

EARLY EFFECTS OF HIGH INTENSITY X-RADIATION ON SKELETAL MUSCLE

By HERBERT B. GERSTNER, ROBERT B. LEWIS, AND EVERETT O. RICHEY

(From the Departments of Radiobiology and Pathology, United States Air Force School of Aviation Medicine, Randolph Air Force Base, Randolph Field)

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Following exposure of isolated frog gastrocnemii to high intensity x-radiation, increased fatigability and contracture of the muscles have been demonstrated in previous studies (3). The present paper presenting an expansion of these previous studies comprises, first, a study of cold blooded muscle during and after exposure to x-radiation and, second, a determination of radiation effects on muscles of intact warm blooded animals.

RADIATION EFFECTS ON COLD BLOODED MUSCLE

The first section of the present study was performed on isolated cold blooded gastrocnemii. This method offers an important advantage. Changes occurring in the muscle during and following irradiation, as compared to a non-irradiated control muscle, must be directly caused by the ionizing radiation, since all connections to other organs through the circulatory and nervous system are interrupted.

Method

The experiments were performed during the fall of the year with leopard frogs (*Rana pipiens*) of approximately equal size. The animals were stored at 6°C. Preparation, radiation, and testing of the isolated gastrocnemii were carried out at 20°C.

Recordings of the isotonic contractions were made according to a method previously described (5). As an essential feature of this method alteration of muscle length produced proportional voltage changes at the slider of a micropotentiometer. These voltage changes were recorded either by means of a cathode ray oscilloscope or an ink writer.

The plastic wet chamber containing the isolated gastrocnemius was placed in the head of a Picker x-ray unit. The conditions of the experiment were as follows: voltage, 260 kvp.; amperage, 18 ma.; inherent filtration, 0.25 mm. copper; additional filtration, 3 mm. plastic wall of wet chamber; and target-muscle distance, 8 cm. Under these conditions a dose rate of approximately 6 kr (6,000 r) per minute was measured in air.

The experimentation was carried out in several distinct steps. Radiation effects were studied (1) on the work capacity, (2) on the single twitch, (3) on the length-force diagram, and (4) on the histology of the muscle.

Work Capacity.—From each frog both gastrocnemii were isolated and mounted in separate wet chambers. Attached to each muscle were a load of 50 gm., a micro-potentiometer, and two needle electrodes through which a rectangular stimulus of 1 msec. duration and 1.5 ma. intensity was applied at intervals of 4 seconds. The signals from the two potentiometers were fed into a dual beam oscilloscope and the cathode ray oscilloscope traces were recorded with a moving film camera. Since the cathode ray oscilloscope sweep was turned off, the signals produced straight line deflections at right angles to the direction of film motion. With a film speed of $\frac{1}{4}$ mm. per second and with stimuli every 4 seconds, the muscle twitches appeared as a series of spikes at 1 mm. intervals. One of the muscles of each muscle pair was then exposed to x-radiation as described above; the other served as a control.

Twitch.—The general method was the same as that employed in the first series; however, a load of 25 gm. and stimulation at 8 second intervals were used to delay the onset and, if possible, to prolong the development of fatigue during radiation. Furthermore, the method of recording was modified. Every 8 seconds the shutter of the camera was opened for $\frac{1}{2}$ second by means of a synchronous motor. The opening of the shutter triggered the common sweep of a four channel cathode ray oscilloscope and, with a delay of 10 msec., the discharge of a rectangular pulse generator. This discharge, the stimulus, elicited single twitches of the irradiated muscle and the control muscle. The signals thereby produced at the potentiometers were fed into two separate channels of the four channel cathode ray oscilloscope. Selection of 20 msec. per cm. as the sweep speed produced well expanded pictures of the complete twitches. The remaining two beams of the oscilloscope were connected to the stimulus circuit and to an audio oscillator set at 100 c.p.s. for the time marking. Thus, each photograph taken by the camera represented a simultaneous record of these four potentials. Since the procedure described was automatically repeated every 8 seconds, a thorough analysis of the functional changes occurring in the muscle under the x-ray beam was possible.

Length-Force Diagram.—The third series of experiments comprised a determination of the length-force diagrams of 20 gastrocnemius pairs in the relaxed and the contracted state. Contraction was elicited by a 100 c.p.s. sine wave stimulus of 1 volt (r.m.s.) amplitude and 1 second duration. The potentiometer signals produced by changes of muscle length were recorded on an ink writer.

