Studies on Vital Reaction to the Systemic Hypothermia.

—Histopathological Changes of the Heart.
(Report 2)

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INTRODUCTION

In the previous paper, prolonged hypothermias at various temperatures were pursued pathohistologically, comparing the process of myocardial changes caused by the length of survival time. And the author obtained a few results. In the hypothermic study, it is not sufficient to observe the systemic hypothermia only from the viewpoint of the lower limit of the body temperature. If hypothermic anesthesia is practically applied to clinical surgery, prolongation of hypothermic duration may be required. For these reasons, the subject of hypothermic duration should be fixed the attention and followed up. However, such experiments were a few. Pertinent knowledges on comparing hypothermic duration with the length of survival have not been obtained fully.

In the present experiment, observation on the cooling condition at 15°C of rectal temperature was performed, because at this temperature myocardial necrosis occurred at first in the previous experiment. And myocardial changes at various hypothermic durations within 2 hours were investigated histologically in accordance with the length of survival.

MATERIALS AND METHODS

Materials used were healthy albino rats (170–200g), which were kept on the similar circumstances in the previous experiment. By means of the similar cooling and rewarming methods to the previous one, rats were cooled down to 15°C, and then maintained continuously for the duration as following 3 groups.

1) No duration of cooling of 15°C.
2) One hour duration.
3) Two hours duration.

These rats were sacrificed at regular intervals, varying from immediately after cooling to five days after rewarming, as follows; a) Immediately after cooling, b) Immediately after rewarming, c) Twenty four hours after rewarming, d)

Forty eight hours after rewarming, e) Three days after rewarming, f) Five days after rewarming. Their hearts were extirpated to examine histologically in detail. The material of the heart was fixed in 10% formalin, sectioned, and submitted to a battery of stains, i. e., hematoxylin and eosin, Van Gieson, and Azan staining.

RESULTS

The first group

In rats sacrificed immediately after cooling, so-called eosinophilic degeneration in the myofibers was seen with greater frequency in the subendocardial muscle layer, and was observed often in groups of fibers. The degree of such a degeneration was moderately noted. But, in the other layer of the myocardial wall, this degeneration was slightly revealed. Moreover, the thinning of sarcoplasma and edematous swelling of myofibers were moderately revealed in the subendo-epicardial muscle layers. And vacuolization in the muscle fibers was seen slightly in the subendocardial muscle layer. In addition to these myocardial degenerations, the disappearance of cross striations, fragmentatio myocardii, and pyknosis of nuclei were scattered in each layer of the myocardium. Blood vessels in the myocardium were strongly dilated, and were congestive. In occasional cases, the subendocardial hemorrhage was noted. In the rats sacrificed immediately after rewarming, myocardial changes somewhat increased generally, and circulatory disturbance developed further. However, in 24–48 hours after rewarming, myocardial degenerations, such as so-called eosinophilic degeneration, thinning of sarcoplasma, edematous swelling and pyknosis of nuclei in muscle fibers increased progressively in the subendo-epicardial muscle layers.

Vacuolization was also found slightly in the subendo-epicardial layers. Moreover, even a few necrotic fibers could be occasionally detected in the subenocardial muscle layer. In contrasts, the dilatation of the blood vessels showed slight decrease. In 3 days, these myocardial degenerations showed strongly declining tendency, and circulatory disturbance was hardly noted. In 5 days these myocardial degenerations were slightly restricted to the subendocardial muscle layer, circulatory disturbance was not evident.

The 2nd group

Myocardial degenerations observed immediately after cooling in this group, were almost similar, or somewhat intenser than those seen at the same condition in the first group. In occasional cases, necrotic fibers in small numbers were already revealed subendo-epicardially muscle layers, and occasionally those were surrounded with a few reactive cells. Dilatation of blood vessels and subendocardial hemorrhage were sometimes noted. By means of rewarming, these myocardial degenerations as well as circulatory disturbances showed slightly increasing

tendency. However, in 24 hours after rewarming, the myocardial degenerations, i. e., edematous swelling, thinning of sarcoplasm, vacuolization, and pyknosis of nuclei became increasingly apparent in the subendo-epicardial muscle layers. Moreover, so-called eosinophilic degeneration was found in each layer, especially in the subendocardial muscle layer. And it was occasionally found massively. Myocardial necrosis also increased progressively in number and size. Therefore, the focal necroses were seen scatteringly in the myocardial wall. At this affected areas, the intense cellular reaction occurred, and showed focal appearance. The focus of the cellular reaction consisted of the infiltrating cells, mainly, lymphocytes, monocytes, and a few neutrophilic cells, and sometimes, moreover this reaction was composed of proliferated endothelial cells, Anitschkow's cell and myogenic cells as described in the previous papers.

