 4 from a proved human case of Weil's disease.* The other icteric dog had focal type 1 lesions in an earlier stage with beginning débridement by macrophages (Fig. 13). The dog with proved renal leptospirosis had multiple, focal, muscle lesions with very severe disintegration of the sarcoplasm and associated marked interstitial edema (Fig. 12). This was classified as type 1 because of the focal involvement. A single fiber in this animal showed changes like those in Figures 3 and 4. The other animal showed no muscle lesions in multiple blocks. Fatty tubular degeneration and slight interstitial calcification at the renal corticomedullary junction was seen in the control dog and probably resulted from metabolic alkalosis. No muscle lesions were seen.

All dark-field preparations and cultures from the rats were negative. Diffuse interstitial myocarditis of unknown cause and liver granulomas due to *Capillaria hepatica* were found in nearly every animal. Less frequent conditions were bronchiectatic lung abscesses and Sarcocystis infestation. One animal had demonstrable trichinosis. Four animals exhibited mild interstitial nephritis (Fig. 5) and hemo-

* From personal slide collection. This case has been reported in the literature.[11]

siderosis of the hepatic portal zones. A type 1 muscle reaction (Fig. 6) was seen in all of these animals, involving rare scattered fibers. Figure 7 from a proved human case of Weil's disease may be seen for comparison. Leptospiras were found in one rat kidney (Fig. 8), adjacent to an area of interstitial nephritis. Interstitial inflammatory cells, chiefly eosinophils, were seen around the Trichinella larvae. All other animals which lacked the liver and renal changes also lacked muscle lesions, regardless of the combination of other conditions. None of the animals exhibited muscle fiber damage or cellular reaction to the Sarcocystis organisms, although some were very heavily infested. The injected hamsters remained healthy, but neither of the rats used showed lesions attributable to leptospirosis.

Hamsters and Guinea-Pigs

Grossly, the hamsters appeared normal until 12 hours after inoculation when rare, circular, pulmonary hemorrhages became evident. These increased in number until 60 hours when they reached their maximum (Fig. 9) and then began to decrease. At that time the first positive direct dark-field examinations on both blood and kidney were obtained. Thereafter, leptospirae were often more numerous in the animal blood than in cultures at the peak of the growth curve. Active leptospirae were seen in kidney emulsion at 48 hours. Blood cultures were positive on all animals after 3 hours. The kidneys were congested at 48 hours and intensely hemorrhagic at all later intervals. The skeletal muscles were normal grossly until shortly before death when interstitial hemorrhage was apparent.

Histologically, focal pulmonary alveolar hemorrhages closely paralleled the gross appearance in size and number. Progressively increasing renal lesions appeared at 60 hours, consisting of diffuse interstitial and glomerular hemorrhage, and hemoglobin casts with marked tubular necrosis in the proximal tubules. Therefore, the established criteria for identification of leptospirae could be met only at the 48th and 60th hours although leptospira-like structures increased progressively in the interstices and necrotic tubular cells. A striking feature in the organs studied was the lack of inflammatory cellular reaction to the leptospiral infection. That the animals were capable of cellular reaction was demonstrated by the occurrence of abscesses in several animals in which organ emulsion had inadvertently been injected subcutaneously.

At the third and sixth hours a focal, type II muscle reaction without associated muscle fiber damage was seen. This change was present in

controls necropsied at the same intervals. No inclusion bodies were seen in either group. Later, similar reaction patterns were seen only in association with gross or microscopic interstitial hemorrhage. At the time of death, focal hyalinization of portions of muscle fibers (Fig. 10) often was seen, but again in association with marked interstitial hemorrhage. A characteristic type I reaction was not observed in any of the animals. Leptospira-like structures were seen within interstitial capillaries but not within the muscle fibers themselves.

