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HYPERPLASIA OF THE GASTRIC MUCOSA PRODUCED BY DUODENAL OBSTRUCTION

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A marked hyperplasia of the gastric mucosa was observed in rats after partial obstruction to the gastric outflow had been produced by tying a ligature around the duodenum. The effect was characterized by increases in the weight, surface area, and mucosal volume of the fundus and antrum, and there were proportional increases in the total parietal and total peptic cell populations. These effects were interpreted to mean that obstruction had caused an increase in the number of glands in the two parts of the stomach. The results suggest that the hyperplasia was due in some way to physical distension of the stomach since all of the other changes observed could be accounted for by the increase that occurred in surface area.

Duodenal or pyloric obstruction is known to cause gastric hypersecretion in man and in dogs,[1, 2] while outlet obstruction causes an increase in the secretion from a stomach pouch in the dog.[3] One hypothesis to account for these effects is that gastric outflow obstruction may cause hyperplasia of the gastric mucosa with an increase in the number of its secretory cells. This hypothesis has been tested by examining the effects of duodenal obstruction on the weight, surface area, mucosal volume, and total parietal and peptic cell populations of the stomach in rats; the suggestion that gastric outflow obstruction causes a preferential increase in the size of the gastric antrum[4] has also been examined in the same experiments. A preliminary account of some of the results obtained has been given elsewhere.[5]

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Materials and Methods

Duodenal obstruction. The experiments were carried out on adult male rats obtained from the closed Wistar colony maintained in the Clinical Endocrinology Research Unit. Obstruction to the gastric outflow was produced by tying a ligature around the duodenum at a distance of 1 cm from the pylorus; the procedure required mobilization of the first part of the duodenum which was carried out under Nembutal anesthesia. In order to standardize the degree of obstruction produced, a bougie

was placed beside the duodenum so that it was included in the ligature; the ligature was then tightened and tied at the point at which the bougie could be just withdrawn. It was considered that by using the same bougie roughly similar degrees of obstruction would be produced in different animals; different sizes of bougie were used so that the degree of obstruction could be varied from one experiment to another. The duodenum was simply mobilized in the control animals used in the experiments. The two procedures—duodenal obstruction or duodenal mobilization—were carried out on a random basis on groups of 4 or 6 rats at a time; although all of the animals in any one group were of similar age and weight, there were considerable differences between groups in both respects. Postoperatively, all animals were maintained under the same conditions and on the same semiliquid diet of rat cake homogenized with milk and glucose. The duration of the experiments was determined on arbitrary grounds and all but 3 of the experimental animals which survived the procedure were killed in the 11th week after operation. The exceptions were 3 animals with severe obstruction which had to be killed between 3 and 5 weeks after operation because they were clinically unwell and losing weight; in all cases the obstructed animal and its control were killed on the same day.

The final degree of obstruction produced in each animal was assessed at autopsy by passing bougies through the obstructed segment via a duodenotomy; this could not always be predicted from the capacity of the ligature used at operation because of variation in the degree of tissue reaction that occurred in different animals. The results of the autopsy assessments were classified as follows: *moderate obstruction* was considered to be present if the obstructed segment admitted a bougie of size F8-10; *severe obstruction* was considered to be present if a bougie of size F8 could not be passed; *ineffective obstruction* was considered to be present if the segment admitted a bougie of the same size (F10 or greater) as the duodenum of the appropriate control animal.

The approximate measurements for the diameter and circumference of the bougies were, respectively, 2.7 mm and 8.5 mm for size F8, and 3.5 mm and 11.0 mm for size F10.