From each of the 20 frogs both gastrocnemii were isolated and placed in separate beakers containing Ringer's solution. One of the muscles was then exposed to a total dose of 100 kr x-radiation; the other served as the control. Following exposure, the two were mounted in separate wet chambers. To stretch the muscle, a load of 200 gm. was employed and one contraction elicited. Following removal of this load, determination of the length-force diagram was started. Resting length and maximal shortening were recorded for the smallest load first. Following a pause of 30 seconds during which the previous load remained attached, the desired weight increase was added. Thereby, the muscles became stretched to a stable length within another 30 seconds. This length was then determined, stimulation was started, and the maximal contraction recorded. The procedure was repeated with increasing weights until the contraction amplitude became too small to be measured. Since for the present study

differences between control muscles and irradiated muscles were of interest, slight distortions of the contraction heights by fatigue were not essential.

Histology.—The gastrocnemii of 28 frogs were isolated in pairs. One of the members of each pair was irradiated; the other served as a control. At various time intervals following exposure the muscles were fixed in formalin for histologic study. After fixation, the blocks were embedded in paraffin, sectioned, and stained with eosin and hematoxylin.

Results

Work Capacity.—Consistent results were obtained in the 20 experiments performed. Throughout the first 8 to 10 minutes of exposure the muscles continued to function normally. Then, rather suddenly, the contraction height of the irradiated muscles decreased steadily to zero. Simultaneously a rise of the base line occurred, caused by the failure of the muscles to return to their resting length during the relaxation period. At 15 minutes following start of radiation all the irradiated muscles were completely exhausted and failed to produce visible twitches. Spontaneous fatigue of the non-irradiated muscles was observed within 20 to 40 minutes following start of stimulation. At the time when fatigue and contracture were noticeable in the exposed gastrocnemii, all the controls were still functioning normally.

Fig. 1 shows a characteristic example of this type of experiment. Of the entire film obtained in this particular experiment only a small section is copied. It represents the interesting time period between the 8th and the 12th minute following start of radiation. Rise of the base line (contracture) and decrease of contraction height (fatigue) can be clearly seen in the upper tracing, the record of the irradiated muscle. Throughout the first 8 minutes of exposure time, which are not included in figure 1, a marked constancy of contraction amplitude prevails, and the twitches of the two muscles correspond in size with the spikes visible at the left side of Fig. 1. These spikes are higher in the upper than in the lower tracing because of higher amplifier gain used for the irradiated muscle to increase the measuring accuracy.

Additional experiments in which load and frequency of stimulation were varied disclosed that by decreasing these two factors the onset of fatigue and contracture of the irradiated muscle was delayed, and the development of the damage to complete exhaustion was prolonged. Thus, for example, with a load of 25 gm. and stimuli at 8 second intervals, impairment of muscle function became evident between the 10th and the 15th minute of irradiation, and abolition of function occurred between the 20th and the 30th minute of exposure.

Twitch.—Close agreement in findings was revealed by the records obtained from 10 muscle pairs. From the 300 photographs taken in one of these experiments 4 pictures showing characteristic phases of the development of radiation damage were selected. They appear in Fig. 2. In each picture the traces (read in

descending order) represent (1) the stimulus appearing as a downward spike close to the left end of the horizontal line; (2) the twitch of the non-irradiated control muscle; (3) the twitch of the muscle under exposure to x-radiation; and (4) the 100 c.p.s. time marker which is visible as two lines of dots indicating 10 msec. between consecutive dots. Photograph 0 (Fig. 2), which was taken at the start of radiation, shows that the two muscles have a latency period of approximately 10 msec., a rise time of 40 msec., and a relaxation time of 40 msec., and shows also that the relaxation phase is followed by a damped oscillation. The