In contrasts, congestive dilatation of the blood vessels showed slightly declining tendency. In 48 hours, these myocardial changes were almost similar, or somewhat intenser than those observed in 24 hours after rewarming. In 3 days however, these myocardial changes showed remarkably declining tendency in general. Consequently, so-called eosinophilic degeneration, swelling, thinning of sarcoplasm in the muscle fibers were slightly remained in the subendocardial muscle layer. On the other hand, the myocardial necrosis was not seen in group of fibers, but were seen only in single fibers. The cellular reaction became poorer in numbers. Therefore, a few cells located only surrounding the necrotic muscle fibers. In 5 days, these changes remained slightly on the gradual decrease.

The 3rd group

The myocardial degenerations recognized immediately after cooling in this group, were somewhat intenser than those seen at the same condition in the 2nd group. Namely, so-called eosinophilic degeneration, thinning of sarcoplasm, edematous swelling, vacuolization, and pyknosis of nuclei in the muscle fibers were moderately revealed in each myocardial layer. But these changes were seen layers with greater frequency, especially in the subendo-epicardial muscle. Among these degenerations, so-called eosinophilic degeneration was prominent in subendocardium, and occurred massively.

Moreover, the occurrences of necrosis in single fibers were noted in the subendocardial muscle layer. Marked dilatation and congestion of blood vessels were observed. Even hemorrhage was found. At the termination of rewarming, these myocardial changes were revealed somewhat on the increase. In occasional cases, necrosis was observed in groups of fibers. In 24 hours after rewarming, the myocardial degenerations and the necrosis with concomitant cellular reaction were remarkably increased, not only in the subendo-epicardial muscle layers, but also in the middle layer of the myocardium. The constituents of the cel-

lular reaction were similar to the cells recognized in the 2nd group.

In 48 hours, these myocardial changes were somewhat increased, and became remarkable. But, in 3 days, myocardial degenerations and necrosis showed moderately the declining tendency. The myocardial necrosis was no longer revealed in group of fibers, but only in single fibers. Therefore, the cellular reaction was slightly observed only surrounding the necrotic fibers. In 5 days, the myocardial changes in general were slightly decreased.

DISCUSSION AND SUMMARY

In the previous paper, the pathohistological study of the heart was performed in order to elucidate the lower limit of the body temperature in the prolonged hypothermia. Consequently the author obtained a little knowledge as described as follows; In rats sacrificed immediately after cooling for 3 hours at 15°C of rectal temperature, necroses were only seen in a few myofibers, but myocardial degenerations were moderately revealed. However, in 24 to 48 hours after rewarming, the myocardial degenerations and necrosis were strongly increased, and became remarkably apparent. Therefore, foci of myocardial necrosis with concomitant intense cellular reaction were seen scatteringly in the myocardial wall. Thereafter, since 3 days after rewarming, these myocardial changes were decreased in accordance with the length of survival time. On the contrary, in rats maintained during 3 hours at 20°C or above, no such necroses were revealed, even in 24 to 48 hours after rewarming. But myocardial degenerations were moderately demonstrated. Then, the present study was undertaken to elucidate the limit of prolongated hypothermia, in view of pathology of the heart. And the findings observed in this experiment were summarized as follows. In rats sacrificed immediately after cooling in the 1st group, there were the myocardial degenerations, such as so-called eosinophilic degeneration, edematous swelling, thinning of sarcoplasma, etc. in the subendo-epicardial muscle layers.

Particularly, the so-called eosinophilic degeneration in muscle fibers was massively seen in the subendocardial muscle layer. In 24 to 48 hours after rewarming, these myocardial changes became increasingly apparent, and for the first time, even a few necrotic muscle fibers were detected in the subendocardial muscle layer. And in 3 to 5 days, these myocardial changes were strongly decreased. The necrotic muscle fibers appeared no longer anywhere. Though dilatation and congestion of blood vessels were strongly noted in the cases sacrificed immediately after cooling or rewarming, these changes showed declining tendency since 24 hours after rewarming.

