Small-Bowel Resection
Oral Intake Is the Stimulus for Hyperplasia

GARY M. LEVINE, MD, JULIUS J. DEREN, MD, and ELIZABETH YEZDIMIR

Small-bowel resection leads to hyperplasia of the residual small intestine. However, the factors initiating small-bowel hyperplasia are not clearly understood, although oral intake either by direct contact with the small bowel or via hormonal or neurovascular factors has been suggested as the major stimulus. In order to determine whether oral intake is an obligatory prerequisite for small-intestinal hyperplasia, we compared rats one week after undergoing a 70-cm proximal intestinal resection with sham-operated animals. Resected, orally fed rats demonstrated small-intestinal hyperplasia, whereas resected and sham-operated intravenously alimented rats did not. There were no differences in gut weight, mucosal weight, mucosal protein, or DNA between resected or sham-operated intravenously alimented rats. These data provide direct experimental proof that oral intake is a necessary stimulus for small-intestinal hyperplasia after resection.

It was first observed in the early 20th century that removal of part of the small intestine leads to "compensatory hypertrophy" of the remaining gut (1). More recent research has indicated that there is an increase in the epithelial cell population (hyperplasia) and consequently an increase in small-bowel function per unit length in the residual bowel (2, 3). However, the stimulus for hyperplasia is poorly understood. Several investigations have suggested that dietary intake initiates hyperplasia either by direct contact with the small bowel (2, 4) or via hormonal or neurovascular factors initiated by dietary intake (5, 6).

This study was designed to test whether dietary factors are obligatory in the development of hyperplasia after small-bowel resection by measuring the response of the residual gut after resection in intravenously alimented rats.

From the Gastrointestinal Section, Department of Medicine, Philadelphia Veterans Administration Hospital, and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Supported by a Veterans Administration Medical Research Project 5218-01 and by grants from J. Aron and Company, New York, New York.

Address for reprints requests: Dr. Gary M. Levine, 111H3, Veterans Administration Hospital, University and Woodland Avenues, Philadelphia, Pennsylvania 119104.

MATERIALS AND METHODS

Preparation of Animals and Tissues. Sprague–Dawley male rats, weighing 240–260 g, were anesthetized with ether, and 70 ± 5 cm of proximal small intestine beginning 5 cm distal to the ligament of Treitz to 35 cm proximal to the ileocecal junction was resected by the technique described by Lambert (7). Control animals were sham operated, undergoing transection and reanastomosis of the small intestine 35 cm proximal to the ileocecal junction. Before abdominal closure, all animals received 62,000 units of penicillin G and 5 mg of streptomycin into the abdominal cavity. A group of 6 resected animals were orally alimented with an elemental diet (containing 30% dextrose, 5% amino acids, electrolytes, and vitamins as previously described) (8) ad libitum. A group of 7 resected and 6 sham-operated animals were intravenously alimented with the same elemental diet, receiving 45–50 ml/day by continuous infusion as previously reported in detail elsewhere (8, 9). Infusion was begun immediately after surgery and continued for 1 week.

At the end of the study period, animals were decapitated, the abdomen opened, and the small intestine rinsed with cold 0.9% saline. The entire small intestine was removed and rinsed again with iced saline, blown with 100 ml of air, and drained. Intestinal length was measured under fixed tension of 15 g, and three segments, each approximately 5 cm long, were identified for further study (Figure 1). Segment 1 was residual jejunum obtained 10 cm distal to the pylorus and at least 5 cm proximal to the anastomosis. Segment 2 was residual ileum obtained from

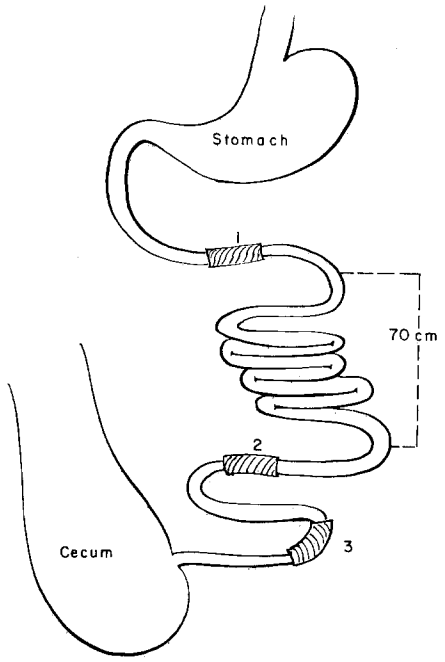

Fig 1. Diagramatic schema showing site of 70-cm resection and the three segments (1, 2, 3) of residual bowel studied.