Two guinea-pigs, 3 days old at the time of injection, succumbed at 146 hours. Two older animals survived without indication of illness and were sacrificed at 11 and 18 days. The other animals were chloroformed at intervals comparable to those for the hamsters. All blood cultures were positive except in the 2 which survived. The dark-field examination of kidney became positive at 72 hours and of blood at 96 hours. Leptospirae were readily demonstrable in the renal tubules at 96 hours and in all others studied at later intervals except in the animal killed at 11 days. All animals except the 2 which survived showed changes grossly similar to, but less extensive than, those in hamsters. These were first recognizable in the lungs at 48 hours, reached a peak at 72 hours, and then decreased. The kidneys bore a striking resemblance to the "flea bitten" kidney of malignant nephrosclerosis. Microscopically, the pulmonary alveolar hemorrhages (Fig. 11) were identical with those in the hamsters. The renal lesions also were similar, but very mild interstitial nephritis was present and the tubular epithelium much better preserved. The animal living 11 days had only mild interstitial nephritis. The animal sacrificed at 18 days had diffuse interstitial nephritis which was similar but less extensive than in the icteric dogs. Kidney emulsion from this animal containing rare, viable leptospirae was injected into a hamster. There was no evidence of leptospirosis on several blood cultures from the hamster or at necropsy 5 days after injection.

Grossly, some of the skeletal muscles of the guinea-pigs showed interstitial hemorrhages. Microscopically, these were associated with focal hyalinization of muscle fibers like that in the hamsters. Characteristic type I reactions were not seen. The skeletal muscles of the controls were normal.

Discussion

It is evident that the ability of skeletal muscle to respond to injury is rather limited[33-35] and similar in many conditions. Various authors[33,34,36,37] have shown that each damaged fiber reacts by formation of a "retraction cap of injury" which histologically has a waxy

appearance like that of Zenker's degeneration. More severely damaged fibers are markedly fragmented and the sarcolemma collapsed. Débridement is begun within 12 hours by invading macrophages and shortly thereafter muscle nuclei begin mitotic and amitotic proliferation to form sarcoblasts. This produces a sarcolemmal tube filled with cells. Often by the second day after injury, regenerating muscle fibers about one fourth the normal size are directed by the sarcolemma into the damaged area, the "peripheral" regeneration. Less frequently, in "terminal" regeneration, growth proceeds from the entire width of the preserved portion of the damaged fibers. All individual injured fibers undergo these changes unless the damage is very extensive, in which case repair by fibrosis is seen. However, there is a wide variation in over-all appearance depending upon the type of noxious agent and the extent of muscle involvement. The muscles involved also vary. With full realization that arbitrary classification of a dynamic pathologic process is inadequate at best, the following general reaction patterns were formulated to facilitate a comparison of leptospiral myopathies with other conditions (Table I).

I. Leptospiral Type. Focal involvement of isolated muscle fibers and parts of fibers with hyalinization, vacuolization, proliferation of muscle nuclei,* invasion by macrophages and occasional neutrophils, but with good preservation of the sarcolemma, confinement of the cellular reaction within the muscle fiber, and repair by regeneration, or occasionally, fibrosis (Figs. 3, 4, 6, 7, 12, and 13).

II. Coxsackie Virus, Rickettsial Type. Diffuse or focal interstitial and/or perivascular infiltration by macrophages, large mononuclear cells, lymphocytes and variable numbers of neutrophils, with or without the muscle fiber involvement designated as type I.

III. Toxemic Type. Diffuse Zenker's hyaline degeneration with repair by fibrosis or fiber regeneration through type I.

IV. Hypothermic Type. Intense diffuse vacuolar degeneration, fragmentation, collapse and disruption of the sarcolemma, and frequent heavy infiltration by neutrophils with repair by diffuse fibrosis or regeneration of surviving fibers through the intermediary of type I.

V. Atrophic-Dystrophic Type. A mixed reaction with focal areas resembling types II and III, pseudo-hypertrophy, regenerative or fibrous repair, and atrophy with replacement by adipose tissue or formation of lymphorrhages.

