PROLIFERATION OF THE GLANDULAR EPITHELIUM OF THE RESECTED RAT STOMACH

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Between 45 and 50% of the wall of the gastric fundus was resected in adult male rats. By pulse labeling and 5 injections of thymidine-H^3 in the course of the 24 h an increase in the number of cells synthesizing DNA and the number of dividing cells of all types was found in the chief glands of the stomach during the first 3 days after resection. On the 5th-10th day the level of proliferation of all types of cells was lower than in intact animals except for the DNA-synthesizing parietal cells. The daily number of DNA-synthesizing cells of all types 3-6 months after the operation had risen to the characteristic level for intact animals. The number of cells on the surface and pit epithelium and the number of mucous neck and parietal cells were increased. Partial reduction and dedifferentiation of the zymogenic cells were observed.

KEY WORDS: resection of the stomach; proliferation of the glandular epithelium; DNA synthesis; mitosis.

A previous investigation showed that after removal of half of the gastric fundus regeneration takes place in the rest of the organ [8]. The area of the mucous membrane 1 month after resection was equal to 60% of the area of the mucous membrane in intact rats but it did not increase further. From 3 to 6 months after resection hypertrophy of the mucous membrane and of the outer muscle coat, with an increase in their thickness, was observed. The weight of the residual part of the stomach 9 months after the operation was close to the weight of the stomach in intact rats of the same age. The character of the changes in DNA synthesis and cell division in the mucous membrane of the resected stomach still awaited explanation.

The investigation described below was carried out for this purpose.

EXPERIMENTAL METHOD

From 45 to 50% of the wall of the gastric fundus was resected in adult male rats in the region of the greater curvature [8]. The mitotic index (MI) and, through the index of labeled nuclei (ILN), the number of DNA-synthesizing cells in the chief glands of the stomach in the early stages after the operation were determined in the experiments of series I. Forty rats weighing 250-300 g were divided into three groups: 1) animals undergoing resection of half of the gastric fundus, 2) animals undergoing a mock operation, and 3) intact rats. The animals were killed 1, 2, 3, 5, and 10 days after the operation and 1 h after a single intraperitoneal injection of thymidine-H^3 (USSR product, specific activity 1.4 Ci/mmole) in a dose of 0.5 μCi/g body weight. The daily number of DNA-synthesizing cells in the chief glands of the rats' stomach was determined in the experiments of series II in the late stages after the operation. In this series 36 rats weighing 160-250 g were divided into two groups: 1) animals undergoing resection of the gastric fundus, and 2) intact rats of the same age (control). Thymidine-H^3 was injected 5 times a day (every 5 h) at the rate of 0.3 μCi/g body weight. As a result of the repeated injections of the isotope all cells in the S-phase of the mitotic cycle in the course of the 24 h could be counted. The rats were decapitated at 9 a.m. after preliminary starvation for 24 h. The material was fixed by injecting Carnoy's mixture into the stomach. Paraffin

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TABLE 1. Index of Labeled Nuclei of Cells in Chief Gastric Glands of Rats in Early Period after Resection (in percent; M ± m)

Time after operation (in days)	Surface and pit epithelium	Mucous neck cells	Parietal cells	Zymogenic cells
1	12,30±1,79	24,10±0,77	0,36±0,014	1,35±0,14
2	15,90±1,58	14,10±0,76	0,39±0,032	4,80±0,18
3	18,50±0,38	11,30±1,01	0,14±0,004	1,97±0,17
5	5,25±0,59	6,00±0,45	0,03±0,004	0,12±0,01
10	1,92±0,31	2,31±0,18	2,17±0,032	0,43±0,07
Control	8,00±0,48	4,83±0,10	0,09±0,01	0,76±0,12
Mock operation	3,98±0,39	1,38±0,03	0,05±0,04	0,04±0,005

TABLE 2. Mitotic Index of Cells of Chief Gastric Glands of Rats in Early Periods after Resection (in percent; M ± m)

