# MITOSES IN THE TUBULAR EPITHELIUM OF THE ALLOGRAFTED DOG'S KIDNEY IN THE EARLY STAGES AFTER TRANSPLANTATION

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Mitoses were found in the tubular epithelium of five of 23 allografted kidneys of mongrel dogs. They were located in the proximal (88 mitoses) and distal (21 mitoses) tubules. Among 29 dividing epithelial cells 3 and 5 days after the operation four pathological mitoses were found, whereas among 80 mitoses in kidneys present for 1 and 2 days in the body of the recipient no pathological mitoses were found. No mitoses likewise were found in the tubular epithelium of the kidneys of intact dogs.

KEY WORDS: dog's kidney; allografting; mitoses.

The question of proliferation of the tubular epithelium of the allografted kidney has received little attention in the literature. The writers showed previously [1, 2] that during the first month after allografting of the human cadaveric kidney mitoses appear in the epithelium of the proximal and distal portions of the nephrons, and their number may reach 100 or more per square centimeter area of section 5-7 μ thick. Attention was drawn to the delay of mitoses in metaphase observed in some cases and also to the appearance of pathological forms of division, especially of C mitoses.

This paper deals with the question of mitoses in the tubular epithelium of allografted dogs' kidneys in the early stages after transplantation.

## EXPERIMENTAL METHOD

Experiments were carried out on 23 mongrel dogs weighing 15-25 kg. Allografting of the kidney into the pelvis was performed by the usual method [3]. As a rule the right kidney was chosen for transplantation and its vessels were sutured end to end to the right iliac or caudal artery and to the right iliac vein of the recipient. The ureter of the transplanted kidney was exteriorized onto the skin. One of the recipient's kidneys was removed. The duration of warm ischemia was 15-20 min. The function of the grafted kidney was tested by the diuresis and the blood and urinary urea concentrations. The development of a rejection crisis was diagnosed by the presence of a change in the dynamics of the circulation in the kidney recorded by a thermoelectric method [5], by changes in kidney function [6], or in the level of chemiluminescence of the urine and blood [4]. At different stages of development of the rejection crisis the allografted kidney was removed and fixed in 10% neutral formalin. Different parts of the cortex and medulla were embedded in paraffin wax. Sections, 5-7 μ thick, were stained with hematoxylin—eosin, with picrofuchsin by Van Gieson's method, or by the PAS and Feulgen's reactions. Sections from the kidneys of intact dogs were used as the control.

## EXPERIMENTAL RESULTS

Morphological evidence of a rejection reaction was found in the allografted kidneys. Macroscopically there was an increase in the size and weight of the kidney, accompanied by

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TABLE 1. Mitoses in Tubular Epithelium of Alografted Dog Kidney

| Time after transplantation (in days) | Number of mitoses in three sections | Total number of mitoses | Phase of mitosis | | | |
|---|---|---|---|---|---|---|
| | | | P | M | A | T |
| 3 | 6, 4, 8 | 18 | 8 | 5 | 1 | 4 |
| 5 | 3, 3, 5 | 11 | 2 | 4 | 0 | 5 |
| 2 | 16, 27, 12 | 55 | 12 | 20 | 5 | 18 |
| 1 | 9, 8, 8 | 25 | 9 | 8 | 2 | 6 |

Legend. P) Prophase; M) metaphase; A) anaphase; T) telophase.

marked edema and severe congestion, so that the boundaries between the cortex and medulla were obliterated. Histologically, characteristic destructive changes in the wall of the arcuate and interlobular arteries were found: fibrinoid degeneration, destruction, and desquamation of the endothelial lining; severe edema of the intertubular connective tissue, a lymphohistiocytic reaction (lymphoid infiltration was particularly well marked in the juxtamedullary zone of the cortex). In 10 of 23 cases evidence of tubular necrosis of the cortex was found. In eight cases abundant round-cell infiltration masked the histological structure almost completely. In five cases, side by side with zones with clearly defined morphological evidence of a rejection reaction, extensive areas with an intact parenchyma and with structurally unchanged vessels were found in the graft. In these areas the malpighian corpuscles were normal in structure (straight capillary glomeruli, correct configuration of the lumen of Bowman's capsule, integrity of the juxtamedullary cell complexes). The epithelium of the proximal tubules in these zones completely preserved its brush border, which was demonstrated particularly clearly by the PAS reaction. The distal portions of the nephrons and epithelium of the loops of Henle also appeared normal. It was in these intact regions of the allografted kidneys that in four or five cases mitoses were found in the tubular epithelium, where they numbered from 3 to 27 per square centimeter of section (Table 1).

