# THE REGULATION OF CELL DIVISION IN EPITHELIAL TISSUE IN PROCESS OF REGENERATION*

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We know that the nervous system plays an important part in regulation of the metabolism of the body, and hence in regulation of the main vital activities of the tissues.

Several workers have shown a relationship between cell division and the functional state of the nervous system [1-8, 10]. Many facts have been accumulated in G. S. Strelin's laboratory, demonstrating a fall in the mitotic activity of cells during excitation of the nervous system. It has been proved experimentally that the reactive inhibition of cell division during painful stimulation is effected through the neurohumoral system, and that a leading part in this process is played by adrenalin which prevents the cell from taking part in mitosis [5-7]. The majority of investigations so far carried out have been devoted to the study of the influence of the functional state of the nervous system on the mitotic activity of cells undergoing physiological regeneration. The relationship between cell division and the functional state of the nervous system during reparative regeneration has not been the subject of special investigation.

The aim of our research was to study the reactive changes in cell division in a focus of regeneration during painful stimulation of an animal by an electric current.

## EXPERIMENTAL METHOD

Experiments were carried out on 66 adult male rats. An injury to the dorsal surface of the tongue was inflicted on the animals by means of a red-hot wire, 5 mm in diameter. The mitotic activity of different areas of a focus of regeneration is known to change in the course of healing [9]. Reactive inhibition of cell division was therefore investigated in our experiments on the 2nd, 4th and 10th days of repair. The rats were subjected to stimulation by an electric current (8-10 v) for 30 minutes, after which they were killed at once. The material was fixed in Bouin's fluid. Vertical sections of the tongue were prepared, 14 $\mu$ in thickness, and stained with hematoxylin by Carazzi's method. Control animals were not exposed to the electric current. The number of mitoses in 100 fields of vision was counted in the following areas: in the area of regeneration, in the immediate vicinity of the wound, some distance from it, and also on the ventral surface of the tongue. We took as normal the number of mitoses in control animals in an area some distance from the wound, since the number of mitoses in such areas agreed with the number of dividing cells in an analagous area of the undamaged tongue.

## EXPERIMENTAL RESULTS

The distribution of mitoses in the region of the wound, in the control and experimental animals, at all stages of regeneration observed, is shown in the Figure. The curve give the mean values. On the 2nd day 9 experimental and control animals were investigated, and on the 4th and 10th days, 12 animals.

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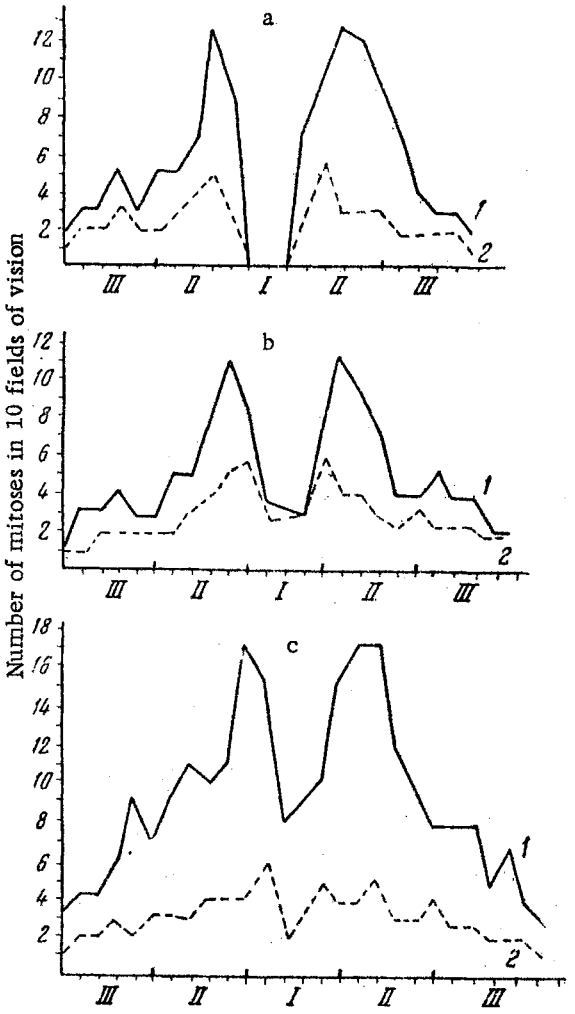


Fall in the mirotic activity of cells of the epithelium of the tongue in the region of the wound in response to stimulation on the 2nd, 4th and 10th days of regeneration.
1) In control animals; 2) in experimental animals; I) area of regeneration; II) area near the wound; III) area at some distance from the wound (each area was split up into smaller ones, corresponding to 10 fields of vision).