5 cm distal to the anastomosis and segment 3 was residual ileum obtained from 10 cm proximal to the ileocecal junction. Following isolation of each segment, the exact length was determined and it was blotted dry and weighed. Each segment was then scraped with a stainless-steel spatula on an iced plate, weighed, and homogenized with 5 times its weight per volume of chilled 0.9% saline. This mucosal homogenate was then analyzed and results expressed as weight per cm of intestine.

Analytic Methods. Mucosal homogenates were analyzed for total protein according to the method of Lowry et al using bovine serum albumin as a standard (10). DNA was determined by an adaptation of the method of Schmidt and Thannhauser (11) with a modified diphenylamine reaction (12) and highly polymerized calf thymus DNA as standard. All results were expressed as the mean ± SE. Statistical analysis was carried out by unpaired Student's *t* tests.

RESULTS

Body Weight. Orally fed resected animals lost a considerable amount of body weight during the one week of observation (259 ± 5 gm initially, 245 ± 6 gm at sacrifice). Their average daily intake was estimated to be 35–40 cc/day. Both intravenously alimented resected and transected animals maintained their body weight during the study period, and there were no significant differences between these groups in their initial (261 ± 4 gm vs 251 ± 3 gm, $P > 0.05$) or their final (264 ± 4 gm vs 257 ± 4 gm, $P > 0.05$) weights.

Effect of Oral Intake following Small-Bowel Resection. Since the purpose of this study was to assess whether oral intake is a necessary prerequisite for initiating small-bowel hyperplasia after small-bowel resection, orally fed resected animals were studied primarily to verify that the diet and the time period used in this study were sufficient to allow small-intestinal hyperplasia to take place. The 6 resected, orally fed animals all demonstrated significant small-bowel hyperplasia both proximal and distal to the anastomosis, but it was more marked in distal residual bowel. All parameters examined (gut weight, mucosal weight, protein and DNA content) in each segment studied were significantly greater than comparable segments in sham-operated orally fed animals (Table 1). The data for resected, orally fed rats is presented in Figures 2 and 3 for the purpose of comparison with the data from intravenously alimented rats.

Effects of Intravenous Alimentation following Small-Bowel Resection. 5 resected, intravenously alimented animals were initially thought to demonstrate hyperplasia of the residual gut (13) as gut and mucosal weight of segments 1 and 2 were greater than controls. However, protein and DNA contents

TABLE 1. COMPARISON OF ORALLY FED RESECTED AND SHAM-OPERATED RATS

	Resected (n = 6) (mg/cm)	*Sham (n = 6) (mg/cm)*	*P*
Gut weight			
1*	78.4 ± 2.94†	51.8 ± 0.75	< 0.01
2	78.1 ± 1.24	38.2 ± 2.13	< 0.01
3	54.1 ± 4.19	34.7 ± 0.678	< 0.01
Mucosal weight			
1	64.5 ± 1.92	41.7 ± 1.67	< 0.01
2	64.0 ± 2.24	27.9 ± 2.12	< 0.01
3	44.4 ± 4.43	25.0 ± 1.21	< 0.01
Mucosal protein			
1	6.65 ± 0.410	3.82 ± 0.389	< 0.01
2	7.63 ± 0.456	2.59 ± 0.228	< 0.01
3	4.60 ± 0.400	2.20 ± 0.186	< 0.01
Mucosal DNA			
1	0.423 ± 0.0215	0.334 ± 0.0260	< 0.05
2	0.474 ± 0.0364	0.244 ± 0.0215	< 0.01
3	0.400 ± 0.254	0.269 ± 0.0250	< 0.01