* The term muscle nuclei refers to proliferating cells within injured muscle fibers which are often called sarcolemma nuclei. The sarcolemma has no nuclei.[45] Furthermore, the identity of the cells in question as muscle nuclei has been shown convincingly in living muscle fibers.[34]

TABLE I

Types of Reaction and Results in Various Myopathic Diseases

Condition	Host	Type of reaction	End results	Author	Remarks
Coxsackie virus Conn. 5, Ohio 1	Mouse	I	Regeneration	Godman *et al.*[33]	
Texas 1, Easton 2	Mouse	II			
Poliomyelitis	Hamster	I(?)	Not stated	Aronson and Shwartzman[38]	Not illustrated; lesions in cortisone treated animals only
Physical injury	Rabbit	I	Regeneration	Clark[36]	
Encephalomyelitis virus	Mouse	II	Calcification & chronic inflammation	Rustigian and Pappenheimer[39]	
Potassium deficiency	Dog	I	Regeneration	Smith *et al.*[40]	Fig. 3, parts C and D, p. 195, ref. 40, indistinguishable from the lesion of Weil's disease
Pneumonia	Human	II	Regeneration	Forbus[37]	Abdominal muscles only
Physico-chemical injury	Tadpole	I	Regeneration	Speidel[34]	Single living fibers studied
Frostbite	Dog	IV	Regeneration	Pirozynski and Webster[41]	
Roentgen rays	Rabbit	IV	No regeneration in 7 days	Lewis[42]	Neutrophilic infiltration
Myasthenia gravis	Human	V	Atrophy	Russell[43]	
Nutritional muscular dystrophy	Rabbit	V	Not stated	Innes and Yevich[44]	
Leptospirosis icterohaemorrhagiae	Human	I	Not stated	Pick[7]	
icterohaemorrhagiae	Human	I	Not stated	Jeghers *et al.*[8]	

icterohaemorrhagiae	Human	I	Regeneration	Sheldon[9]	
icterohaemorrhagiae	Human	III(?)	Not stated	Fialho[10]	Cited by DaCorso[16]
icterohaemorrhagiae	Human	I	Not stated	Cowden *et al.*[11]	
icterohaemorrhagiae	Human	I	Not stated	Sheldon[12]	Antibody demonstrated in muscle lesion
Leptospirosis canicola	Human	I(?)	Not stated	Wolff *et al.*[13]	Not illustrated
canicola	Human	I(?)	Not stated	Turrell and Hamburger[14]	Lesion not evident in illustration
icterohaemorrhagiae	Dog	Interstitial hemorrhage	Not stated	Monlux[15]	
canicola	Dog	Interstitial hemorrhage	Not stated	Monlux[15]	
icterohaemorrhagiae	Dog	I(?)	Not stated	DaCorso[16]	Type III illustrated but description suggests type 1
This study					
icterohaemorrhagiae(?)	Dog	I			See Figs. 3 & 13 of this article
icterohaemorrhagiae(?)	Rat	I			See Fig. 6
canicola(?)	Dog	I			See Fig. 12
canicola (Korgan)	Hamster	Interstitial hemorrhage	Focal "retraction caps" at death attributed to interstitial hemorrhage		
canicola (Korgan)	Guinea-pig	Interstitial hemorrhage	Focal "retraction caps" at death attributed to interstitial hemorrhage		See Fig. 10

It is evident from Table I that a type I muscle reaction in man is characteristic of *Lept. icterohaemorrhagiae* infection. It is not specific as shown by its possible occurrence in other conditions. Theoretically, familial periodic paralysis (potassium deficiency) and infectious pleurodynia (Coxsackie virus) might be expected to have a type I lesion, but these could hardly be confused clinically with leptospirosis. Rickettsial infection has been confused with Weil's disease on muscle biopsy,[9] but careful study of several slides should reveal a type II pattern with pronounced vascular changes. The occurrence of a type I lesion in canicola fever has not been demonstrated convincingly. Reports of muscle lesions in the other leptospiral diseases were not found.

Both dogs with proved leptospirosis and another with typical gross and microscopic findings had skeletal muscle lesions. The negative dark-field examinations, cultures, and animal inoculations are not disturbing since penicillin is known to affect leptospirae *in vivo*.[46] Furthermore, because of marked fragmentation, many fields had to be surveyed before finding an intact organism or group of organisms in the kidney sections. Probably the organisms were dead and the dogs died because of cellular damage sustained before therapy was started. In general, the icteric form of canine leptospirosis is caused by *Lept. icterohaemorrhagiae* and the uremic form by *Lept. canicola,* but exceptions are relatively common.[47] Quite probably, the icteric dogs showing type I muscle reactions were infected with the former.