Observations on the gastric mucosa. The stomach was removed as quickly as possible after death, cleaned of its mesentery, vascular supply, and fat, and opened along the greater curvature; the organ was next pinned, serosal surface downwards on a sheet of unexposed X-ray film in such a way as to eliminate mucosal folds and the entire preparation was fixed by immersion in 10% formol-saline. In the rat, the fundus and antrum of the stomach are readily distinguished from one another on eye examination (see fig 1); after fixation the antrum was separated from the fundus using fine scissors to cut along the fundic-antral junction, so that observations could be made on the two parts separately. The fixed specimens were weighed after being dried by swabbing and the surface area, height, and volume of the mucosa of the fundus and antrum and the total parietal and peptic cell populations of the stomach were estimated subsequently according to the methods described by Cox and Barnes[6] and Card and Marks[7]; no quantitative observations were made on the submucosal or muscular layers of the stomach. The parietal and peptic cell populations were determined from the counts of each cell type made on histological sections cut at right angles to the surface of the mucosa; the sections were stained by the method of Marks and Drysdale[8] and counts were made in perpendicular columns 0.1 mm wide stretching from the base to the surface of the mucosa in fields which included the entire length of the gastric glands. The average thickness of the sections used and the cross sectional diameters of the parietal and peptic cells were determined from direct measurements[9] so that the actual number of each cell type underlying a unit area of the mucosa could be calculated for individual stomachs.[10] The volume of the fundic and antral mucosa was calculated as the product of the surface area and the mean height of the mucosa in each part, mucosal height (or thickness) being measured as the distance from the upper surface of the muscularis mucosa to the lumenal surface of the glands in the histological sections; since the density of a cell is about unity, the measurement of the volume of the mucosa approximates that of its mass. The exact methods used in the present experiments and the errors involved have been described elsewhere[11, 12]; it should be emphasized that all of the histological observations were made in ignorance of the identity of the tissue under consideration in order to eliminate observer bias.

Results

The results, noted on table 1, were classified according to the degree of obstruction observed at autopsy. Differences between the means obtained in the control and obstructed animals in the groups with moderate and ineffective obstruction were

TABLE 1. *The effects of duodenal obstruction*[a]

	Ineffective obstruction			Moderate obstruction			Severe obstruction	
	Control rats (n[b] = 5)	Obstructed rats (n = 5)	Value of P	Control rats (n = 10)	Obstructed rats (n = 10)	Value of P	Control rats (n = 3)	Obstructed rats (n = 3)
Body weight (g)								
Initial	263 ± 36	271 ± 41	NS[c]	281 ± 25	281 ± 25	NS	299 ± 63	306 ± 62
Final	337 ± 44	344 ± 48	NS	346 ± 25	349 ± 22	NS	303 ± 11	256 ± 24
Stomach weight (mg)								
Total	1738 ± 93	1675 ± 110	NS	1618 ± 43	2716 ± 188	<0.001	1485 ± 11	3622 ± 43
Fundus	963 ± 44	907 ± 44	NS	872 ± 32	1523 ± 113	<0.001	701 ± 33	1727 ± 96
Antrum	257 ± 20	275 ± 35	NS	234 ± 10	478 ± 62	<0.005	224 ± 7	560 ± 43
Surface area (cm^2)								
Fundus	12.0 ± 0.7	11.2 ± 0.5	NS	11.0 ± 0.3	15.8 ± 0.6	<0.001	9.3 ± 0.5	21.4 ± 1.2
Antrum	4.2 ± 0.3	4.3 ± 0.3	NS	3.9 ± 0.2	6.3 ± 0.6	<0.005	3.2 ± 0.2	8.4 ± 1.3
Mucosal height (mm)								
Fundus	0.453 ± 0.024	0.453 ± 0.019	NS	0.454 ± 0.020	0.494 ± 0.021	NS	0.413 ± 0.010	0.392 ± 0.018
Antrum	0.150 ± 0.008	0.130 ± 0.005	NS	0.139 ± 0.010	0.165 ± 0.015	NS	0.160 ± 0.001	0.129 ± 0.012
Mucosal volume (mm^3)								
Fundus	541 ± 32	507 ± 28	NS	494 ± 21	785 ± 44	<0.001	387 ± 31	834 ± 12
Antrum	53 ± 4	56 ± 5	NS	55 ± 3	105 ± 14	<0.005	51 ± 3	107 ± 5
Total parietal cell population (millions)	57.2 ± 5.2	54.6 ± 3.4	NS	52.5 ± 1.5	71.8 ± 2.1	<0.001	42.5 ± 3.3	71.9 ± 6.2
Total peptic cell population (millions)	85.8 ± 8.7	78.5 ± 6.9	NS	79.2 ± 3.3	105.4 ± 4.8	<0.001	64.1 ± 3.2	104.0 ± 5.2
Peptic cell population/ parietal cell population	1.50 ± 0.05	1.43 ± 0.07	NS	1.52 ± 0.07	1.47 ± 0.06	NS	1.52 ± 0.13	1.35 ± 0.06
Average number of parietal cells per unit area[c]	23.4 ± 2.0	23.9 ± 1.3	NS	23.1 ± 0.3	21.8 ± 0.7	NS	22.3 ± 0.7	17.7 ± 1.3
Average number of peptic cells per unit area[d]	35.3 ± 3.7	34.4 ± 2.9	NS	35.8 ± 1.7	32.9 ± 1.5	NS	33.8 ± 2.0	23.9 ± 1.4

