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Experimental Jejunal Ulcer: Relative Importance of Mechanical and Chemical Factors.

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The purpose of this work was to study the respective rôles of "acid neutralization" and trauma in the pathogenesis of the experimental ulcers produced in dogs by the duodenal drainage operation of Mann and Williamson.[1] Since the inception of our studies other investigators, notably Beaver and Mann,[3] Morton,[2] Matthews and Dragstedt,[4] have made significant contributions to the problem, which are quite in accord with our observations.

Methods. The technique described by Mann and Williamson and by Morton was followed. The operation consisted of dividing the stomach and duodenum at the pylorus, turning in the blind end of the duodenum, dividing the duodenum and jejunum at approximately the duodenal-jejunal flexure, joining the stomach to the divided end of the jejunum by an end-to-end anastomosis, and attaching the distal end of the duodenum to the small bowel by a side-to-side or an end-to-side anastomosis. The point of this union, that is, the site of duodenal drainage, was varied, being near the gastro-enterostomy stoma in some and the ileo-cecal valve in others. In the first series, all other factors were kept constant, except for some variation in the size of the gastro-enterostomy stoma resulting from differences in the size and age of the dogs. The purpose of these experiments was to study the importance of the site of duodenal drainage, *i. e.*, high or low in the intestine, in the incidence and rapidity of ulcer formation.

The second series was designed to study the rôle of trauma. In addition to carrying out the same procedures as in the first group, traumatic lesions were produced within the first few centimeters of the jejunum, just distal to the gastro-enterostomy, by the application of a clamp in the manner described by one of us (W.J.G.)[5] In normal animals such lesions heal in from 15 to 31 days.

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[1] Mann, F. C., and Williamson, C. S., *Ann. Surg.*, 1923, **77**, 409.

[2] Morton, Charles Bruce, *Ann. Surg.*, 1927, **85**, 207.

[3] Beaver, Meredith G., and Mann, F. C., *Ann. Surg.*, 1931, **94**, 1116.

[4] Matthews, Warren B., and Dragstedt, Lester R., "Experimental Studies of Gastric and Duodenal Ulcer." *Surg., Gynecol., Obstet.*, in press.

[5] Gallagher, William J., *Arch. Surg.*, **15**, 689.

Results. Table I shows a summary of the results obtained in the first group. Typical jejunal ulcers developed in 17 of the 22 animals, an incidence of 77.3%. This is somewhat lower than that obtained by Mann and Williamson and by other workers. Death from perforation of the ulcer and subsequent peritonitis occurred in 5 animals. Marked inanition was present in 14 dogs, and seemed to produce death. In 11 of these, ulcers were present, but in 3 others, death resulted from inanition without ulcer formation. In these, the anastomosis was high, and the cause of inanition was not apparent. After the operation an initial loss of weight occurred which was followed by a period of maintenance or even of gain in weight. With proper care the animals seemed to do quite well for an indefinite period. With the appearance of loss of appetite and rapid loss of weight, ulcer formation was suspected and usually confirmed at autopsy within a few weeks.

TABLE I.
The Effect of the Site of Drainage on Ulcer Formation

Days Duration	Circumference Stoma	Dist. from Site of Drainage to Stoma	Dist. from Site of Drainage to Ileo-cecal Valve	Ulcer Formation	Cause of Death	Remarks
	cm.	cm.	cm.			
100	—	59	140	0	Inanition	Distemper and Acute Parotitis
182	4.0	68	242	Present	"	
619	—	Lower Ileum	—	"	Sacrificed	Lost wt. rapidly last 4 mos.
187	4.0	62	170	"	Inanition	
354	4.2	82	216	"	Hemorrhage and Inanition	
357	3.5	123	283	0	Distemper	
210	4.0	80	225	Present	Peritonitis from perforated ulcer	
130	—	82	212	"	" "	
351	3.5	145	220	"	Inanition	
59	—	—	—	"	"	
89	4.0	280	186	"	"	
126	4.0	54	123	"	Peritonitis from perforated ulcer	
35	6.0	250	50	"	Inanition	
29	4.5	180	50	"	"	
30	3.5	203	56	"	Peritonitis from perforated ulcer	
23	4.0	217	62	0	Distemper	
187	—	12	228	Present	Peritonitis from perforated ulcer	
289	3.0	9.5	214	0	Inanition	
169	—	12	—	0	"	
150	—	12	—	Present	"	
356	4.1	16	258	"	Hemorrhage and Inanition	
54	3.0	12	—	"	" "	

Total No. 22. Incidence of ulcer formation 77.3%.