The diagnosis in rats was conclusive in only one instance, but the combination of hemosiderosis and interstitial nephritis made it likely in the unproved cases. Rats harbor only *Lept. icterohaemorrhagiae*.[6] Therefore, the correlation of these findings with a type I lesion and the lack of correlation with any of the many other conditions also support the diagnosis.

Lept. canicola was used for experiments on the guinea-pig and hamster only because a lethal strain of *Lept. icterohaemorrhagiae* could not be isolated or obtained by mail. The former produces severe myalgia in man, presumably because of muscle lesions like those of Weil's disease. Therefore, it was expected that *Lept. canicola* would produce typical lesions in animals. The absence of characteristic lesions was quite surprising. Ever-increasing leptospiremia in both experimental groups should have afforded the organisms ample opportunity for burrowing into the muscle fibers. Indeed, their demonstration in the renal tubular epithelium of the hamsters and guinea-pigs is taken as evidence of their burrowing capability. One may conclude that in guinea-

pigs and hamsters, *Lept. canicola* (Korgan) does not burrow into muscle fibers or produce characteristic muscle lesions. Whether the same holds true for *Lept. icterohaemorrhagiae* and other strains of *Lept. canicola* in these animals remains to be seen. To assume from this study that the muscle lesion of human Weil's disease is not caused by burrowing organisms would be completely fallacious. In fact, recent histo-serologic evidence[12] supports the burrowing concept. A plausible explanation for the lack of a typical muscle reaction in the hamsters and guinea-pigs and its common occurrence in human Weil's disease is the possibility of electrokinetic phenomena which vary with the host and the leptospiral sero-type.[48] Renal hypopotassemia[49] is another possibility, but seems unlikely. However, it is interesting that dogs with leptospirosis often exhibit motor paralysis of the hind legs. Finally, it appears that young guinea-pigs are susceptible to large doses of *Lept. canicola* (Korgan) without showing outward signs of disease. If these observations can be repeated with smaller doses and other strains of *Lept. canicola,* young guinea-pigs may prove to be as valuable as hamsters in the clinical diagnosis of canicola fever.

Summary and Conclusions

Lesions of skeletal muscle identical with those described in human Weil's disease are reported for the first time in naturally infected dogs and wild city rats with leptospirosis. The literature on reported leptospiral myopathies is summarized and findings compared with muscle lesions in other conditions, using a histologic classification based upon general reaction patterns to various noxa. Guinea-pigs and hamsters experimentally infected with *Leptospira canicola* did not develop characteristic muscle lesions. Young guinea-pigs all developed visceral lesions typical of leptospirosis after large doses of *Lept. canicola* (Korgan). While not specific, in the sense of a tubercle containing acid-fast bacilli, the skeletal muscle lesion of Weil's disease (*Lept. icterohaemorrhagiae*) is sufficiently characteristic to be of diagnostic significance in human disease when interpreted in the light of the clinical history. As far as is known, type I reaction (focal damage to isolated fibers) in humans has been reported only in Weil's disease. The presence or absence of these muscle lesions in man and animals infected with leptospirae other than *Lept. icterohaemorrhagiae* remains to be shown.

Acknowledgment is made to the Department of Medical Illustration, University of Colorado Medical School, for Figure 1 and to Mr. I. S. Stephens for all other photomicrographs, and to Drs. L. S. Peavy and J. R. Naylor for dogs from their practices.

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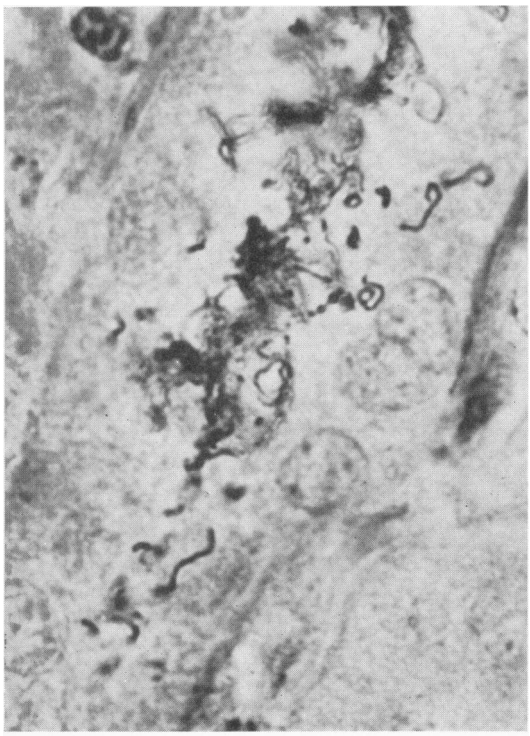
LEGENDS FOR FIGURES

FIG. 1. Kidney of dog with leptospirosis of uremic type. Numerous leptospirae visible. Dieterle's stain. × 1750.

