# MITOTIC ACTIVITY OF THE REGENERATING RAT KIDNEY

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The greatest increase in mitotic activity in the regenerating kidney was observed in the region of the wedge of regenerating tissue formed in the remnant of the organ and in the adjacent zone of renal parenchyma. The increase in mitotic activity reaches similar heights in the zone of regenerating kidney distant from the wound and the zone of the kidney undergoing compensatory hypertrophy.

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Regeneration of the kidney is a complex process associated with changes both at the wound surface and at a distance from the site of injury. The view is widely held that regenerative processes in internal organs [2, 3, 5] and, in particular, in the kidney [4, 8-10] have the character of regeneration hypertrophy – a scar is formed on the wound surface and reactive changes are observed predominantly in the remnant of the organ, taking place more or less uniformly throughout its extent. One of the writers (F. Kh. Sh) [12], who shares this view, showed experimentally that mitotic activity is increased in the epithelium of the convoluted tubules of the remnant of the organ in rats after unilateral nephrectomy and simultaneous removal of $^1/_3$-$^1/_4$ of the second kidney. This increase was found on the second day after the beginning of the experiment, reached a maximum on the 5th day, and remained substantially higher than normal for 3 months.

Counting the number of mitoses separately along the wound surface and at a point distant from it subsequently showed [11] that a significant difference exists between the number of mitoses in these two zones only 2 days after injury. During this time the mitotic index (MI) in the zone of resection is almost twice as high as at a distance away from it.

Further investigations of regeneration in the resected rat kidney showed [1, 7] that as a result of trauma a wedge-shaped area of the renal parenchyma undergoes necrosis. The base of this wedge is the amputation surface, and its apex faces the papilla of the renal medulla. During the week after injury this wedge is gradually replaced by bands of dedifferentiated epithelium, presumably formed from surviving cells of the necrotic zone, mainly on account of the proximal ends of the ducts and collecting tubules of the medulla adjacent to the zone of necrosis. Next to the developing area of regeneration lies a zone of reactively changed renal tissue, easily distinguished because of the greatly dilated lumen of the tubules.

The object of this investigation was to study the mitotic activity of the regenerating kidney, taking the zones mentioned above into consideration. Accordingly, mitoses were counted in the cortex in the following zones separately: 1) in the regenerating wedge, 2) in the zone of reactively changed tubules next to the wedge, and 3) at a distance from the zone of regeneration.

## EXPERIMENTAL METHOD

Experiments were carried out on sexually mature male albino rats weighing 105-120 g, divided into three groups. The left kidney was removed and one-quarter of the right kidney resected from the animals of group 1 (84). Left-sided nephrectomy only was performed in group 2 (82). The rats (70) of group 3 were controls. All operations were performed between 10 a.m. and 12 noon. The experimental and control rats were sacrificed in batches of 10-14 at a time by decapitation 1, 2, 5, 10, 15, 30, and 60 days after the operation, always at about 12 noon.

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TABLE 1. Mitotic Activity of Rat Renal Cortex (in %)

| Time of investigation (in days) | After removal of left kidney and 1/4 of right | | | After removal of left kidney | Intact right kidney |
|---|---|---|---|---|---|
| | In zone of regeneration | Adjacent to zone of regeneration | Far away from regeneration | | |
| 1 | 0,64±0,13 | 0,79±0,14 | 0,70±0,17 | 1,44±0,07 | 0,71±0,04 |
| 2 | 1,78±0,17 | 2,87±0,31 | 2,18±0,17 | 3,38±0,20 | 0,72±0,04 |
| 5 | 4,23±0,56 | 5,74±0,43 | 3,09±0,24 | 1,93±0,14 | 0,77±0,04 |
| 10 | 5,48±0,48 | 4,95±0,32 | 3,01±0,16 | 1,67±0,008 | 0,73±0,03 |
| 15 | 4,04±0,15 | 2,76±0,24 | 1,63±0,14 | 1,36±0,07 | 0,82±0,04 |
| 30 | 2,29±0,21 | 1,39±0,17 | 1,02±0,07 | 1,08±0,05 | 0,74±0,03 |
| 60 | 1,74±0,12 | 0,92±0,03 | 0,82±0,05 | 0,90±0,04 | 0,69±0,02 |

The kidneys were fixed in 10% neutral formalin solution and embedded in paraffin wax. Sections 5 $\mu$ in thickness were stained with Ehrlich's hematoxylin and eosin. Statistical analysis of the results was carried out by Oivin's method [6] and differences were regarded as significant if the probability of random deviation (P) was less than 0.05.