[a] Differences between the means in the groups with ineffective and moderate obstruction were tested by Student's t test, and the value for P is given for the significance of the differences between the control and experimental animals for each of the observations made. Results are expressed as means plus or minus standard error.

[b] n, number of rats.

[c] NS, not significant.

[d] "Count per unit area" refers to the estimated number of cells underlying a unit of the surface area of the mucosa with the dimensions 100 μ by 4.9 μ.

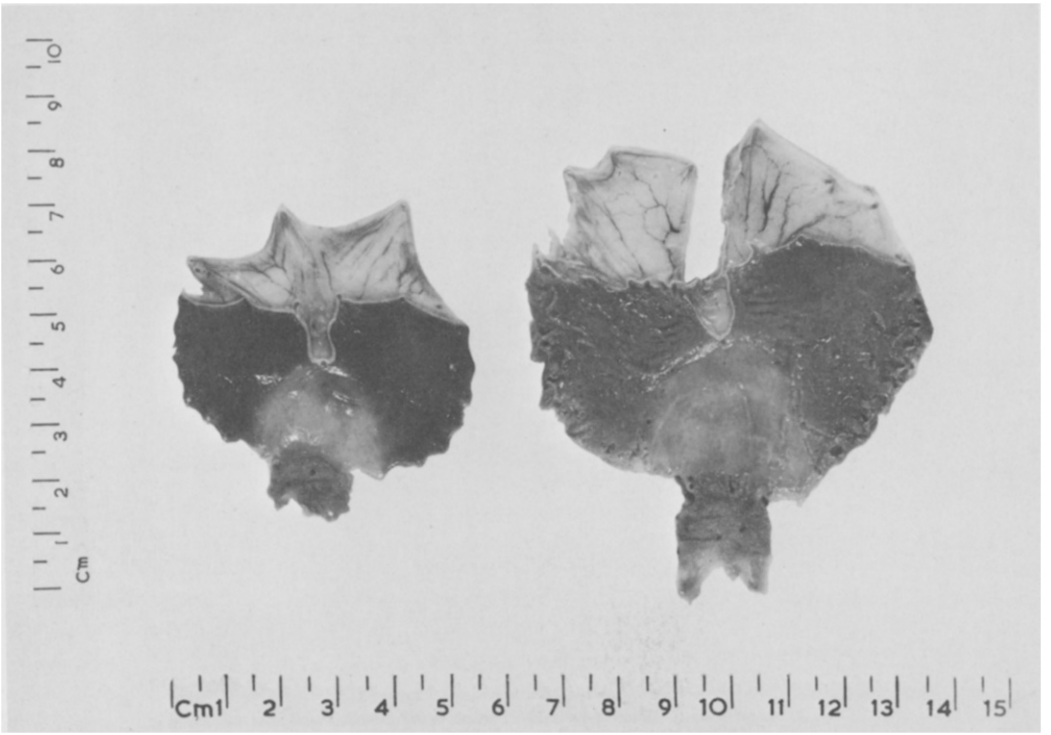

FIG. 1. The stomach of a rat killed after 11 weeks of moderate obstruction (*left*) compared with its control (*right*). The 2 animals were of the same age and body weight.

tested by Student's t test; the test was not applied to the group with severe obstruction, because of the small number of animals available for consideration.

