# ON THE EFFECT OF PROLONGED NOCICEPTIVE (PAIN) STIMULI ON THE HEATING OF EXPERIMENTAL CUTANEOUS WOUNDS

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It has been conclusively shown in numerous investigations that nociceptive stimuli cause significant changes in the vital activities of animals and man [2, 3]. In particular, they influence the intensity of the reparative process.

Since nociceptive stimuli are usually accompanied by injury to the cutaneous coverings, we considered it of unquestionable interest to investigate the effect of these stimuli on healing of cutaneous wounds. However, despite the theoretical and practical significance of this line of investigation, we were almost unable to find any works in the literature on this question.

L. Yu. Sozon-Yaroshevich and L. O. Zeval'd [5], in experiments on rabbits, established that prolonged stimulation of the central end of the sciatic nerve (suturing it to muscles) leads to slowing of wound healing on the side of stimulation. Prolongation of the cutaneous wound healing periods (skin, subcutaneous tissue, fascia) was noted by N. I. But [1] in experiments on rabbits and guinea pigs, wherein the circumference of the wound was stimulated every day for 10-15 min by scratching with pins.

These works presented only general data pertaining to the inhibition of the healing of experimental wounds under the influence of nociceptive stimuli. The purpose of this work was to study the dynamics of the actual process of healing during prolonged nociceptive stimulation.

## EXPERIMENTAL METHODS

The investigation was performed on white rats, equally distributed in the experimental and control groups according to weight (135-170 grams), age, and sex. We carried out 2 series of experiments on 80 rats. The I series of experiments was performed in two intervals: in the summer (May) and winter (October) months, with stimulation of both sciatic nerves; in the II series of experiments (40 rats), we stimulated the sciatic nerve only on one side (right). In each series, half the animals were controls.

Cutaneous wounds were inflicted on all the animals, as close to the same depth and size as possible (two each, symmetrically placed on each side of the backbone), approximately 2 $cm^2$ in area. The area of the wound was measured immediately after the operation, and then daily up until complete healing. The contours of the wound were applied to sterile wax paper; the area which they bounded was measured with the aid of graph paper.

The prolonged nociceptive stimulation was created immediately after application of the wounds, by the method which we described earlier [4]. Following formation of a focus of prolonged nociceptive stimulation, the behavior of the animals changed markedly: without exception, all the rats were scarcely mobile and inadequately clean for a long time; a portion of the animals manifested aggressiveness.

The obtained data was analyzed statistically.

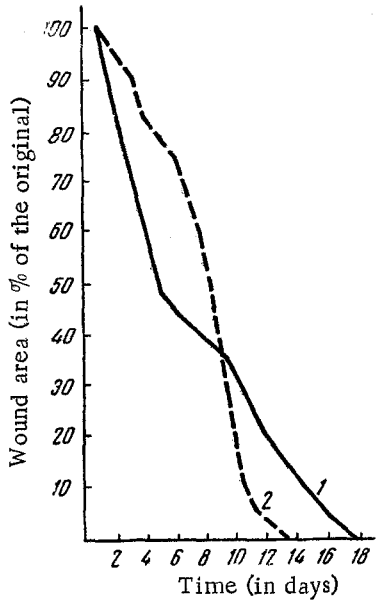


Fig. 1. Dynamics of cutaneous wound healing in rats with the action of prolonged nociceptive stimulation. Summer group. 1) Experimental; 2) control.

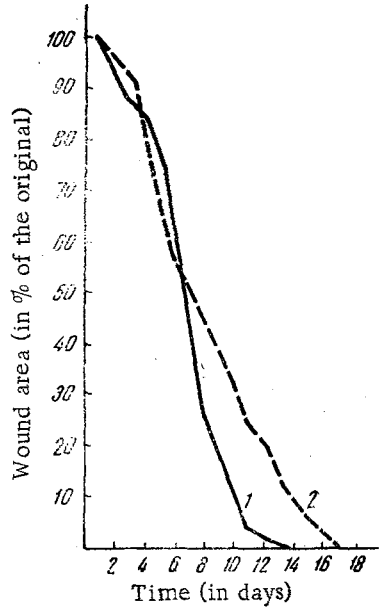


Fig. 3. Dynamics of cutaneous wound healing in rats with prolonged nociceptive stimulation of the right sciatic nerve. 1) Right side; 2) left side.

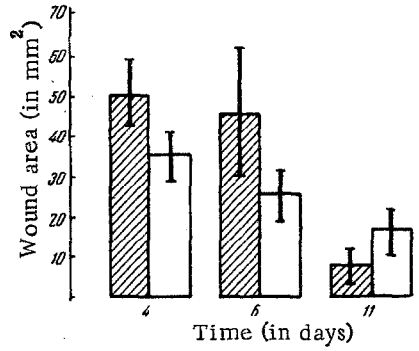


Fig. 2. Cutaneous wound healing in rat with the action of prolonged nociceptive stimulation in experimental (cross-hatched columns) and control (light columns) groups (with the error limits shown). The size of the area of one wound is shown (M ± m; ± c).