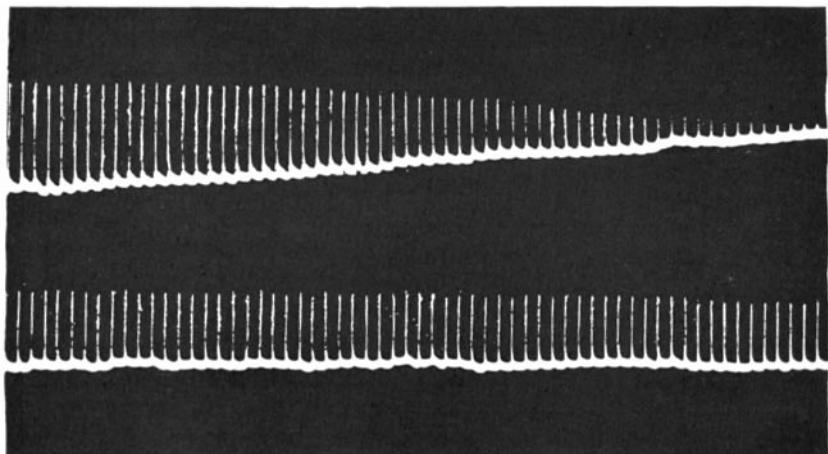


FIG. 1. Work records of gastrocnemius pair isolated from the same animal. The upper muscle is exposed to 6 kr per minute x-radiation, the lower muscle is the non-irradiated control. Stimulation occurs every 4 seconds; the load is 50 gm.

lower twitch in photograph 0 has a greater amplitude than the other because of higher amplifier gain used for the irradiated muscle to increase measuring accuracy.

In all 10 cases the twitch of the exposed muscle remained normal during the first 10 minutes of irradiation. Then, as the first sign of radiation influence, the amplitude of the damped oscillation gradually decreased and disappeared completely within 15 to 20 minutes following start of radiation. Subsequently an even more striking difference between control and irradiated muscles became evident. The irradiated gastrocnemii exhibited a decrease in contraction height, a prolongation of relaxation phase, and a failure to return to the initial resting length. The beginning of this stage of the damage is shown in photograph 165 of Figure 2. Within a few minutes thereafter, this radiation damage became more and more pronounced and progressed to complete abolition of function as demonstrated by photographs 180 and 195 in Fig. 2. In all 10 experiments, impairment of function became noticeable after 10 to 15 minutes and complete

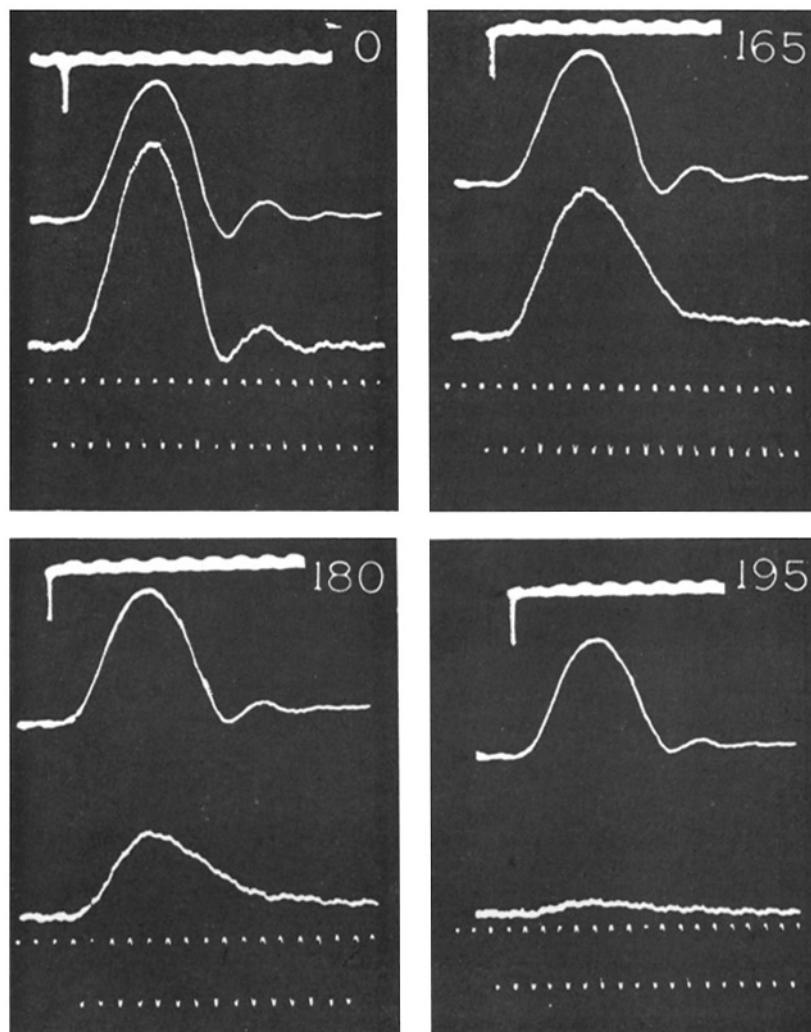


FIG. 2. Isotonic muscle twitches of gastrocnemius pair isolated from the same animal. The upper muscle is the non-irradiated control, the lower muscle is exposed to 6 kr per minute x-radiation. Stimulation occurs every 8 seconds; the load is 25 gm. The represented cathode ray oscilloscope records were taken at the following time intervals after start of radiation: photograph 0, 0 minutes; 165, 22 minutes; 180, 24 minutes; 195, 26 minutes.

exhaustion after 20 to 30 minutes of exposure. At this time all the controls were still exhibiting twitches of either normal or slightly decreased amplitude. In regard to time of latency and rise time, the 10 records revealed no obvious radiation effects.