FIG. 2. Kidney of dog with leptospirosis of uremic type. Lymphocytes and plasma cells predominate, but scattered neutrophils also are present. Hematoxylin and eosin stain. × 120.

FIG. 3. Gastrocnemius muscle of dog with proved icteric leptospirosis. Sarcolemmal "tube" formation. Hematoxylin and eosin stain. × 120.

FIG. 4. Human gastrocnemius muscle from serologically proved Weil's disease. Hematoxylin and eosin stain. × 120.



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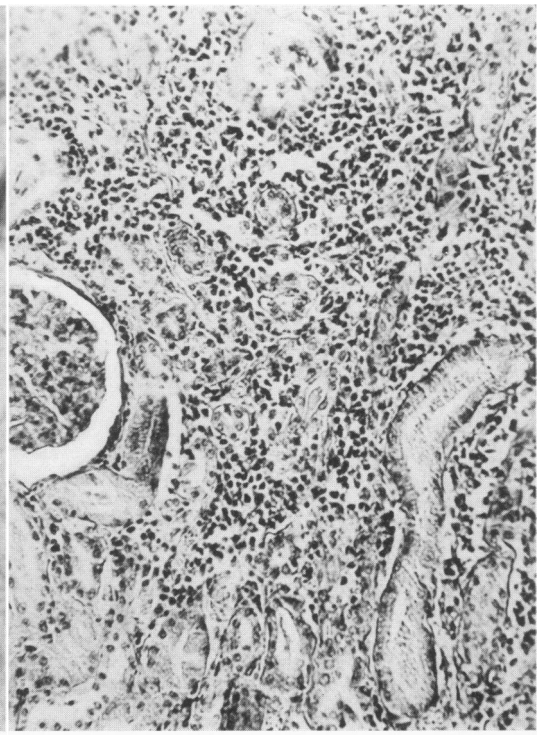

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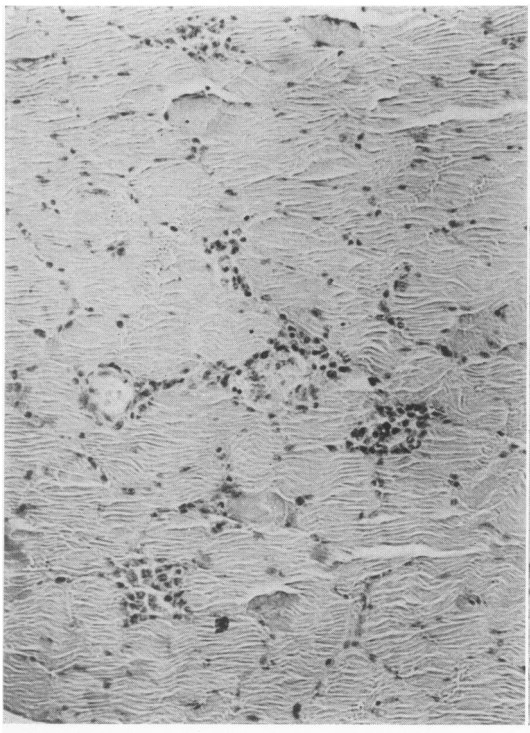