Group 1—moderate obstruction (fig. 1). The mean growth curve for the animals with moderate obstruction was indistinguishable from that of their controls, and there were no significant differences between the two groups with respect to initial or final body weight (table 1); however, there were marked differences between the stomachs of the two groups. Thus, the mean values for the weight, surface area, and mucosal volume of both the fundus and antrum, and the total parietal and total peptic cell populations were all much greater in the obstructed animals than they were in the controls, the value for P for the difference between the two groups varying between <0.005 and <0.001 for individual observations. It should be noted that there were no significant differences between the two groups with respect to the height of the fundic or antral mucosa; since mucosal height was not affected, the large increases observed in the volume of the fundic and antral mucosa can be attributed entirely to the increases that occurred in the surface area of the two parts. Similarly the increases that occurred in the total parietal and total peptic cell populations after obstruction could only be due to an increase in the total area of the fundus, since the number of cells per unit area was not affected; moreover, the data suggest that the parietal and peptic cell populations increased in proportion to one another since the ratio between them did not differ significantly between the control (1.52 ± 0.07) and obstructed animals (1.47 ± 0.06).

Group 2—severe obstruction. Severe obstruction was produced in 10 animals; 7 died within 7 days of the operation from perforation of a gastric ulcer, and these animals have been excluded from consideration in the results. Three animals with

severe obstruction survived the immediate postoperative period but, as stated previously, they had to be killed between 3 and 5 weeks later because they were clinically unwell and were losing weight; all 3 had multiple gastric ulcers associated with severe inflammatory change throughout the stomach and there was marked hyperplasia of the gastric mucosa in each. The increases that occurred in the parietal and peptic cell population and in the volume of the fundic and antral mucosa were again due to an increase in surface area. The great increase in the weight of the whole stomach and its constituent parts was probably due to inflammatory edema; it will be noted that otherwise the effects of severe obstruction were of the same order of magnitude as those of moderate obstruction although the duration of the experiments in the two groups was very different (3 to 5 weeks and 11 weeks, respectively).

Group 3—ineffective obstruction. In this group, ligatures had been tied loosely around the duodenum and the lumen was of the same size in the obstructed and control animals; there were no demonstrable differences between the stomachs of the two groups.

Discussion

The results of these experiments establish the fact that obstruction to the gastric outflow causes a marked hyperplasia of the gastric mucosa in the rat; gross observations suggest that a similar effect occurs in the dog.[2, 13, 14]

The effects produced in the present experiments can be attributed almost entirely to an increase in the surface area of the stomach, and this effect alone accounted for the increases observed in mucosal volume and in the total populations of the parietal and peptic cells. Moreover, since the effect on surface area was not accompanied by any significant changes in the height of the mucosa or in the density of the secretory cells, the increase in the total populations of the parietal and peptic cells must have been caused by an increase in the actual number of the gastric glands. These effects are interpreted to mean that the hyperplasia represented the overgrowth of an otherwise normal gastric mucosa in which normal dimensional and cellular proportions were maintained; this conclusion is strengthened by the fact that the mean value obtained for the ratio between the total parietal and total peptic cell populations in individual stomachs was not significantly altered as a result of obstruction.

The foregoing considerations suggest that the hyperplasia observed was due to distension of the stomach because of the retention of food and secretions. The implication that physical distension is capable of stimulating the growth of the gastric mucosa can be supported by the observations that stretching or local tension stimulates cell mitosis in tissues such as the skin[15] and uterine wall,[16] while acute obstruction of the common bile duct stimulates a striking but transient overgrowth of the biliary epithelium[17, 18]; further evidence in the same direction is provided by the observation that physical distension is a prerequisite for the regeneration of the urinary bladder.[19] The exact mechanisms by which local stretching may stimulate cell division and tissue growth are not known; however, the effect may represent an escape from contact inhibition of cellular growth[20] or, alternatively, it may be due to a decrease in the production of local inhibitors of cell mitosis because of tissue damage.[21]