In rats maintained for one hour at 15°C, myocardial changes seen immediately after cooling, were revealed relatively severer than those seen in rats sacrificed immediately after cooling of 15°C in the 1st group. Moreover, a few necrotic

muscle fibers were scatteringly observed in the subendocardium only. However, in 24 to 48 hours, myocardial degenerations and necrosis were increased progressively and intensely. Foci of necrosis extended to any portions of the myocardial wall. The necrotic focus was replaced by the reactive cells. The cellular reaction was similar to those observed in the cases maintained for 3 hours at 15°C, and consisted of the infiltrating cells, mainly, lymphocytes, monocytes, and neutrophilic leucocytes and proliferations of Anitshkow's cells, endothelial cells and myogenic cells. But, in 3 to 5 days, the occurrences of degeneration and necrosis were markedly decreased. Thereafter, no sign of necrosis was noted in groups of fibers, but it occurred in single fibers. And a necrotic fiber was occasionally surrounded by a few reactive cells. In rats maintained for 2 hours at 15°C, at the survival times, varying from immediately after cooling to 5 days after rewarming, myocardial changes were almost similar, or somewhat severer than those maintained for 1 hour at 15°C. Therefore, the author points out the following views, from the present findings as described above and the previous observations; generally myocardial changes seen immediately after cooling, did not show a significant difference in the influences due to the hypothermic duration within 3 hours at least. The pathohistological apparances due to the influences of hypothermic duration, however, became apparently distinct in signs of myocardial necrosis, in accordance with the length of survival time. Namely, in rats sacrificed immediately after cooling for 1 to 2 hours at 15°C, myocardial necroses were so small in number that necroses did not appear as focus. However, in 24 to 48 hours after rewarming, necrotic foci with concomitant intense cellular reaction were seen apparently in the myocardial wall. Whereas, in the 1st group rats, necroses were only revealed in a few fibers, even in 24 to 48 hours after rewarming. So, large necrotic focus was never seen at any intervals of survival after rewarming. In the earlier reports on the duration of hypothermia. Sarajas[17] demonstrated that in dogs sacrificed immediately after hypothermic duration for one hour or two hours at 21–22.5 °C, necrotic muscle fibers were observed, and these were occasionally surrounded with lymphocyte-like cells and a few mesenchymal cells. And then, in 5 to 7 days after rewarming, at first the small focus of necrosis was seen in the myocardium. The affected area was replaced by the reactive cells, such as mesenchymal cells, etc.. Hayashi[19] reported that the myocardial necrosis and subsequent cellular reaction were detected neither in dogs maintained for 1 hour at 25°C, nor for 2 hours. But, he found that in dogs sacrificed in 14 days after hypothermic duration for 1 hour at 25°C, there were pyknosis of the nuclei, myofibers stained poorly or hardly, and vacuolization in muscle fibers of the interventricular septum, in addition to the slight hyperemia or congestion in the interstitial tissues, and that in dogs sacrificed in 14 days after hypothermic duration for 2 hours at 25°C, swelling, vacuolization, and cloudy swelling in

the heart muscle fibers were noted apparently. And he described that in dogs sacrificed in 18 days after cooling for 1 hour at 20°C, the sign of calcification was scatteringly observed in the affected areas throughout the myocardium, except myocardial degenerations as mentioned above.