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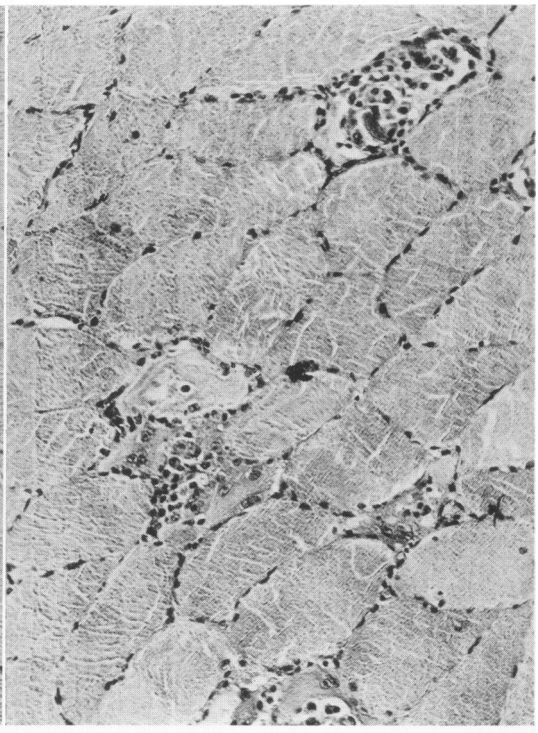

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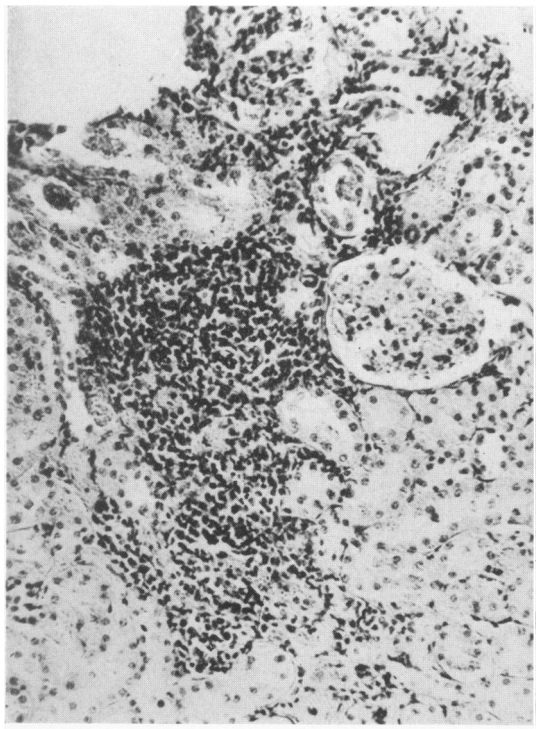
FIG. 5. Kidney of the rat illustrated in Figures 6 and 8. Hematoxylin and eosin stain. × 120.

FIG. 6. Gastrocnemius muscle of the rat illustrated in Figures 5 and 8. Hematoxylin and eosin stain. × 120.

FIG. 7. Cross section of the human gastrocnemius muscle illustrated in Figure 4. Hematoxylin and eosin stain. × 516.

FIG. 8. Rat kidney illustrated in Figures 5 and 6. The organisms overlie an intact nucleus in a slightly different focal plane, but under the microscope were definitely within the cytoplasm. Steiner's stain. × 970.

FIG. 9. Heart, lung, and kidney from a hamster which died of canicola fever. Of note is the absence of cortical markings on the sectioned kidney below the "butterfly" lungs. × 2½.



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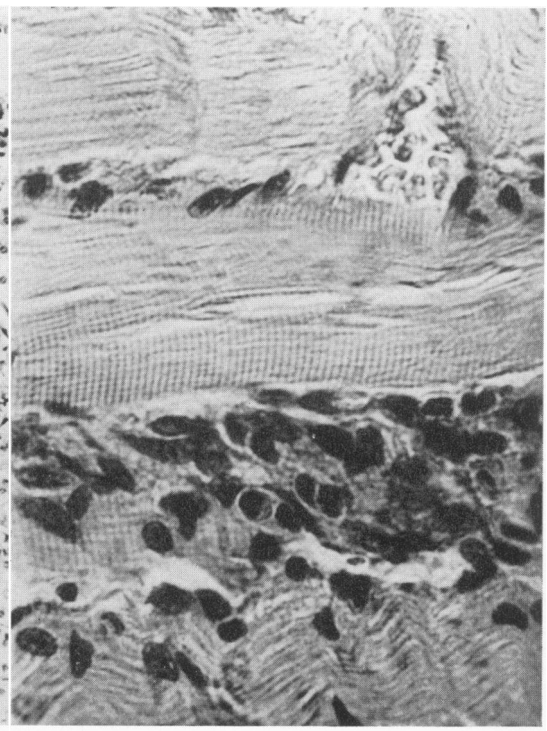