Time after operation (in days)	Surface and pit epithelium	Mucous neck cells	Parietal cells	Zymogenic cells
1	5,77±0,78	17,64±0,85	1,96±0,04	0,39±0,04
2	8,55±1,01	5,44±0,30	1,63±0,15	0,40±0,04
3	6,05±0,80	9,56±0,37	0,05±0,06	0,84±0,17
5	3,34±0,11	0,92±0,07	0,52±0,04	—
10	0,21±0,00	0,88±0,17	0,41±0,09	—
Control	5,13±0,17	0,56±0,06	0,60±0,07	0,15±0,06
Mock operation	2,22±0,18	0,75±0,04	0,57±0,01	0,10±0,02

sections 5 μ in thickness were coated with dilute liquid type M (Scientific-Research Institute of Photographic Chemistry) emulsion. Exposure continued for 1 month. After development, the autoradiographs were stained by the Dominici–Kedrovskii method. Mitoses and labeled cells were counted in 50 longitudinally sectioned glands of the gastric fundus, still retaining their characteristic structure and situated not less than 30 glands away from the defect. Cells were regarded as labeled if there were at least 4 grains of silver above their nucleus. MI was expressed per thousand cells and the number of DNA-synthesizing cells (ILN) in percent.

EXPERIMENTAL RESULTS

On the 1st-3rd day after the operation the number of DNA-synthesizing and dividing surface epithelial and mucous neck cells was considerably increased (Tables 1 and 2). Labeled mitoses, mainly the early phases – prophases and especially metaphases – were found at these same times in both types of mucus-forming cells. On the 5th to 10th day the proliferative activity of both these types of cells was sharply reduced, especially in the epithelium of the pits. DNA synthesis also was considerably intensified in the zymogenic cells during the first 3 days after resection, but the number of mitoses was increased only on the 3rd day. A decrease in proliferative activity also was observed starting on the 5th day. The cytoplasm of the zymogenic cells did not stain with toluidine blue on the 2nd-3rd day after the operation. This phenomenon is evidently explained by changes in metabolism and in the state of the intracellular structures. During the first days after resection, mucus formation was observed in small groups of zymogenic cells in the basal portions of some of the glands, sometimes in individual cells. On the 5th-10th day those zymogenic cells whose character of secretion was unchanged stained with toluidine blue and exhibited basal basophilia. ILN was increased in the parietal cells on the 1st-2nd day, reduced on the 3rd-5th day, and sharply increased again on the 10th day (Table 1). The number of mitoses was maximal on the 1st-2nd day (Table 2). Labeled mitoses appeared in the parietal cells on the first day and in the zymogenic cells on the 2nd day. In the rats undergoing the mock operation no regular changes in ILN or MI at the various times after resection were observed in any type of cell. If the results obtained in all animals undergoing the mock operation were added together, ILN in the mucus-forming and parietal cells was half that in the intact rats and one-twentieth of its value in the zymogenic cells. The number of mitoses in the surface cells was half the control figure, and in the other types of cells there was no significant difference from the control. As a

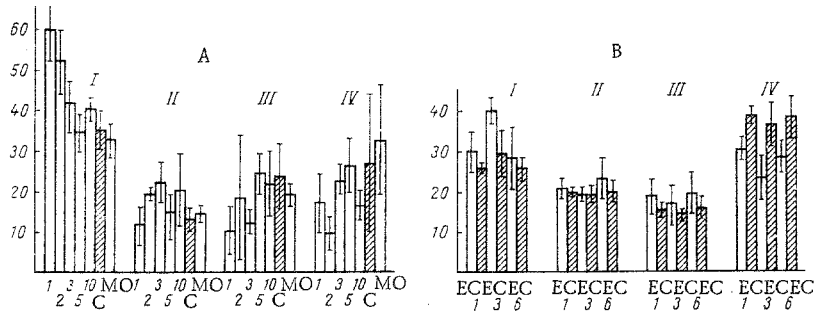

Fig. 1. Number of cells of different types in chief glands of the rat stomach in the early (A) and late (B) periods after resection: E) experiment, C) control (intact animals), MO) mock operation; I) cells of surface and pit epithelium, II) mucous neck cells, III) parietal cells, IV) zymogenic cells. Limits of variations of parameters are indicated. Abscissa, time after operation: in days (A), in months (B); ordinate, number of cells of different types as a percentage of the total.