These changes were inclined to appear near the blood vessels in the interstitial tissues. According to Omori et al's report,[9] in dogs sacrificed immediately after cooling of 20°C, besides circulatory disturbances, such as hyperemia or congestion, even subendocardial hemorrhage was revealed. Moreover, pyknosis of the nuclei, vacuolization of cytoplasm, and edema of the interstitial tissue were frequently seen in the subendocardial muscle layer. These myocardial changes were increased by means of rewarming. The fact that damage of the heart becomes mere or less severe by means of rewarming, was substantiated by the recent study of Kawano.[10] The author also confirmed that myocardial change and circulatory disturbance became increasingly distinct by rewaming. However, the assumptions as mentioned in the previous paper, that histological changes of the heart in the hypothermia result from cooling process, could be admitted in the present experiment, too. In connection with hypothermia, Okuchi[33] studied histologically on dogs and rabbits frozen to death. The temperature of the death from cold was wide range between 14°C to 21°C, and the cooling duration extended from 2 to 5 hours. The histological appearances showed swelling, irregular staining, disappearance of cross striation, and vacuole formation in the heart muscle fibers, in addition to the passive congestion and slight hemorrhage in the interstitial tissues. Nagashima et al[34] reported that functional disturbances of the vital organs after cooling at 26°C or so, could be experimentally recovered by rewarming. However, at cooling of 16°C or so, the intense circulatory disturbances and parenchymal damages, accompanying with the inflammatory cell infiltration appeared in the myocardium, and consequently these findings led to the irreversible changes extending over several days. The author's results and the earlier observations as described above, tended to substantiate the assumption that the myocardial necrosis was prone to occur with greater frequency and degree, after passage of a certain time following hypothermia for 1 hour or over at 15°C, and the resultant changes might cause fatal cardiac failure. And these pathological changes of the heart are of more significance for the explanation of the post-hypothermic or so-called rewarming death.

However, Watanabe et al[35, 36, 37] reported that despite of cardiac arrest for 120 minutes in deep hypothermic condition (14°C to 16°C), the dogs could survive for long periods after rewarming. Their histological changes of the heart were so mild, that any changes were not detected except basophilic degeneration. The author thought that in case of hypothermia, especially cooled down at 15°C, it was desirable to rewarm the rat as immediately as possible after hypothermia,

and it had to be fixed attention not to prolong the hypothermic duration more than 1 hour. The present study pointed out that even if functional disorders of the heart were never revealed during the hypothermic anesthesia, the heart should be taken care for longer periods after hypothermia.

CONCLUSION

In order to study the influences of hypothermic duration to the vital organ, myocardial changes in rats maintained for various hypothermic durations at 15°C, were studied pathohistologically in accordance with the length of survival time after rewarming. And the present study obtained were the following conclusions:

1) The case of hypothermia at 15°C without duration of cooling. (the 1st group): In rats sacrificed immediately after cooling, myocardial degenerations were slightly revealed in the subendo-epicardial muscle layers. But, myocardial necrosis was not observed yet. Generally, these degenerations were moderately developed in 24–48 hours after rewarming. Moreover, at this time necrosis was detected in single fibers. But, since 3 days after rewarming, these myocardial changes showed decreasing tendency. Myocardial necrosis was no longer revealed.

2) Myocardial degenerations as mentioned above, included so-called eosinophilic degeneration, thinning of sarcoplasma, edematous swelling, vacuolization, and pyknosis of nuclei in the myofiber.

3) In the cases sacrificed immediately after hypothermia at 15°C for 1 or 2 hours duration, the case maintained for 2 hours showed the similar or relatively severer myocardial changes than those observed in the case maintained for 1 hour. Then, these myocardial changes consisted mainly of degeneration in the myofibers, and necrotic change of myofibers was scarcely visible.

4) These myocardial neceosis was increased strongly in 24–48 hours after rewarming. Consequently necrosis appeared focally in the myocardium. Then, in the focus, intense cell reaction was observed. In 3 days, the necrotic foci with concomitant cellular reaction were decreased markedly.

5) In the cases of hypothermia at 15°C for various hypothermic durations, circulatory disturbances, such as dilatation and congestion of the blood vessels were strongly seen. And even subendocardial hemorrhage was revealed.

These changes showed slightly increasing tendecy in accordance with hypothermic duration.

6) In the cases immediately rewarmed after cooling of 15°C without hypothermic duration, myocardial changes could be recovered reversibly with the passage of time. On the contrary, in the cases that hypothermic duration was kept for 1 hour or more, myocardial damages were difficult to recover, and

remained longer thereafter.

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Table 1.

