

# PHYSIOLOGICAL REGENERATION OF THE JEJUNAL EPITHELIUM AFTER BILATERAL SUBDIAPHRAGMATIC VAGOTOMY IN RATS

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Seven days after bilateral subdiaphragmatic vagotomy in rats the mean diurnal number of mitoses in the jejunal epithelium is increased by 1.5 times. The character of the diurnal rhythm of mitosis is unchanged but fluctuations in the curve of mitotic activity are reduced. Vagotomy does not disturb the ratio between the volumes of cell populations of the villi and crypts, which indicates that the steady state of renewal of the cell composition of the crypt-villus system is maintained under these conditions.

**KEY WORDS:** regeneration; epithelium; jejunum; mitotic; mitosis; crypt; villus.

T. A. Grigor'eva and her collaborators demonstrated experimentally that besides vascular and inflammatory changes in organs with a disturbed innervation proliferative changes also are found, namely, an increase in the number of mitotically dividing cells. Recently published investigations devoted to the quantitative analysis of this phenomenon have shown an increase in the absolute number of mitotically dividing cells in slowly renewed organs (liver, pancreas) after a disturbance of their innervation, but the character of the diurnal rhythm of mitotic activity of the tissue remains substantially unchanged [2, 5].

Rapidly renewed organs, especially the jejunum, are of the greatest interest from this point of view because, considering their high reactivity, influences of the integrative systems of the body on the renewal of their cell composition can be analyzed more clearly (as regards both the intensity of the response to a particular stimulus and the time of its appearance). However, they have been inadequately studied from this aspect and only a few papers on the problem can be found in the literature [2, 8, 10, 11]. In some of them mitotic activity of the tissue was studied at one fixed time of day, whereas in others only certain parameters of renewal of the cell population of the tissue were investigated, so that a complete picture of this process cannot be painted.

The object of this investigation was to study proliferation of the jejunal epithelium after bilateral subdiaphragmatic vagotomy. The jejunum was chosen as the test object because of the morphology of its mucous membrane, as a result of which the reproductive and functional divisions of the epithelium are clearly distinguishable, and the process of renewal of their cellular composition can therefore be studied separately [1, 6, 9, 12]. This is an important factor when defining the kinetics of physiological regeneration of the cell population of the tissue. When studying the proliferation of the jejunal epithelium the diurnal rhythm was taken into account, an absolute necessity if sufficiently complete information about them is to be obtained [3, 4, 7].

## EXPERIMENTAL METHOD

Experiments were carried out on 74 male albino rats weighing 140-160 g. Bilateral subdiaphragmatic vagotomy was performed on 35 of the rats and the other 39 formed the control. The tests were carried out 7 days after the operation and 24 h after the last meal. The control and experimental animals were given

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an intraperitoneal injection of colcemid in a dose of 4  $\mu\text{g}/100$  g body weight 4 h before sacrifice. The animals were killed with ether vapor every 4 h during the 24-h period, starting at 2 a.m. Serial histological sections, 7  $\mu$  in thickness, were stained with Ehrlich's hematoxylin, after which mitoses were counted in 50 crypts and the total number of cells were counted in 25 villi and 25 crypts. Only those villi and crypts were regarded as suitable for counting if they were cut along their long axis. The mitotic coefficient was calculated by the usual formula and expressed in promille, and the volume of the populations of villi and crypts were expressed as absolute numbers of cells in them. All the quantitative results were subjected to statistical analysis by the Fisher-Student method.

## EXPERIMENTAL RESULTS

The curve reflecting diurnal fluctuations in mitotic activity of the intestinal epithelium of the control animals was unimodal in character with a maximum at 10 p.m. (252.4 $\text{‰}$ ) and a minimum at 6-10 a.m. (84.9 and 98.3 $\text{‰}$ , respectively). The mean diurnal mitotic coefficient in the control was 159.6 $\text{‰}$ . In animals undergoing bilateral subdiaphragmatic vagotomy the curve of the diurnal rhythm of mitosis was similar in principle to that for the control animals: The number of mitotically dividing cells reached a maximum at 10 p.m. (294.5 $\text{‰}$ ) and a minimum at 10 a.m.-2 p.m. (216.5 and 199.5 $\text{‰}$ , respectively). However, the amplitude of the diurnal fluctuations of mitotic activity in the experimental animals was much less than in the control. The mean diurnal mitotic coefficient for the vagotomized rats was 252.1 $\text{‰}$ . Comparative analysis of the dynamics of the changes in populations of the crypts and villi showed no significant difference between the experimental and control series: In both groups the diurnal fluctuations of these parameters were within the limits of statistically allowable error. The mean diurnal volumes of the cell populations of the villus and crypt were 140.03 and 59.3, respectively for the control rats and 144.3 and 50.1 for the vagotomized rats.

The results of these experiments can be summed up in the statement that vagotomy leads to an absolute increase in mitotic activity of the intestinal epithelium (by 1.5 times based on mean diurnal values) and to a decrease in the fluctuations of the curve of diurnal changes in the number of mitoses (without any change in its temporal structure), but the steady state of cell proliferation is undisturbed.

The results of this investigation agree, on the one hand, with those of others in which mitotic activity of the intestinal epithelium was studied in animals (dogs, rats) undergoing pyloroplasty combined with vagotomy [10, 11], but on the other hand they disagree with results of investigations in which this same parameter was determined in human subjects undergoing operations for gastric ulcer (subdiaphragmatic total vagotomy, thoracic vagotomy, vagotomy and pyloroplasty [8]). In the last investigation cited no significant changes in mitotic activity of the jejunal epithelium were observed. This discrepancy can be explained by the species-specific character of response of the organ to denervation, by the influence (nervous or humoral) of the pathologically changed stomach on the small intestine, and by differences in the times of taking the material, and so on. It is particularly interesting to compare the results of the present investigation with those of studies of mitotic division in the liver and pancreas under analogous experimental conditions. Comparative analysis of these data revealed certain general principles governing the course of cell division of the tissue after vagotomy: The mitotic activity of the tissue increases but the character of its diurnal rhythm remains substantially unchanged. Since disturbance of the innervation of an organ leads to the development of degenerative changes in it (including death of some of the cells), increased mitotic activity in it must evidently be regarded as a compensatory reaction aimed at maintaining the balance of its cell population.

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