*Segment Number.
†Mean ± SE

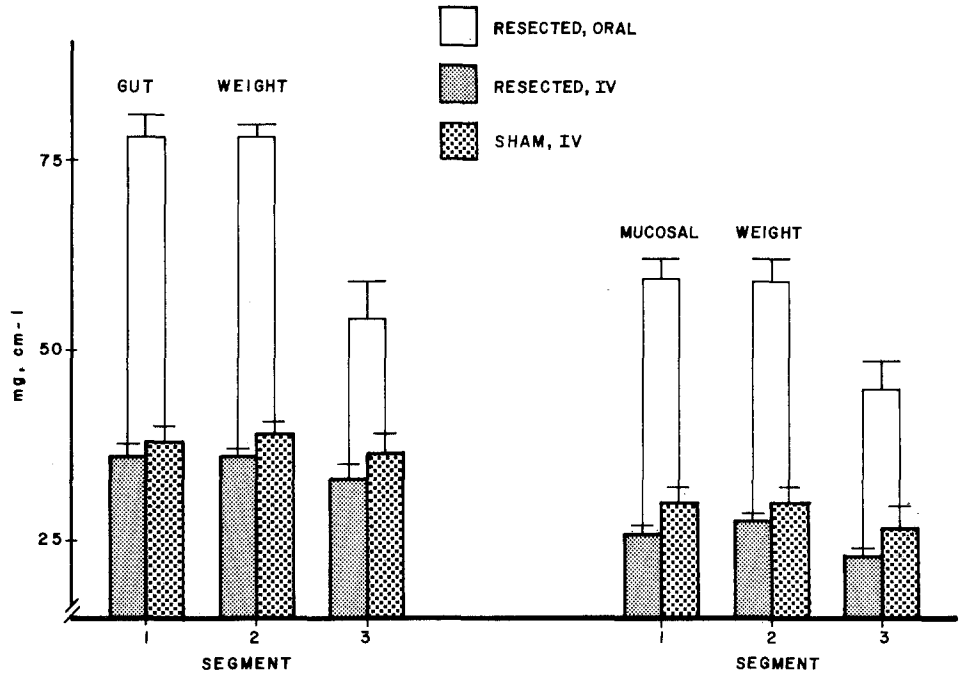

Fig 2. Gut and mucosal weight per cm ± SEM, of intravenously alimented resected and sham-operated rats. Data for orally fed resected rats is provided for comparison.

of these segments were not significantly different from controls, therefore hyperplasia did not occur. Since there appeared to be incomplete obstruction of the anastomosis in these rats, we purposely obstructed the anastomosis in a group of resected rats and reproduced these findings. For these reasons, partially obstructed animals are not included in our comparisons.

In order to establish whether small-intestinal resection by itself leads to hyperplasia, we compared

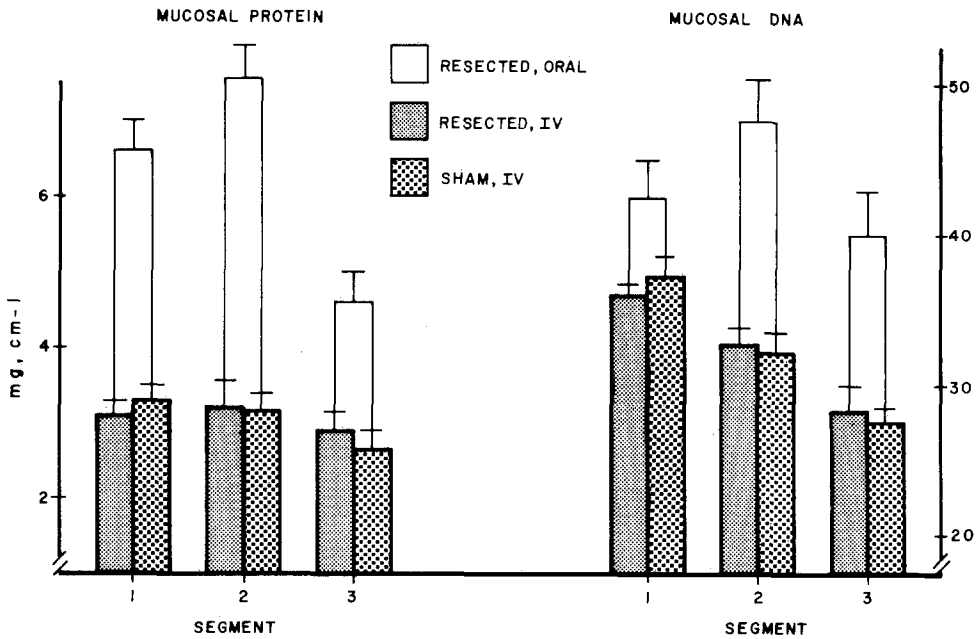

Fig 3. Mucosal protein and DNA per cm ± SEM. Legend as in Figure 2.

intravenously alimented resected rats to intravenously alimented sham-operated animals. In all 7 animals undergoing small-bowel resection, there was no demonstrable effect as compared to the 6 animals undergoing transection. Figure 2 graphically illustrates that gut weight and mucosal weight were not significantly different in intravenously alimented resected and sham-operated animals, but significantly lower than these parameters in orally fed resected animals. Figure 3 illustrates that mucosal protein and DNA were also similar in the resected and sham-operated intravenously alimented animals and significantly lower than in orally fed resected animals.

DISCUSSION

This study establishes that oral intake is an obligatory prerequisite for small-intestinal hyperplasia after resection, as the removal of a large part of the small bowel, in itself, does not provide the signal for hyperplasia. While resected animals orally fed an elemental diet underwent hyperplasia, our study groups maintained on intravenous alimentation did not differ in any respect despite the removal of 70 cm of proximal intestine in the resected animals. A criticism of our study might be that intestinal hyperplasia following resection is delayed in intravenous as compared to orally fed animals. We consider this very unlikely since small-intestinal mass responds rapidly to manipulation (8; Levine, Fox, and Deren, unpublished data). In addition, Feldman et al (14) presented in abstract form a study comparing dogs fed orally or intravenously for 6 weeks following intestinal resection. Their intravenously alimented resected animals failed to show hyperplasia despite the long time interval following resection.