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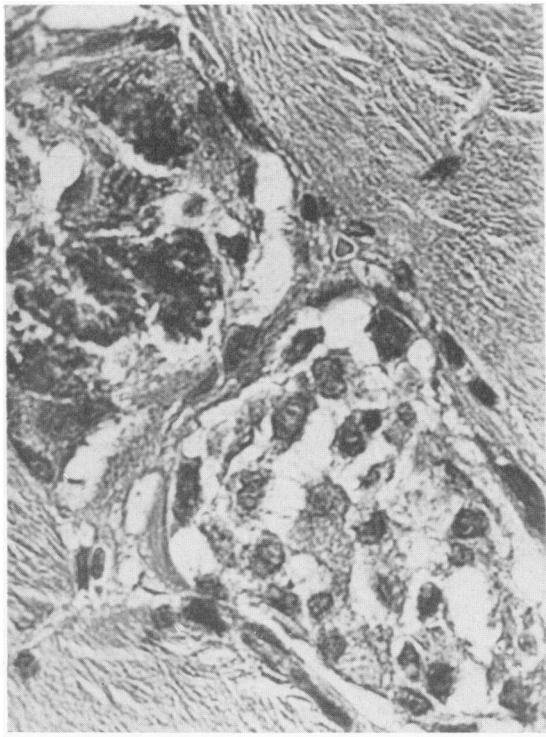

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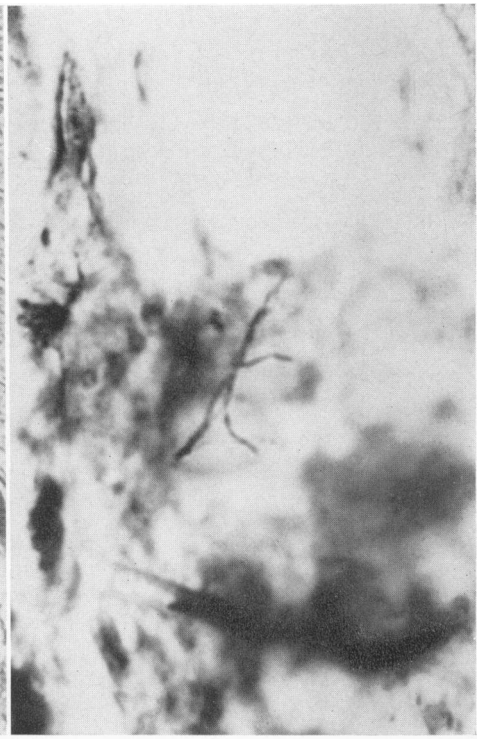

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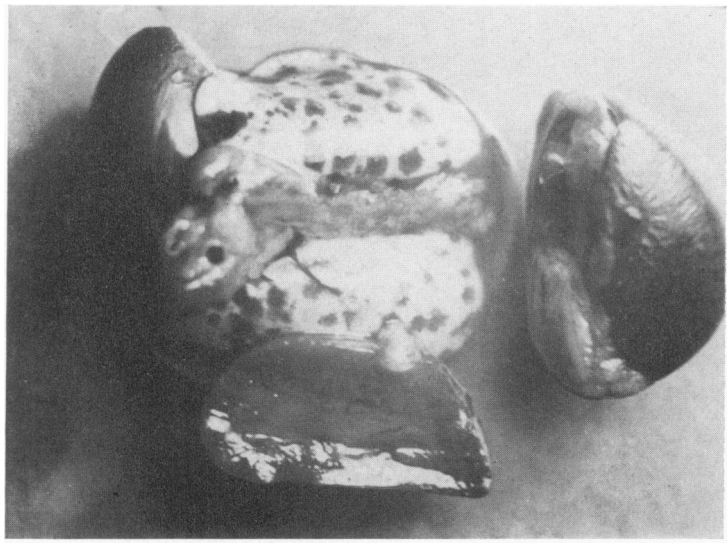