The site of the drainage did not influence the frequency or rapidity of ulcer formation. In dogs 163, 172, 175, 179, and 196 the site of drainage was high; the animals lived 187, 289, 169, 150, and 356 days respectively. In dogs 6, 28, and 34, on the other hand, the drainage was low and yet the animals lived 619, 351, and 89 days respectively. The great variability in ulcer formation is illustrated by the time required for the dogs with very high anastomoses, that is, in which the point of drainage was placed within 16 cm. of the

TABLE II.
Rôle of Operative Trauma in Ulcer Formation.

Days Duration	Circumference Stoma cm.	Dist. from Site of Drainage to Stoma cm.	to Ileo-cecal Valve, cm.	Ulcer Formation	Traumatic Lesions	Cause of Death
36	—	170	95	Present	Healed	Hemorrhage, Inanition
48	2.6	117	70	0	"	"
35	3.5	280	35	Present	"	Peritonitis from perforated ulcer
22	4.0	115	50	0	"	Inanition
*59	4.0	166	56	Present	Chr. Ulc.	Peritonitis from perforated ulcer
71	5.0	165	34	"	Healed	Inanition
14	4.0	190	50	0	"	Distemper
65	3.0	120	50	Present	"	Inanition
31	3.5	170	47	0	"	"
23	3.5	170	80	Present	"	Peritonitis from perforated ulcer
26	—	—	50	0	"	Intussusception of ileum
57	3.5	220	56	Present	"	Peritonitis from perforated ulcer
78	4.0	160	105	"	"	Inanition
45	3.0	110	40	"	"	Peritonitis from perforated ulcer
57	2.5	170	57	"	"	" "
*19	3.5	220	75	"	Unhealed	" "
59	3.2	135	80	0	Healed	Foreign body (sponge) abscess
*39	3.0	170	100	Present	Chr. Ulc.	Peritonitis from perforated ulcer
41	3.0	210	110	"	Practically healed	" "
26	3.5	7.0	—	0	Healed	Sacrificed
147	2.5	28	217	Present	"	Peritonitis from perforated ulcer
94	4.0	5.0	—	"	"	Inanition
33	2.5	7.0	—	0	"	"
33	3.5	6.5	—	0	"	"
88	3.0	7.0	210	Present	"	Peritonitis from perforated ulcer

Total number 25. Incidence of ulcer formation, 64% (16 cases).
Incidence of unhealed traumatic lesions, 12% (3 cases).
*The possibility cannot be excluded that these are instances of spontaneous ulcer formation occurring at the site of the trauma, but independent of it.

gastro-enterostomy stoma, to develop ulcers and die: 187, 289, 169, 150, 356, 54, 94, and 88 days.

Table II shows the group in which traumatic clamp lesions were also produced. The incidence of spontaneous ulcer formation was somewhat lower than in the first group, being 64%. The traumatic lesions apparently healed easily even though spontaneous ulcers developed near by. In 3 instances the traumatic lesions apparently failed to heal. It must be admitted that even in these 3 a spontaneous ulcer might have formed at the same site if trauma had not been applied. In this group as in the first, no direct relationship was noted between the incidence and rate of ulcer formation and the distance between the stoma and the point of duodenal drainage.

Ulcer formation was noted in 33, or 70.2% of the total of 47 cases in the 2 groups. The incidence of death from peritonitis secondary to perforation of the ulcer was 34% (16 cases).

Many of the lesions were solitary (Fig. 1), but frequently they were multiple. In one instance (Fig. 2), 8 discrete ulcers were seen. The lesion nearest the stoma was invariably the largest. The site of predilection was the anterior superior wall of the jejunum, 0.5 to 1.0 cm. distal to the suture line. Occasionally the ulcer extended back to the suture line. The lesions varied in size, usually

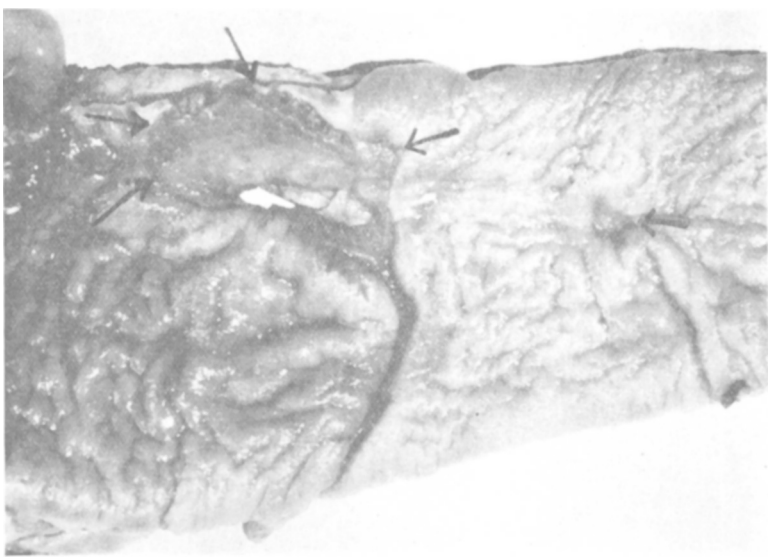

FIG. 1.