Duration of cooling of 15°C	Time of sacrifice	No. / Change	So-called eosinophilic degeneration	Thinning of sarcoplasma	Edematous swelling	Vacuolization	Necrosis	Fragmentatio myocardii	Loss of cross striation	Cellular reaction	Dilatation of blood vessel	Bleeding	Proliferation of granulation tissue	Edema of the interstitium	Degeneration of nucleus
Immediately rewarmed without duration	immediately after cooling of 15°C	37	++	+	+	−	−	±	±	−	++	−	−	±	+
		36	+	±	±	−	−	−	±	−	+++	−	−	−	+
		64	±	±	+	−	−	−	−	−	+++	−	−	−	±
	immediately after rewarming	14	+	±	+	−	−	−	−	−	+++	±	−	−	±
		62	+	±	±	−	−	−	−	−	++	−	−	−	±
		65	+	±	+	±	−	−	±	−	++	−	−	−	±
	24 hours after rewarming	95	++	±	+	−	−	±	±	−	+	−	−	±	+
		96	±	+	+	−	−	−	±	−	+	±	−	±	+
	48 hours after rewarming	71	+	±	±	−	−	±	±	−	+	−	−	−	±
		83	+	+	+	−	−	−	±	−	±	−	−	−	+
		85	++	±	++	−	±	±	+	±	±	−	−	±	±
	3 days after rewarming	97	−	±	±	−	−	±	±	−	±	−	−	−	±
		100	±	+	++	−	−	±	−	−	−	−	−	±	−
	5 days after rewarming	98	−	±	+	−	−	−	−	−	±	−	−	−	−
		99	±	+	−	±	−	±	±	−	−	−	−	−	−
One hour	immediately after cooling of 15°C	52	++	±	++	±	±	±	−	−	++	±	−	±	+
		61	+	±	+	−	−	±	±	±	++	−	−	−	±
		63	+	±	±	−	±	−	±	−	+++	−	−	−	−
	immediately after rewarming	12	+	+	±	−	−	−	+	±	++	−	−	−	±
		58	++	+	+	−	±	−	+	±	+++	±	−	−	+
		60	+	+	+	−	+	−	±	−	+++	±	−	±	+
	24 hours after rewarming	40	++	±	+	±	+	−	+	+	++	±	−	−	++
		72	+++	±	++	±	++	±	+	+	+	−	−	±	++
	48 hours after rewarming	73	++	+	++	−	+	±	±	±	±	−	−	±	+
		21	++	±	+++	±	−	−	+	++	−	−	±	±	+
	3 days after rewarming	45	±	+	±	−	±	±	+	±	−	−	−	−	−
		46	+	±	++	±	−	±	±	−	−	−	−	−	±
	5 days after rewarming	93	±	±	±	±	−	−	±	−	−	−	−	−	−
		94	+	+	±	−	±	±	+	±	−	−	−	−	±

Table 2.

Duration of cooling of 15°C	Time of sacrifice	No. \ Change	So-called eosinophilic degeneration	Thinning of sarcoplasma	Edematous swelling	Vacuolization	Necrosis	Fragmentatio myocardii	Loss of cross striation	Cellular reaction	Dilatation of blood vessel	Bleeding	Proliferation of granulation tissue	Edema of the interstitium	Degeneration of nucleus
Two hours	immediately after cooling of 15°C	5	+	±	+	−	−	±	−	−	++	−	−	−	++
		18	++	±	++	−	±	−	±	±	++	±	−	±	±
		1	+	+	+	−	±	−	±	−	++	−	−	±	+
	immediately after rewarming	44	++	±	++	±	±	−	±	−	+++	±	−	±	+
		47	+	+	+	−	±	±	−	±	++	−	−	−	+
		48	±	±	+	−	−	−	±	−	++	−	−	−	+
	24 hours after rewarming	28	++	+	++	±	++	−	±	+	+	±	−	+	++
		31	+	±	++	−	+	−	±	+	+	−	−	±	+
		32	+	−	+	−	+	−	±	±	+	−	−	−	++
	48 hours after rewarming	74	+++	±	++	±	++	±	±	±	+	−	±	+	++
		25	+	±	++	±	++	±	−	±	±	±	−	±	++
		50	++	±	++	−	±	−	±	+	+	−	−	+	++
	3 days after rewarming	23	+	±	+	±	±	±	±	±	±	−	−	±	+
		26	+	+	+	−	±	−	−	±	±	−	±	−	++
	5 days after rewarming	30	±	±	±	−	−	±	−	−	−	−	±	−	+
		76	−	−	±	±	±	±	−	±	±	−	−	−	±

EXPLANATION OF PLATES

PLATE 1

Fig. 1. Remarkable cellular reaction at the focal myocardial necrosis in the subepicardium. 48 hours after hypothermia for 2 hours duration at 15°C.