An alternative explanation for the effects observed in the present experiments is that they represent a work hyperplasia due to chronic stimulation of the gastric mucosa by the hormone gastrin which is produced in continuous excess under the conditions of sustained distension of the antrum.[14, 22] The observations of Rigler et al.[14] provide some support for this hypothesis. These workers obtained a marked increase in the acid output of a denervated gastric pouch in dogs after the pylorus had been partially obstructed; the rate of development of the change in secretion in their experiments suggests that the effect might well have been due

to hyperplasia of the pouch mucosa, and at autopsy there was obvious hyperplasia of the mucosa of the main stomach. However, in experiments carried out in this laboratory chronic administration of the gastrin-like pentapeptide Peptavlon (I.C.I. 50,123) to rats induced hyperplasia of the parietal cell population only, without producing any other significant changes in the gastric mucosa (Crean, Marshall, and Rumsey, *data to be published*).

Whatever the mechanisms involved, the fact that the hyperplasia produced by severe obstruction of relatively short duration (3 to 5 weeks) was of the same order of magnitude as that produced by a moderate or lesser degree of obstruction for a longer period of time (11 weeks) is worthy of comment. The likeliest explanation for this finding is that the effect is related both to the degree and duration of obstruction; an alternative possibility which has to be considered is that the stimulus responsible for hyperplasia depends on some threshold value for obstruction rather than on its duration. The former explanation is supported by preliminary studies which indicate that the hyperplasia produced by a standard degree of obstruction increases with time after operation (Crean and Rumsey, *unpublished observations*).

The suggestion that gastric outflow obstruction causes a disproportionate increase in the size of the gastric antrum[4] was examined by calculating the ratios that obtained between the antrum and the fundus with respect to weight, surface area, and mucosal volume for individual animals included in the experiment (see table 2). Analysis of variance of these data showed that there were no significant variations in the values obtained for these ratios between the animals with obstruction and those without, suggesting that duodenal obstruction affects the size of the fundus and antrum of the stomach to the same degree at least in the rat.

The experimental effects described are of interest in relation to one aspect of the problem of duodenal ulceration in man. It has been established that hyperplasia of the gastric mucosa occurs at least in some patients with duodenal ulcer,[23] and although the mechanisms responsible are not known, it seems possible that this effect may also represent the overgrowth of an otherwise normal gastric mucosa. This possibility is supported by the classical study of Cox[23] which suggests that the effect is due in large part to an increase in the surface area of the stomach; the close relationship observed between parietal cell population and mucosal volume in the data of Card and Marks[7] provides evidence in the same direction since it implies that the increase in the parietal cell population in duodenal ulcer subjects may be accounted for by an increase in the growth of the gastric mucosa as a whole. These observations suggest that the obstructed stomach may serve as a useful model for the study of the pathophysiological changes that occur in the gastric mucosa

TABLE 2. *The relative effects of duodenal obstruction on the fundus and antrum*[a]

	Ineffective obstruction		Moderate obstruction		Severe obstruction	
	Control rats (n[b] = 5)	Obstructed rats (n = 5)	Control rats (n = 10)	Obstructed rats (n = 10)	Control rats (n = 3)	Obstructed rats (n = 3)
Weight of antrum/weight of fundus	0.269 ± 0.023	0.301 ± 0.031	0.272 ± 0.017	0.312 ± 0.028	0.321 ± 0.006	0.328 ± 0.036
Surface area of antrum/surface area of fundus	0.352 ± 0.009	0.384 ± 0.014	0.362 ± 0.013	0.395 ± 0.022	0.345 ± 0.019	0.393 ± 0.039
Mucosal volume of antrum/mucosal volume of fundus	0.116 ± 0.004	0.112 ± 0.009	0.111 ± 0.005	0.131 ± 0.012	0.134 ± 0.011	0.128 ± 0.004

[a] Mean values (± standard error) were obtained for the ratios between the antrum and the fundus with respect to weight, surface area, and mucosal volume. On analysis of variance, there were no significant variations in the values obtained for any of the three ratios between the six groups.

[b] n, number of rats.

in association with duodenal ulcer; indeed they prompt the speculative question whether the hyperplasia that occurs in duodenal ulcer may not be due at least in part to obstruction to the gastric outflow produced by the presence of the lesion itself.

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