Length-Force Diagram.—Piloting experiments disclosed, first, that the damage to the muscles caused by irradiation seemed to progress in the postexposure time and, second, that the sensitivity of the muscle to x-radiation depended on the physiological condition of the animals from which the gastrocnemii were isolated. Muscles from fresh, strong frogs appeared less sensitive than those from animals weakened through long storage.

Since for statistical analysis¹ it was desirable to measure muscles under conditions as uniform as possible, a single shipment of frogs, stored for 3 to 4 days, was employed and determination of the length-force diagram was completed within 2 hours following exposure. Tables I and II contain measurements

TABLE I

The Effect of 100 Kr X-Radiation on the Length-Force Diagram of 20 Isolated Frog Gastrocnemii
Stretch (in mm.) of muscle in response to various loads.

	Load, gm.											
	10		100		200		300		400		500	
	Control	Irradiated	Control	Irradiated	Control	Irradiated	Control	Irradiated	Control	Irradiated	Control	Irradiated
Mean.....	0.5	0.2	4.0	3.8	6.4	6.2	8.6	8.5	10.7	10.6	12.7	13.0
Standard deviation of observations.....	0.4	0.2	0.5	0.6	0.6	0.6	1.0	0.6	1.1	0.7	1.1	1.0
P value*.....	0.02		0.19		0.27		0.47		0.50		0.30	

* Based on Student's *t* test of differences between members of each pair. *P* represents the probability that the mean of differences could be even larger than observed by chance alone.

obtained with some of the loads employed and Fig. 3 shows the mean values of the length changes found for the irradiated and the non-irradiated groups of the 20 muscle pairs. The resting muscle length, amounting to approximately 30 mm. in each of the gastrocnemii, is not represented because its accurate determination poses a difficult problem. Fig. 3 reveals that the stretching curves for the relaxed state of the two muscle groups closely parallel each other. With increasing force the irradiated gastrocnemii are, on the average, stretched slightly less than the controls, except for the highest load (500 gm.) at which a reversal of this behavior occurs. It should be emphasized, however, that the decreased stretching of the irradiated group, in most cases, appears at 10 gm. Thereafter, addition of load causes added stretching which is not significantly

¹ The statistical evaluation of the experimental results was performed by Dr. William F. Taylor, Department of Biometrics.

different between the two groups. When the data are subjected to the analysis of variance technique, it is revealed that there is no over-all significant difference between the stretching of control and irradiated gastrocnemii. Thus, it must be concluded that irradiation does not obviously affect the static elasticity of muscle. However, Fig. 3 discloses pronounced changes of muscle contractility. The contraction amplitudes produced by the irradiated group are considerably smaller than those of the control group. When, for statistical analysis, the differences in contraction heights between muscle pairs are computed for each load and the mean differences so obtained are compared with that found for zero load, the result is as follows: (1) Significant differences (0.05 significance

TABLE II
The Effect of 100 Kr X-Radiation on the Length-Force Diagram of 20 Isolated Frog Gastrocnemii
 Muscle contraction (in mm.) caused by direct stimulation—30 c.p.s., 1 volt, 1 second—with various loads attached to the muscle.

	Load, gm.											
	0		100		200		300		400		500	
	Control	Irradiated	Control	Irradiated	Control	Irradiated	Control	Irradiated	Control	Irradiated	Control	Irradiated
Mean.....	6.5	6.1	7.6	6.3	7.2	4.5	5.1	1.9	1.1	0.1	0.2	0.0
Standard deviation of observations.....	0.6	0.7	0.5	1.2	0.5	2.5	2.1	2.1	1.2	0.2	0.2	0.0
P value*.....	0.03		<0.01		<0.01		<0.01		<0.01		<0.01	

* See footnote to Table I.

level) between the control and the irradiated group exist throughout the entire load range. These differences become more striking as the load increases up to 250 gm. Above 250 gm., the control muscles show rapidly decreasing contraction amplitudes, but they still shorten significantly more than the irradiated muscles. (2) The variation of contraction heights in the irradiated group is considerably greater than in the control group. This is due to the fact that some irradiated muscles already start to show functional impairment at low loads and show limited contraction when compared with the other irradiated muscles (see Table II). Thus, the sensitivity of the individual muscles to radiation must be assumed to vary greatly. (3) Additional application of analysis of variance methods supports the first statement. Both the difference between control and irradiated groups—consequently the “radiation effect”—and the relationship between load and radiation damage are highly significant.