TABLE 3. Daily Number (in percent) of DNA-Synthesizing Cells in Chief Gastric Glands of Rats in Late Periods after Resection (M ± m)

Time after operation (in months)	Group of animals	Surface and pit epithelium	Mucous neck cells	Parietal cells	Zymogenic cells
1	Experimental	20,16±1,07	6,80±0,50	0,17±0,03	0,19±0,04
	Control	43,52±1,79	10,99±1,12	0,57±0,05	0,16±0,03
3	Experimental	32,02±4,25	7,59±1,12	0,11±0,04	0,26±0,10
	Control	43,68±4,70	8,16±2,25	0,17±0,05	0,15±0,06
6	Experimental	56,42±4,20	4,96±0,78	0,23±0,07	0,15±0,09
	Control	51,84±3,16	6,19±1,63	0,40±0,06	0,17±0,05

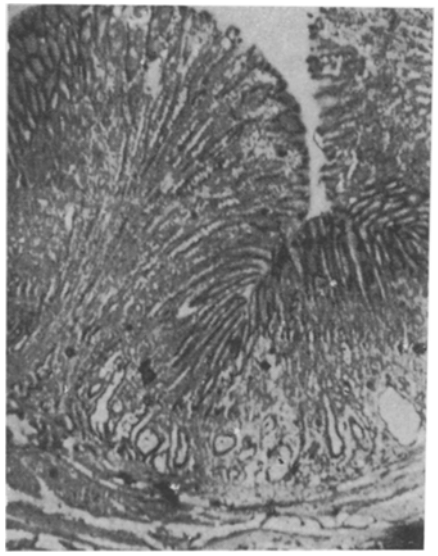

Fig. 2. Section through hypertrophied mucous membrane of the rat stomach 3 months after resection: cystic dilatation of the basal zones of some glands and proliferation of interglandular stroma between them can be seen. Dominici–Kedrovskii's stain, 70×.

result of the change in the level of proliferation in the epithelium of the resected stomach in the first two days after the operation the number of cells of the surface and pit epithelium was almost doubled (Fig. 1A), and by the 3rd and 10th days the number of mucous neck cells was significantly increased. On the 5th-10th day the number of surface epithelial cells was close to the control level but the number of mucous neck cells remained increased. The number of parietal cells was reduced on the 1st days and returned to normal by the 5th-10th day. After an initial tendency to decrease, the number of zymogenic cells returned to normal on the 5th day but fell again by almost half by the 10th day. The pyloric epithelium also responded to resection of the fundus by a change in the level of proliferation: by the 10th day ILN fell to 4.07 % ($P = 0.016$). In the early periods after resection of the stomach, as of other internal organs (liver, kidneys, lungs, pancreas, thyroid, and adrenal glands [1-7, 10-13]), activation of proliferation during the first days after removal of part of the organ was followed by inhibition.

The level of proliferation of all types of cells except the parietal cells remained low 1 month after resection of the gastric fundus. In the parietal cells the daily synthesis of DNA was increased threefold (Table 3). After 3-6 months the proliferative activity of all types of cells was stabilized at the level characteristic of intact animals. The marked hypertrophy of the mucous membrane at these times was a

manifestation of the adaptation of the organ to the conditions created. The increase in the number of cells of the surface epithelium by 6 months after resection (Fig. 1B) explains the increased depth of the pits of the glands. The increased number of mucous neck cells corresponded to a change in the size of the gland necks; these were increased in length and often reached the basal zones of the glands. The number of zymogenic cells was reduced and some of them showed destructive changes. The number of parietal cells was increased. In the same rat the structure of the mucous membrane could differ in the region of the fundal part. This was particularly noticeable 6 months after the operation. Besides hypertrophy of the mucous membrane (Fig. 2) the basal zones of the glands showed cystic dilatations and increased development of the interglandular stroma, and the dedifferentiated chief glands could be replaced by mucus-secreting glands. Areas of atrophy of the mucous membrane were found. In most rats, however, hypertrophy of the mucous membrane of the resected stomach was predominant and the general condition of the animals was perfectly satisfactory, indicating morphological and functional adaptation of the organ to the new conditions.

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