On the second day or regeneration (see Figure, 1a), the epithelial tissue of the tongue bordering on the edge of the wound, was wedge-shaped on section. The area of regeneration itself occupied 1-2 fields of vision. As seen from the figure, a characteristic feature of the control animals on the 2nd day was absence of mitoses in the regenerating tissue and an outburst of cell division in area II, closest to the site of injury. The number of cells undergoing division here was roughly 3 times greater than in area III, at some distance from the wound: whereas in this area the number of mitoses, with considerable fluctuation throughout the series, averaged 38.8, at the place of the outbreak their number rose to 95.5 on the average per 100 fields of vision. On the 4th day of regeneration (see figure, b) the mitotic activity of the cells in the area immediately next to the wound remained high – on the average 70.9 mitoses per 100 fields of vision, but at this period a large number of dividing cells appeared in the area of regeneration itself – to as many as 42 per 100 fields of vision. On the 10th day of repair (see figure, 1c ) high mitotic activity was shown by the cells of the area of regeneration (138 mitoses per 100 fields of vision on the average for the area), together with a high mitotic coefficient for the area around the wound.

At all the stages at which we studied the healing of the wound of the tongue, we thus observed around the injured area in the epithelium of the control animals an outburst of mitotic activity and an increase in the number of dividing cells in the area of regeneration.

When the animals were stimulated with an electric current on the 2nd, 4th and 10th day of regeneration (see figure, 2,a, b, c) in area II in the immediate vicinity of the wound a stronger suppression of mitotic activity was observed than in the more distant area III. This is clearly shown in the figure. On the 2nd day of healing, the number of dividing cells in the area around the wound (II) fell during stimulation on the average by 65.2%, whereas at a distance from the wound (area III) it fell by only 46%. When the rats were stimulated by the electric current on the 4th day of regeneration, the number of dividing cells around the would fell on the average by 58.6%, and at a distance from it, by 40%. Stimulation of the animals on the 10th day was accompanied by a fall in mitotic activity near the wound by 65.3% and at a distance from it, by 48.6%.

When the results of the experiments carried out at all three periods of regeneration were combined, then under the influence of electrical stimulation of the animals, the mitotic activity in the area next to the wound (II), characterized by maximum activity of cell division, fell on the average by 60.9%. In the area at some distance from the wound (III), the fall reached only 43.8% compared with the controls. The difference in the degree of suppression of mitotic activity (17%) was statistically significant.

The fall in mitotic activity in the area of regeneration itself was insignificant on the 4th day, when a quite large number of mitoses could be seen there (I), in contrast to the area II next to the wound, and it amounted to

only 10%. The difference observed here in the degree of suppression of mitotic activity in the area of regeneration and in the more distant area was 33%; this difference was statistically significant. The area of regeneration could be described at this period as are active for the reduction in cell division in its epithelium during stimulation was less marked than in normal conditions (area III).

Counts of the number of dividing cells on the ventral aspect of the tongue showed that here the normal mitotic activity was a lower in intensity than on the dorsal surface. When the animals were stimulated by the electric current, the reactive suppression of cell division on the ventral surface of the tongue was less marked than in the dorsal epithelium. A similar feature was observed by V. V. Kozlov [3] in the corneal epithelium in mice. In areas with a lower mitotic activity, as in our case, the inhibition of cell division during stimulation of the animals was relatively weak.

The results obtained showed that reactive inhibition of mitosis is shown more clearly in the epithelium around a wound, in which proliferative processes are enhanced, than in intact epithelium. In the epithelial layer creeping over the wound surface, on the other hand, reactive inhibition was almost absent. In regeneration after trauma, therefore, there is a change in the reactivity of the tissue to the factor regulating mitotic activity. A change in the reactivity of tumor tissues has been demonstrated by V. V. Kozlov [3] and L. A. Alov [1]. It must be emphasized, however, that in the case of a tumor this is purely a matter of a fall in the power of reactive inhibition of cell division. During regeneration the reactivity of the tissue may either fall or it may rise. Differences are found between regeneration and the growth of tumors so far as the integrating system of the body is concerned.

## SUMMARY

A burn was inflicted on rats on the dorsal surface of the tongue. Reactive inhibition of cellular division was examined on the 2nd, 4th and 10th day of regeneration in animals which were stimulated with electric current.

Reactive inhibiton of mitosis is more pronounced in the epithelium surrounding the wound (in which the proliferative processes are enhanced) than in intact epithelium.

Reactive inhibition, on the contrary, is almost absent in the epithelial layer, creeping over the wound surface.

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