Histology.—As shown in Table III, no pathologic changes were observed in muscles fixed immediately and 2 hours after irradiation; whereas, 4 of 6 muscles

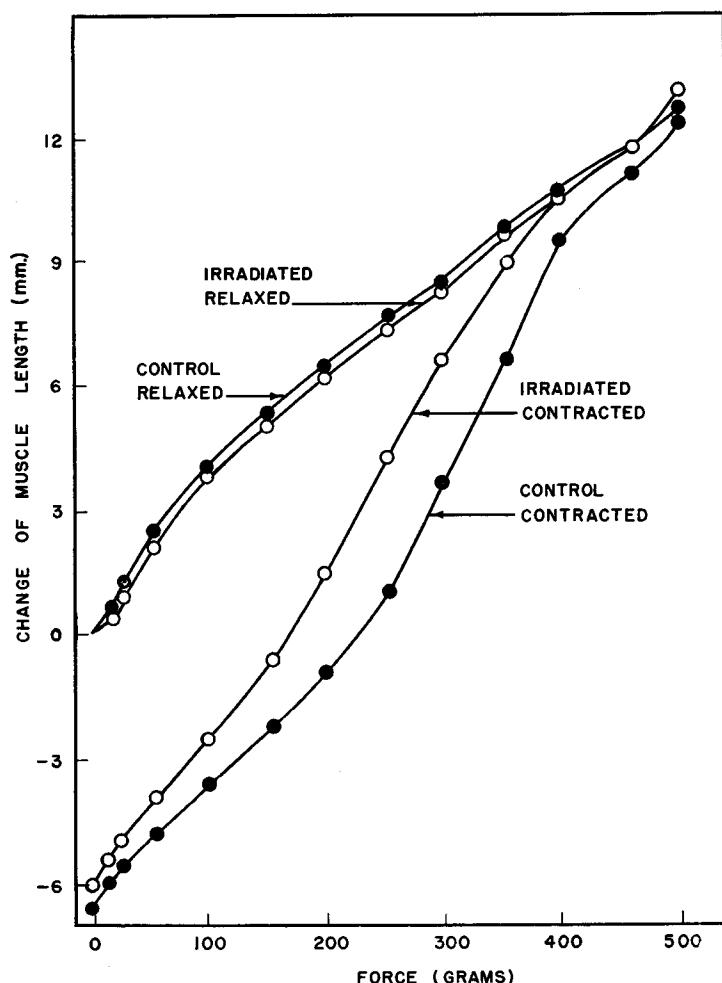


FIG. 3. The effect of 100 kr x-radiation on the length-force diagram of the isolated frog gastrocnemius. Represented are the mean values of 20 irradiated muscles and of 20 controls isolated from the same animals.

fixed after 8 hours showed acute destructive lesions of the myoplasm. These changes consisted of hyalinization and breaking up of single muscle fibers or small groups of fibers. Nuclei of muscle cells were either absent or showed karyorrhexis, and the sarcolemma was destroyed in the degenerated areas

(see Fig. 4). The unexposed opposite gastrocnemii, even when fixed 8 hours after isolation, showed no pathologic changes.

RADIATION EFFECTS ON WARM BLOODED MUSCLE²

The earlier report (3) and the first section of the present paper clearly demonstrate that high intensities of x-radiation affect isolated cold blooded muscles almost immediately. Logically the question arises whether or not ionizing radiation will similarly act upon intact warm blooded muscles possessing

TABLE III
The Effect of Various Doses of X-Radiation on the Microscopic Structure of the Isolated Frog Gastrocnemius

No. of muscles	Total dose kr.	Time interval between exposure and fixation hrs.	Microscopic findings
2	30	0	Normal
2	60	0	Normal
5	120	0	Normal
3	120	2	Normal
3	120	8	1 normal, 2 pathologic
3	180	0	Normal
3	180	2	Normal
3	180	8	1 normal, 2 pathologic
2	240	0	Normal
2	480	0	Normal

normal nerve and blood supply. As a first attempt to answer this question, pilot experiments were conducted with rabbits at the lower end of the dose range found effective in frog muscles.