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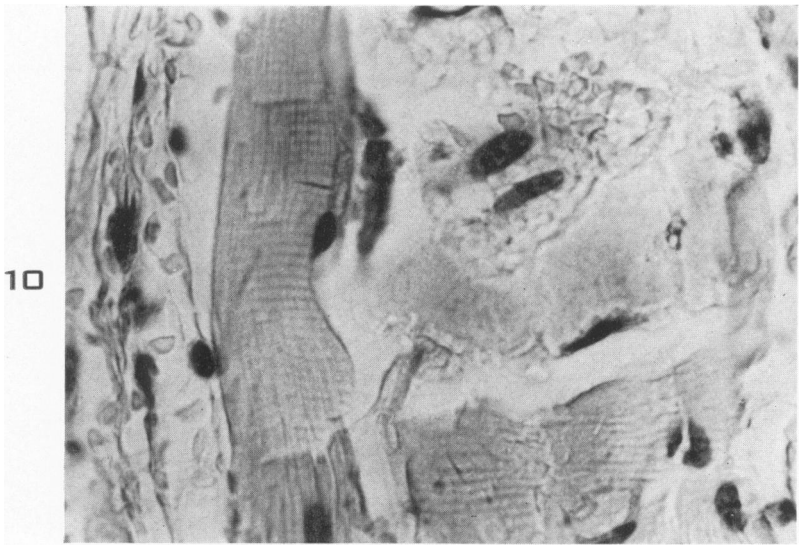
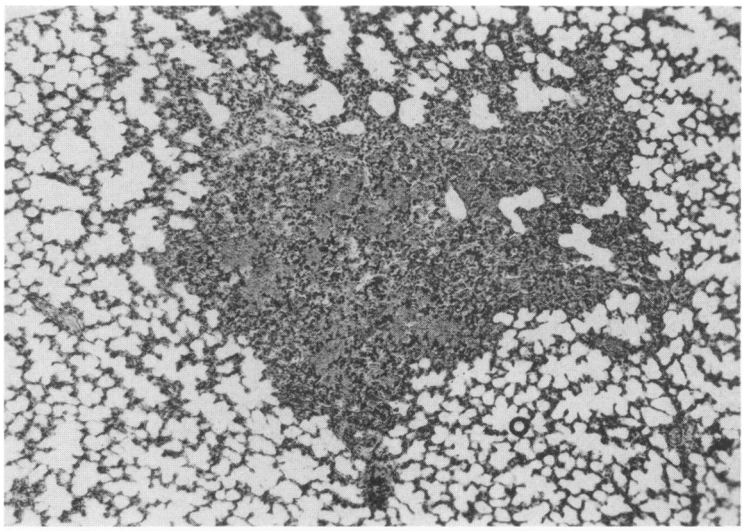
FIG. 10. Gastrocnemius muscle from a hamster which died of canicola fever. The hyalinized portions of three fibers lie below a zone of hemorrhage and the better preserved portions have retracted. Hematoxylin and eosin stain. × 516.

FIG. 11. Typical pulmonary hemorrhage in canicola fever from a guinea-pig which was normal to inspection while alive. Hematoxylin and eosin stain. × 60.

FIG. 12. Gastrocnemius muscle of a dog with proved leptospirosis of uremic type. Of note is the collapsed sarcolemma at the upper end of the degenerated fiber, the preservation of the adjacent fibers, and the marked interstitial edema. Hematoxylin and eosin stain. × 120.

FIG. 13. Gastrocnemius muscle of an icteric dog. One end of the damaged fiber and of the adjacent fibers is preserved. A normal segment of this same fiber was seen on the other end just beyond the edge of the field illustrated. Macrophages have begun débridement of the necrotic portion. Hematoxylin and eosin stain. × 120.





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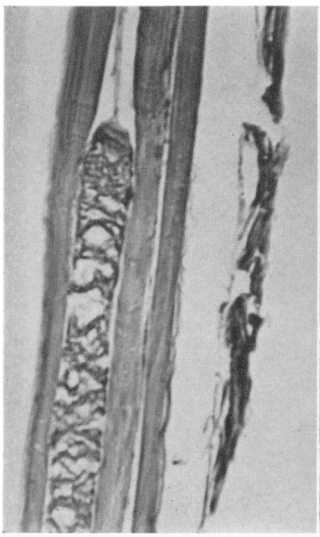

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