

# CHANGES IN CELL REACTIONS TO ADRENALIN AT DIFFERENT TIMES OF DAY

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In a study of mitotic activity of the corneal epithelial cells, responses to adrenalin hydro-tartrate were found to differ at different times of day. Application of the drug to the cornea in the morning gave rise to a marked antimitotic effect, whereas in the afternoon and evening this reaction was weak.

Cell responses to identical stimuli (including to certain drugs) have been shown to vary with the time of day. Mice differ in their sensitivity to ethanol [7], the endotoxin of *Escherichia coli* [5], and to strophanthin [6]. The mortality after administration of *E. coli* endotoxin and strophanthin during the day was higher than at night. Growth hormones and sarcosyl induced different changes in mitotic activity in various tissues depending on the time of their administration [2, 8].

With these observations in mind it was decided to study the antimitotic action of adrenalin when the drug was administered at different times of day. When injected into an animal or given by local application, adrenalin considerably delays the initiation of mitosis by the cell and thus depresses mitotic activity [1, 3, 4]. This reaction was used as a test to study the changes in the cell response to adrenalin.

## EXPERIMENTAL METHOD

Twenty albino mice aged about 3 months were used and the test substance was applied locally to the cornea. A drop of adrenalin hydrotartrate solution made up in physiological saline (1:100,000) was applied to the right cornea, and a drop of physiological saline was applied to the left (control cornea of the same animal). The drop remained on the cornea for 10 sec, and was then carefully removed by means of a swab. The adrenalin was applied at 8 A.M. and 8 P.M. The animals were sacrificed 1 h after application. Mitoses were counted in total preparations of the cornea stained with trioxymethatein (in 100 fields of vision of each specimen). The total number of mitoses was expressed in absolute terms, and the ratio

TABLE 1. Changes in Mitotic Activity under the Influence of Adrenalin Hydrotartrate

Time of day	Group of animals	No. of animals	Mitotic activity	Ratio between phases of mitosis, %				Decrease in mitotic activity, %
				P	M	A	T	
8 A.M.	Control Expt.	7	240,4	15,2	18,0	1,5	65,3	48,5
		7	123,8	13,2	9,0	1,4	76,3	
8 P.M.	Control Expt.	7	100,8	6,1	35,4	2,5	56,0	26,4
		7	74,1	4,5	26,7	2,4	66,3	

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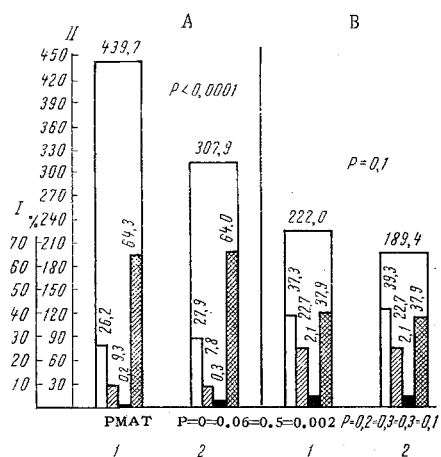


Fig. 1. Diurnal changes in mitotic activity and relative percentages of phases of mitosis during action of adrenalin hydrotartrate on corneal epithelium during morning (A) and evening (B): 1) control; 2) after application of adrenalin hydrotartrate; P) prophase; M) metaphase; A) anaphase; T) telophase. Ordinate: I) phases of mitosis (in %), II) number of mitoses (absolute figures).

between the phases of mitosis in percentages. Statistical analysis of the results was carried out by the Fisher-Student method.

## EXPERIMENTAL RESULTS

The experimental results showed that the mitotic activity in the corneal epithelium of the control mice exhibits diurnal fluctuations with high values in the morning and low values in the evening. Adrenalin hydrotartrate caused a sharp decrease in mitotic activity, but this effect varied with the time of day (Fig. 1). When the drug was applied in the morning, the mitotic activity in the right cornea was reduced by 29.9% relative to the control ( $P=0.0001$ ). When the drug was applied at 8 p.m., it also lowered mitotic activity, but the decrease relative to the control in this case was only 14.6% ( $P=0.1$ ). The ratio between the phases of mitosis in the control and experimental groups remained unchanged during both morning and evening.

These experiments were repeated in two analogous series, and identical results were obtained. In series 2 (Table 1), after application of adrenalin hydrotartrate in the morning, mitotic activity was reduced by 48.5% ( $P<0.0001$ ), whereas after application in the evening, the number of mitoses was reduced by only 26.4% ( $P=0.1$ ). The results of these experiments thus show that the reaction of the cells to the antimitotic action of adrenalin hydrotartrate varies with time of day.

The highest antimitotic effect was observed in the morning, but in the evening this reaction was weak and not always statistically significant.

In view of the importance of these results to pharmacology, further studies must be made of the diurnal response of different tissues to drugs.

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