Method

Irradiation.—Under light sodium pentothal anesthesia, 5 male rabbits of approximately 2,500 gm. body weight were placed on a lead shield closing the tube head of the Picker x-ray unit. Strings and lead bricks kept the left hind limb of the animal in such a position that the region between knee and ankle covered a hole cut in the center of the shield. At 1 cm. above this hole, and without additional filtration, the dose rate was 1.2 kr per minute. Thus at the end of 1 hour, the exposure time used in these experiments, the muscles of the lower leg had received a total dose of about 72 kr. Precautions were taken to keep irradiation of other body regions, especially the right leg and the lower abdomen (which were closest to the hole), at a minimum

² An essential part of the development of apparatus and of the experimentation for this section of the study was performed by M/Sgt. Alois J. Dugi, Department of Radiobiology.

by suitable positioning and additional shielding of these regions. Measurements with the rabbit in position disclosed that the amount of radiation reaching the protected parts of the animal during the entire exposure time was approximately 500 r for the right leg, 300 r for the lower abdomen, and of negligible value for the rest of the body.

Functional Examination.—The force developed by the directly stimulated gastrocnemius-soleus complex was used as a criterion of muscle function. To determine

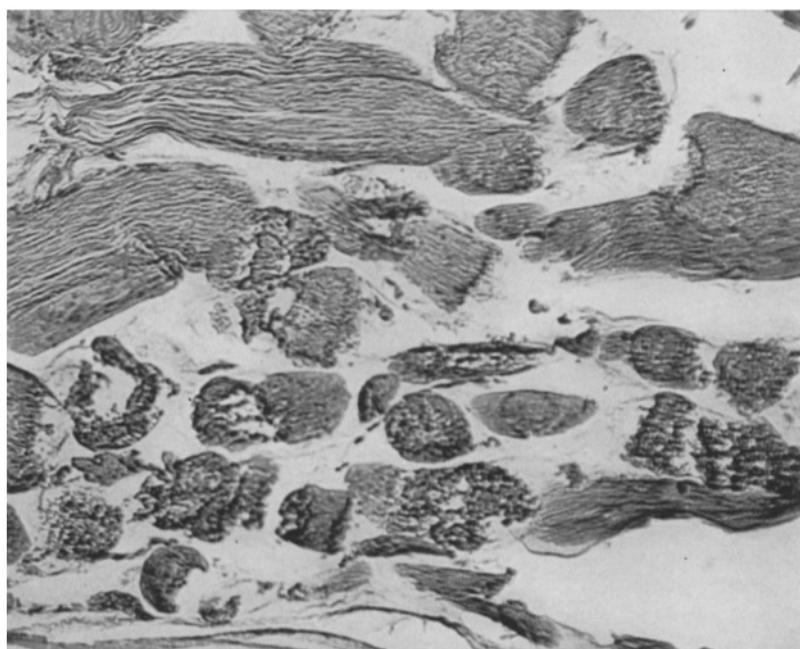


FIG. 4. Histologic alteration of isolated frog gastrocnemius fixed 8 hours following exposure to 120 kr. Several contiguous muscle fibers show degeneration. Some are broken up into amorphous masses and others show fenestration. Eosin and hematoxylin stain. $\times 123$.

this force the anesthetized animal was placed on its back. Then, by means of clamps, the test limb was immobilized in such a way that only the foot and the muscles of the lower leg were able to move freely. One end of a long string was tied around the toes and the other attached to a spring scale. Two needle electrodes were inserted into the calf muscle and connected to an audio oscillator through a tap-switch.

The stimulus, alternating current of 100 c.p.s. applied for 1 second, caused extension of the test foot and thereby a pull at the spring scale. The force measured by the scale indicated the functional condition of the gastrocnemius-soleus complex.

This test was performed on the two hind legs of each animal at various time intervals prior to and after exposure to x-radiation.

Histologic Examination.—The animals were sacrificed at the following intervals after irradiation: 1 after 12 hours, 2 after 24 hours, 1 after 3 days, and 1 after 6 days. The gastrocnemius and soleus (triceps surae) were removed from each animal, fixed in formalin, and sections cut which were stained with eosin and hematoxylin.