## EXPERIMENTAL RESULTS

The results of the investigation are presented in Figs. 1, 2, and 3. In both series of experiments the rate of wound healing differed between the experimental and control rats. In the summer period, wound healing in the experimental animals during the first 6 days proceeded much more intensely than in the rats that had no focus of nociceptive stimulation. Thus, on the 4th day after the operation, the wound area in the experimental animals had decreased by 37% of the starting measurement (from 2280 to 1436.4 mm$^2$), while in the control animals – by a total of 18% (from 2230 to 2035.2 mm$^2$). The same relations were observed on the 6th day: the wound area in the experimental animals had decreased by 56% (from 2280 to 1040 mm$^2$), while in the control animals – by 24% (from 2260 to 1840 mm$^2$). The picture of cutaneous wound healing was also analogous in the group of rats investigated in the winter period, except that the accelerated wound healing in the experimental animals lasted for a period of 8 days after the operation.

After 6 days in the summer group, and after 8 days in the winter group, the picture changes: the rate of wound healing in the control rats rises, and in the experimental animals, decreases. On the 9th day in the summer group, and on the 11th day in the winter group of rats, we observed equalizing of the wound area in the control and experimental animals: at this time the wound area in the summer group had decreased by 63% and in the winter group – by 58% of the original size. After this we observed a marked lag in the cutaneous wound healing of the experimental group of rats as compared with the control, which lasted for the entire subsequent period of the investigation, up to complete epithelization. Thus, on the 11th day after

the operation, the wound area in the control animals of the summer group had decreased to 280 $mm^2$ (by 93% of the original measurement), while in the experimental animals – to 560 $mm^2$ (by 75%). In the summer group of experimental animals, complete wound healing occurred on the 18th day, while in the controls – on the 13th day after the operation. In the winter group of animals, healing of the wounds was observed respectively on the 21st and 15th days after the operation. In general, the period of cutaneous wound healing in the rats that were subjected to prolonged nociceptive stimulation was extended by 5-7 days.

Statistical analysis of the experimental results showed that the observed effect was statistically significant (see Fig. 2).

Therefore, prolonged nociceptive stimulation doubtlessly inhibits cutaneous wound healing, but its influence is accomplished biphasically: initially it stimulates wound healing, and then, at later intervals, it retards and inhibits healing.

The purpose of the II series of experiments was to resolve the question of cutaneous wound healing intervals in the rats on the same side as the stimulation and on the symmetrical side. With this goal, wounds were inflicted on 20 rats, in the same fashion as all the others, but the focus of prolonged nociceptive stimulation was established on the right posterior extremity; 20 rats served as controls.

Figure 3 shows that in the first 6 days after the operation the rate of wound healing on the right (on the side of stimulation) and on the left differed little, although we did observe a certain tendency toward inhibition of wound healing on the side of stimulation during the first 2 days. The initial tendency toward retarded wound healing on the right side that arose subsequently became still more manifest, and was then retained up to complete healing of the wounds. Statistical analysis of the obtained data showed this difference to be significant. Complete healing of the wounds on the right side was observed on the 17th day, and on the opposite side – on the 14th day, after the operation. In the rats of the control group, as in the case of the I series of experiments, wound healing was recorded on the 12th day after the operation.

Thus, prolonged nociceptive stimulation does not exert a marked influence on wound healing in the first few days, but subsequently leads to its slowing on the side of the stimulation.

The biphasic character of the cutaneous wound healing following the formation of a focus of prolonged nociceptive stimulation may be explained by the fact that in the first period after formation of this focus the defense mechanisms of the organism are mobilized and the nociceptive stimuli exert a stimulatory action. As the constant irritation continues, however, this influence, at the later intervals, begins to convert to an inhibitory, retarding, action. Apparently, this is manifested in the wound healing characteristics under the conditions of our experiments. We do not have direct proof of the correctness of this hypothesis, but the biphasic character which we observed seems extremely interesting and important to us. Subsequent investigations should be devoted to a detailed analysis of this fact.

## SUMMARY

A study was made of the effect produced by prolonged nociceptive (pain) stimulation on healing of cutaneous wounds in rats. In the first experimental series, carried out during the summer and winter months, prolonged stimulation of both sciatic nerves was applied (40 rats), whereas in the second series, the sciatic nerve was stimulated only on one side (40 rats). Half of the animals in both series served as the control. As demonstrated, wound healing was biphasic: during the first 6-8 days, prolonged nociceptive stimulation stimulated wound healing, whereas at a later period, it inhibited it. Wound healing occurred 5 to 7 days earlier in control rats than in the experimental animals. Asymmetry in healing of the skin wounds was observed: the wounds healed 48 h later on the side of the stimulation.

## LITERATURE CITED

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