## EXPERIMENTAL RESULTS

The results are given in Table 1, showing that MI for the control animals (sacrificed on various days during the autumn-winter period) is reasonably constant, with a variation for the cortex between 0.69 and 0.82%.

The values of MI in the animals of group 1 in the zone of regeneration after two days were almost 2.5 times higher than in the control, 5.5 times higher after 5 days, and reached a maximum after 10 days, when they were 7.5 times higher than the control. Differences at all times were statistically significant ($P < 0.01$). The mitotic activity began to decline two weeks after the operation, but even at this time MI for the experimental rats was 5 times higher than the control ($P < 0.02$). Later in the experiment a gradual decrease in MI took place, although it still remained significantly higher than the control, being 3 times greater after 30 days and 2.5 times greater after 60 days ($P < 0.02$ and $< 0.05$ respectively).

In the zone of renal parenchyma lying next to the regenerating tissue a sharp increase in mitotic activity took place 2 and, in particular, 5 days after trauma, when the value of MI reached a maximum, more than 7.5 times higher than the control ($P < 0.001$). At these two times MI was higher than in the regenerating tissue itself by 62.2 and 35.7% respectively. The difference is statistically significant ($P < 0.02$ and $< 0.05$). Later, however, MI in tissue adjoining the regenerating tissue gradually decreased and became smaller than in the regenerating wedge itself. After 30 days MI was still almost twice as high as in the control ($P < 0.05$). MI in tissue lying next to the regenerating wedge 60 days after the operation was lower than MI for the regenerating zone itself. This difference is statistically significant ($P < 0.02$).

Away from the zone of regeneration, MI was three times higher than in the control after 2 days, and almost 4 times higher after 5 days, when it reached its maximum, remaining at this level until 10 days. Differences from the control at these times are statistically significant ($P < 0.02$). A decrease in mitotic activity took place after the 15th day after operation. MI 30 days after trauma was 1.4 times higher than the control, the differences being statistically significant ($P < 0.05$). Differences from the control ceased to be statistically significant only after two months.

In the rats of group 2 undergoing left-sided nephrectomy, one day after operation MI for the renal cortex was twice as high as in the control ($P < 0.05$). After two days MI reached its maximum in the cortex and was 4.6 times higher than in the control ($P < 0.02$). On the 2nd and 5th day after operation MI showed a sharp decrease. By the 10th day MI had fallen to half its previous maximum value. At this time MI was only 2.3 times higher than in the control ($P < 0.02$). The decrease in mitotic activity continued, but MI 30 days after the operation was still higher than in the control by a statistically significant degree ($P < 0.05$).

Comparison of the dynamics of changes in mitotic activity in the various zones of the resected kidney showed that MI reached its highest level in the regenerating zone and in the comparatively narrow zone of renal parenchyma in direct contact with it. The maximum level of mitotic activity far away from the zone of regeneration, i.e., remote from the site of trauma, at some periods was considerably lower than in the regenerating zone and alongside it.

Comparison of mitotic activity in the resected kidney and in the kidney undergoing compensatory hypertrophy showed that in this respect the latter resembles most the zone of regenerating kidney far removed from the site of trauma. Mitotic activity in both these cases reached about the same level and the difference between MI for this zone and for the kidney undergoing compensatory hypertrophy was no longer statistically significant after the 15th day ($P > 0.05$). However, the increase in mitotic activity took place earlier in the kidney undergoing compensatory hypertrophy and reached its maximum sooner. On the other hand, a high level of mitotic activity persisted much longer in the resected kidney and in the zone far removed from the wound.

In the regenerating kidney the greatest increase in mitotic activity in response to trauma thus takes place in the region of formation of the wedge of regenerating tissue and in the adjacent zone of renal parenchyma.

The zone of regenerating kidney far removed from the wound and the kidney undergoing compensatory hypertrophy show the greatest resemblance in their maximum level of mitotic activity.

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