FIG. 5. Edema of the irradiated rabbit's leg, 24 hours following local exposure to 72 kr x-radiation.

Results

General Picture.—Within 30 minutes following exposure the animals fully recovered from anesthesia, spontaneous activity became normal, and the irradiated limb was freely used. Local examination of the irradiated part of the leg revealed a slight swelling and a decrease in sensitivity to pin-prick. During the following 8 hours this swelling gradually increased and spread into the regions of the leg adjacent to the irradiated zone. The decrease in sensitivity to pin-prick became pronounced. While resting or slowly moving the rabbit

kept the foot of the irradiated limb in normal position but a severe disturbance of coordination occurred during rapid motion. Twenty-four hours following irradiation a striking picture had developed. With the exception of the upper third of the thigh, the leg exhibited a marked swelling as seen in Fig. 5 and a complete loss of sensitivity to pin-prick. There was an absence of active motion of the foot. The irradiated foot with its dorsal side down was dragged along the floor whenever the animal spontaneously moved. These alterations prevailed throughout the observation period. On the 3rd postirradiation day ulceration and exudation of the skin indicated the beginning of gangrene and infection.

Functional Examination.—Since the number of animals used in this pilot study was too small to justify a detailed analysis of the test results, only a brief general description of consistent findings will be given. Compared with its

TABLE IV
The Effect on Muscle Force of Local X-Radiation Administered to the Left Leg of a Rabbit

Stimulus intensity	Prior		Following irradiation										
	1 hr.		0 hrs.		1 hr.		2 hrs.		4 hrs.		24 hrs.		
	R*	L*	R	L	R	L	R	L	R	L	R	L	
<i>volt</i> s													
0.53	175	150	250	200	240	80	240	0	150	0	250	0	
1.35	375	400	400	375	375	125	400	80	410	10	400	10	
2.32	600	600	700	750	600	325	600	250	580	80	520	50	
3.18	720	750	760	750	825	400	750	320	750	250	700	75	
3.90	800	800	760	750	850	550	820	350	800	300	850	120	

* R, right leg, non-irradiated; L, left leg, irradiated, 72 kr.

pre-irradiation value, the force developed by the exposed left legs had decreased more than 50 per cent within 8 hours, and more than 80 per cent within 24 hours following irradiation. No obvious changes were found in the force developed by the non-irradiated right legs. These findings are clearly demonstrated by Table IV containing test values obtained from 1 of the 5 rabbits. Tabulated is the force in grams developed by extension of the foot *versus* the intensity of the stimulus, 100 c.p.s. alternating current of 1 second duration.

Pathologic Examination.—In the gross, all irradiated legs showed edema, especially of the subcutaneous tissues and to a lesser extent of the muscles. After 24 hours small hemorrhages were visible and within 72 hours gross muscle necrosis was apparent. Microscopic examination revealed interstitial edema and extensive coagulation necrosis of the triceps surae muscle group in all 5 animals. Twelve hours following exposure the muscle fibers were swollen, often hyalinized with loss of cross-striations, fenestrated, or broken up into amorphous masses. Inflammatory exudate with numerous polymorphonuclear leukocytes was

abundant. The same changes as well as a number of small hemorrhages were observed after 24 hours (Fig. 6). After 3 and 6 days macrophages besides granulocytes were numerous in the necrotic muscle and several quite large arteries revealed necrosis of the walls and thrombi in the lumens. There was no evidence of fibrous replacement of the necrotic muscle even after 6 days. The muscles of the unexposed legs showed no pathologic changes.