Fig. 2. Cellular reaction at the small necrotic area in the subendocardium. 24 hours after hypothermia for 2 hours duration at 15°C.

Fig. 3. Cellular reaction at the necrotic area in the subendocardium, and edematous swelling of myofibers around the necrotic area. 48 hours after hypothermia for 1 hour duration at 15°C.

Fig. 4. Slight cellular reaction surrounding one or two necrotic fibers. 48 hours after hypothermia without hypothermic duration at 15°C.

Fig. 5. So-called eosinophilic degeneration (↑) of myofibers and congestive dilatation of blood ressel. Immediately after cooling for 1 hour duration at 15°C.

Fig. 6. Congestion in the middle layer of myocardium. Immediately after cooling for 1 hour duration at 15°C.

PLATE 1

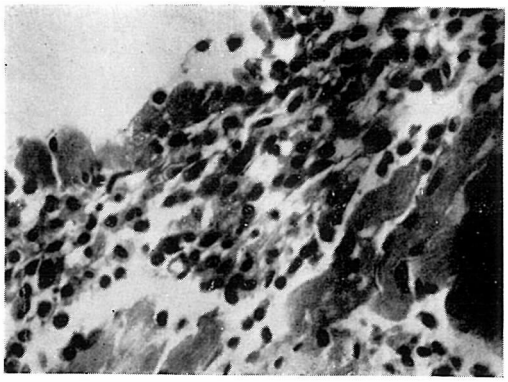

Fig. 1.

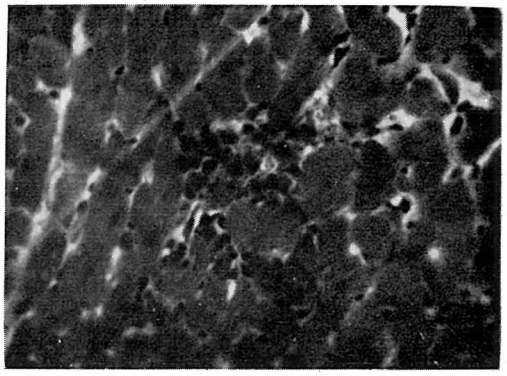

Fig. 2.

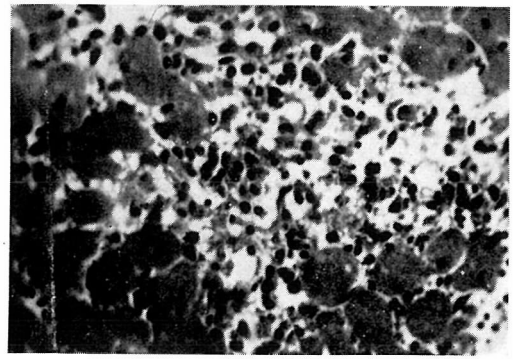

Fig. 3.

Fig. 4.

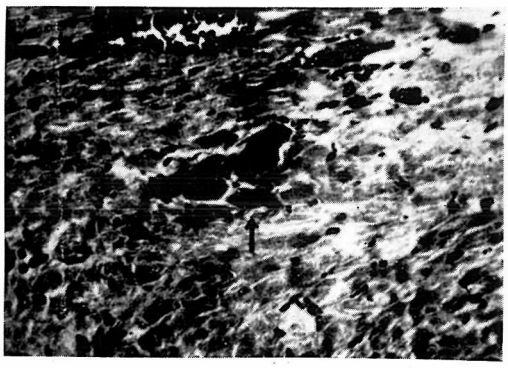

Fig. 5.

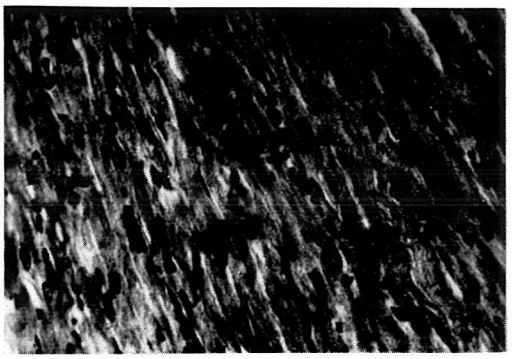

Fig. 6.