Dog No. 111. Duration of life 39 days. Death due to peritonitis from perforated ulcer. The smaller lesion is located at the site of clamp trauma.

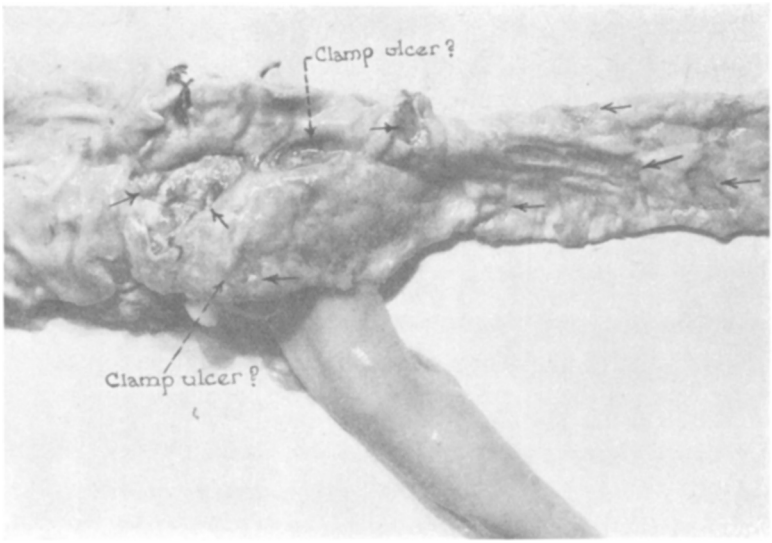

FIG. 2.
Dog. No. 109. Duration of life 19 days. Death due to peritonitis from perforated ulcer. Photograph shows 8 discrete ulcers, 2 occurring at the approximate site of clamp trauma.

being from 1 to 3 cm. in diameter and 0.5 to 1.0 cm. in depth. They were crater-like, indurated, with precipitous or sloping margins.

The time required for death due to ulcer formation ranged from a minimum of 19 days to a maximum of 356 days. In one experiment the animal was sacrificed after 619 days, an ulcer being found at autopsy. The explanation of this variability is not apparent.

No relationship seemed to exist between the size of the stoma and the rapidity with which the lesion developed. This has been confirmed by Jenkins,[6] who has regularly found ulcers in such animals even though a wide side-to-side gastro-enterostomy stoma is employed.

Studies were made of the gastric acidity following operation, the test stimulus used being a milligram of histamine injected subcutaneously. Free acidity was invariably present, the maximum concentration of hydrochloric acid as determined by titration usually being between 0.2% and 0.4%.

This work is further confirmation of the original observations of Mann and Williamson, although the incidence of ulcer formation was slightly less than in their series. The site of duodenal drainage, *i. e.*, whether high or low, seems to be of relatively little importance.

The regularity with which the traumatic lesions heal even though

[6] Jenkins, H. P., to be published.

new ulcers form seems to us to definitely exclude operative trauma as a significant factor in the pathogenesis of the ulcers. It is difficult to understand, however, how a chemical factor alone can be the effective agent. The clamp lesions heal in the same areas in which new ulcers form, bathed by the same fluid. An attractive hypothesis is suggested by the work of Whitlow, who found that the gastric mucosa bleeds readily when the protective layer of mucus is wiped away and hydrochloric acid or acid gastric juice is then applied to the unprotected surface. It may be that the continued ejection of acid gastric chyme is similarly effective in removing the protective layer of mucus from a certain small area of the jejunal mucosa and in traumatizing the cells, thus rendering them susceptible to the attack of chemical agents.

Conclusions. 1. In a total series of 47 animals, the duodenal drainage operation of Mann and Williamson resulted in jejunal ulcer formation in 38 instances, 70.2%. 2. The incidence of death from peritonitis secondary to perforation was 34%. 3. There was no relationship between the site of drainage, *i. e.*, whether high or low in the intestine, and the incidence or rapidity of ulcer formation. 4. Traumatic lesions of the jejunum healed promptly in spite of the formation of new ulcers in adjacent areas. 5. The experimental ulcers under consideration are not due to operative trauma, or merely to the chemical digestive action of the gastric juice, or to the two together. It is quite possible, however, that the continued mechanical and chemical trauma inflicted on the cells of the jejunal mucosa by the ejected acid chyme may be entirely responsible for the formation of the lesions.

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Bromide and Chloride Distribution Between Serum and Cerebrospinal Fluid.

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The report that bromide, after administration by mouth, exists in a higher concentration in the blood serum than in the cerebrospinal fluid attracted our attention because of the following considerations. If equilibrium exists between serum and cerebrospinal fluid, if bromide ions are freely diffusible, and if the protein ions are the only