Altogether in 12 sections 109 mitoses were found, made up of 88 in the proximal and 21 in the distal portion of the nephron. At later stages (3 and 5 days), among 29 cells dividing by mitosis four pathological mitoses (C metaphases) were found, whereas in the allografted kidneys present in the recipient's body for 1 or 2 days, no pathological forms were found among 80 mitoses. No evidence of a clearly defined metaphase block likewise could be found (the fraction of telophases reached 30%). In the control kidneys of intact healthy dogs no mitoses were observed in the tubular epithelium.

These results were compared with data in the literature on mitotic activity of the tubular epithelium of mammalian kidneys under experimental conditions and also with observations on the mitotic activity of the tubular epithelium of human allografted kidneys. There is information in the literature on mobilization of the proliferative pool of the renal epithelium of rats after prolonged ischemization of the kidneys and subsequent restoration of the blood flow, after removal of the contralateral kidney [7-9]. It is considered, in particular [8], that during mobilization of the proliferative pool of the renal epithelium of rodents the following stages can be distinguished: 1) a stage of nonspecific activation of mitotic activity observed during the first 24 h after ischemia of the kidney or after removal of the contralateral kidney; 2) a stage of organ-specific activation of mitosis, observed on the third to fourth days after the operation. This rule is evidently characteristic also of the epithelium of the dog's kidney in the early stages after transplantation.

It is most interesting to compare the mitotic activity of the tubular epithelium of the allografted dog's kidney with the mitotic regime of allografted human cadaveric kidneys. Differences concerned with qualitative features of the mitotic regime are immediately apparent. For instance, in the proximal tubules of allografted kidneys of dogs not receiving immunodepressive therapy, virtually no pathological forms of division were found, whereas in allografted kidneys of persons subjected to intensive immunodepression many pathological mitoses, especially C metaphases, were found. The question of the connection between the genesis of C mitoses and the cytostatic action of imuran inevitably arises. It is evidently from this aspect that the appearance of the metaphase block in the dividing cells of the tubular epi-

thelium must be assessed. The final verdict on the connection between the metaphase block of the tubular epithelium of the allografted kidneys and the appearance of pathological C mitoses and immunodepressive therapy will be reached after a series of experiments, which the writers have planned on dogs with transplanted kidneys to which various doses of immunodepressants and cytostatic agents will be administered, have been carried out. So far as the actual phenomenon of the appearance of mitoses in the allografted dogs' kidneys is concerned, it must probably be attributed to postischemic mobilization of the proliferative pool as described in the literature.

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# DIURNAL RHYTHM OF MITOSIS AND IN NUMBER OF DNA-SYNTHESIZING CELLS AFTER ADRENALECTOMY IN MICE


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Diurnal changes in the number of DNA-synthesizing cells and in the number of mitoses were studied in the corneal epithelium and liver of intact and adrenalectomized mice. The curve of diurnal changes in the number of labeled nuclei in the corneal epithelium of the mice after adrenalectomy became bimodal and the amplitude of fluctuations in the mitotic index in the course of the 24-h period increased sharply compared with the control. The rhythm of DNA synthesis in the liver was similar in the control and experimental series, and the rhythm of mitosis in the experimental animals became biphasic in character. Adrenalectomy thus disturbs the phase structure of the rhythms of DNA synthesis and of mitosis in the tissues studied.



KEY WORDS: diurnal rhythm; adrenalectomy; DNA synthesis; mitotic activity.


Glucocorticoid hormones have a powerful effect on cell division in mammalian tissues. This phenomenon is manifested differently in different tissues and the role of adrenocortical hormones in the regulation of cell division is not yet fully clear.

There are data in the literature indicating a possible effect of glucocorticoids on the entry of cells into the phase of DNA synthesis [7]. If this is so, a fall in the blood glucocorticoid level could cause disturbance of synchronization of the entry of cells into the S period of the mitotic cycle.

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