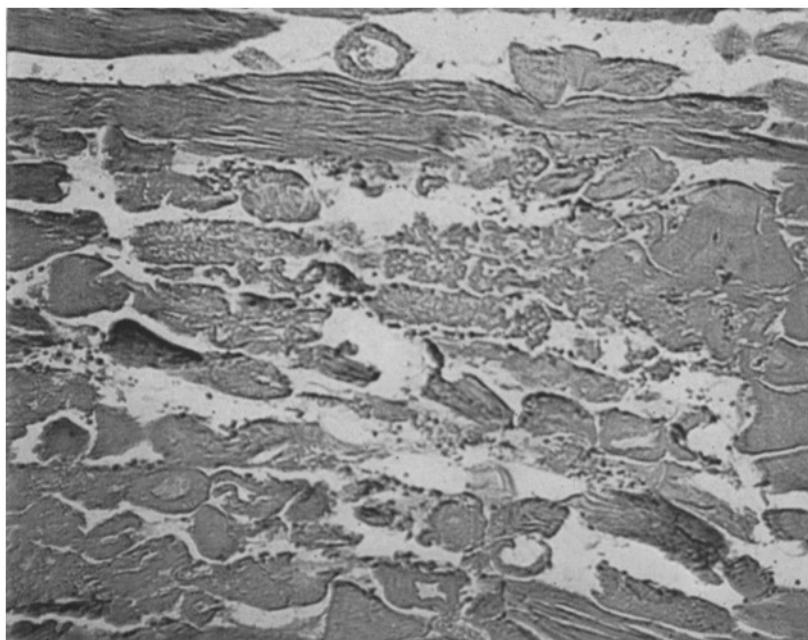


FIG. 6. Histologic alteration of rabbit muscle fixed 24 hours following exposure to 72 kr. Muscle fibers are swollen and hyalinized with loss of striations. Many fibers are broken up with loss of nuclei. Considerable numbers of polymorphonuclear leukocytes are present. Eosin and hematoxylin stain. $\times 123$.

DISCUSSION

The literature concerning effects of high intensity x-radiation on the skeletal muscle is limited and contradictory. No obvious functional impairment of the cold blooded muscles was found by Fenn and Latchford (2), whereas Bacq and collaborators (1) reported a progressive decrease in excitability accompanied by contracture. In studies employing warm blooded muscles, severe functional and structural alterations were observed by Henshaw (4) in contrast to the negative functional findings of Wilde and Sheppard (7).

The former report (3) and the present study demonstrate that high intensity

x-radiation produces early effects on function and structure of both the isolated cold blooded and the intact warm blooded muscle. Evidently, the experimental material is still too limited to allow an actual understanding and discussion of the chain of events linking the primary action of ionizing radiation with the final biologic result. However, the reported observations are extensive enough to suggest a preliminary concept of radiation damage to the muscle. Two general statements may be made: (1) *As long as the muscle stays in conditions of rest or low activity, early stages of radiation damage remain concealed, whereas they rapidly become evident when high performance is demanded.* This statement is based on the experimental findings that (a) the development of fatigue and contracture is accelerated in irradiated muscle when load and/or frequency of stimulation are increased; (b) that the difference in the length-force diagrams of irradiated and control muscles is significantly more pronounced in the higher than in the lower load range; and (c) that throughout the first 8 hours following exposure the rabbit is able to keep the foot of the irradiated leg in normal position while in rest or slowly moving, whereas severe impairment is manifested during motion. (2) *After cessation of radiation the damage to the muscle progresses spontaneously.* This statement is based on the experimental findings that during the postradiation period, the work capacity decreases (3), the distortion of the length-force diagram becomes accentuated, the gross morphologic alterations progress (3), the histologic lesions appear (see Table I), and the muscle force of the rabbit's irradiated leg gradually declines (see Table IV).

In addition to these two statements, the facts may be emphasized that latent period and rise time of the muscle twitch are not obviously affected in contrast to the markedly prolonged relaxation time, and that muscles isolated from frogs in poor physiologic condition are more sensitive to irradiation than those obtained from animals in excellent health. These observations together strongly point in the direction of muscle metabolism as primarily attacked.

The assumption may be made that because of irradiation the muscle loses its faculty to form that substance which is capable of supplying the chemical energy for contraction. Then, the time throughout which the muscle is able to function will depend on (1) the amount of energy-supplying material stored, (2) the mechanical work performed, and (3) the rate of metabolism during rest. The sensitivity of muscles from weak animals may be explained by the first general statement, given above. The influence of load and frequency of stimulation is explained by the second. The progressive nature of the process is explained by the third, since the resting metabolism finally will exhaust the energy store and, thereby, uncover the damage. It may be significant that contractility and adenosinetriphosphate (ATP) concentration of the muscle parallel each other and that a decrease in the amount of ATP causes fatigue, contracture, or rigor (6, p. 26).

SUMMARY

Comparative studies of x-radiation effects on both isolated cold blooded (frog) and intact warm blooded (rabbit) muscles were performed. Frog muscles irradiated with doses above 50 kr showed early fatigue, contracture, prolongation of relaxation time, decreased contraction amplitude for heavy loads, and histologic changes noticeable 8 hours after exposure. Rabbit muscles exposed to 72 kr exhibited a gradually progressing impairment of function. Complete abolition of function was reached within 24 hours following irradiation and was accompanied by severe histologic alterations.

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