Although oral intake is the initial stimulus, this study does not imply that hormonal or neurovascular factors may not have a role in mediating changes in gut mass, since feeding may lead to profound changes in the hormonal and neurovascular milieu. The fact that hyperplasia occurred proximal as well as distal to the anastomosis in our study as well as those reported in the literature (2) suggest that factors other than intraluminal nutrition mediate hyperplasia.

Johnson et al (15) have reported that chronic gastrin infusion in intravenously alimented rats sustains gut mass as compared to controls, and they have suggested that gastrin is a trophic hormone for the gut. Furthermore, studies in man (16) and the dog (17) have reported elevated serum gastrin levels following massive intestinal resection. Touloukian and coworkers (6) have shown that there are changes in the adrenergic innervation of the gut following resection and Tutton and Helme (18) have demonstrated that adrenergic stimuli effect changes in crypt cell activity. These two studies suggest that neurovascular factors may participate in mediating the response to intestinal resection. However, our study indicates that physiologically, feeding is necessary to directly or indirectly initiate responses leading to an increase in intestinal renewal and subsequent hyperplasia.

In conclusion, this study further demonstrates that the control of small-intestinal mass is a complex phenomenon, but it appears to involve a physiologic response to feeding.

ACKNOWLEDGMENT

The authors gratefully acknowledge the secretarial assistance of Mrs. Marianne Adams.

REFERENCES

1. Flint JM: The effects of extensive resections of the small intestine. Bull Johns Hopkins Hosp 23:127–143, 1912
2. Dowling RH, Booth CC: Structure and functional changes following small intestinal resection in the rat. Clin Sci 32:139–149, 1967
3. Weser E, Hernandez MH: Studies of small bowel adaptation after intestinal resection in the rat. Gastroenterology 60:69–75, 1971
4. Gleeson MH, Cullen J, Dowling RH: Intestinal structure and function after small bowel bypass in the rat. Clin Sci 43:731–742, 1972
5. Tilson MD, Wright HK: Adaptation of functioning and bypassed segments of ileum during compensatory hypertrophy of the gut. Surgery 67:687–693, 1970
6. Touloukian RJ, Aghajanian GK, Roth RH: Adrenergic denervation of the hypertrophic gut remnant. Ann Surg 176:633–637, 1972
7. Lambert R: Surgery of the Digestive System of the Rat. Charles C Thomas, Springfield, Illinois, 1965, pp. 32–35, 413–416
8. Levine GM, Deren JJ, Steiger E, Zinno R: Role of oral intake in maintenance of gut mass and disaccharidase activity. Gastroenterology 67:975–982, 1974
9. Steiger E, Vars HM, Dudrick SJ: A technique of long term intravenous feeding in unrestrained rats. Arch Surg 104:330–332, 1972
10. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: Protein measurement with the folin phenol reagent. J Biol Chem 193:265–275, 1951

11. Schmidt G, Thannhauser SJ: A method for the determination of deoxyribonucleic acid, ribonucleic acid, and phosphoproteins in animal tissues. J Biol Chem 161:83–89, 1945
12. Croft DN, Lubran N: The estimation of deoxyribonucleic acid in the presence of sialic acid: Application and analysis of human gastric washings. Biochem J 94:612–620, 1965
13. Levine GM, Deren JJ: Dietary and nondietary factors mediating hyperplasia of residual gut mucosa after small bowel resection in the rat. Clin Res 22:363, 1974 (abstract)
14. Feldman EJ, Peters TJ, McNaughton J, Dowling RH: Adaptation after small bowel resection: Comparison of oral versus intravenous nutrition. Gastroenterology 66:691, 1974 (abstract)
15. Johnson LR, Lichtenberger LM, Copeland EM, Dudrick SJ, Castro GA: Action of gastrin on gastrointestinal structure and function. Gastroenterology 68:1184–1192, 1975
16. Strauss E, Gerson CD, Yalow RS: Hypersecretion of gastrin associated with the short bowel syndrome. Gastroenterology 66:175–180, 1974
17. Wickbom G, Landor JH, Buskin FL, McGuigan JE: Changes in canine gastric acid output and serum gastrin levels following massive small intestinal resection. Gastroenterology 69:448–452, 1975
18. Tutton PMJ, Helme RD: The influence of adrenoreceptor activity on crypt cell proliferation in the rat jejunum. Cell Tiss Kinet 7:125–136, 1974