

Gastrointestinal Adaptation Following Small Bowel Bypass for Obesity

STANLEY J. DUDRICK, M.D., JOHN M. DALY, M.D., GILBERT CASTRO, M.D., MOHAMMED AKHTAR, M.D.

Small intestinal morphologic and biochemical changes were studied following jejunio-ileal bypass for obesity after body weight stabilization had occurred. Four patients underwent biopsy of in-continuity and bypassed jejunal and ileal segments of the small intestine 11 to 22 months after the bypass operation. Microscopically, marked mucosal villus hypertrophy of the in-continuity bowel was observed, especially in the ileum. Bypassed jejunal mucosa underwent atrophy compared with pre-bypass jejunum, whereas bypassed ileum appeared similar microscopically to pre-bypass ileum. The specific activities of mucosal disaccharidase enzymes (maltase, sucrase, lactase and trehalase) in units per mg protein remained similar to pre-bypass levels in segments of the in-continuity jejunum and the bypassed jejunum and ileum. On the other hand, elevated mucosal disaccharidase levels were measured in biopsy specimens of the in-continuity ileum. Total enzyme activity per unit length of intestine, however, was estimated to be elevated in both in-continuity jejunum and ileum secondary to mucosal villus hypertrophy. These data indicate that following small bowel bypass: (1) the in-continuity ileum undergoes greater biochemical and morphologic adaptation than the jejunum; and (2) intraluminal nutrients and chyme appear to be essential to maximal intestinal adaptation.

SURGICAL TREATMENT of morbid obesity with small bowel bypass procedures has been utilized with increasing frequency despite complications such as wound infection, diarrhea, steatorrhea, anemia, nausea, vomiting, jaundice and severe kwashiorkor.^{4-6,9,10,16,17,20} Following operation, maximum weight loss in these patients usually occurs within the first 6 to 9 months. During this period of time, significant alterations in hepatic structure and function are frequently recognized, perhaps as a result of severe protein-calorie malnutrition and/or bacterial overgrowth in the bypassed segment.^{4,5,10,16-18} Body weight eventually plateaus as protein and calorie assimilation equal expenditures. Despite documentation of intestinal adaptation following massive intestinal resection and jejunio-ileal bypass in animals, little is known

From the Departments of Surgery, Physiology and Pathology, The University of Texas Medical School at Houston, Texas Medical Center, Houston, Texas

about gastrointestinal changes in man following jejunio-ileal bypass.^{1,3,8,12,13,15,18-23} The morphologic and enzymatic changes in the small intestine which occur after jejunio-ileal bypass in four patients are reported.

Materials and Methods

Massively obese patients, weighing greater than 100% above ideal body weight, underwent psychiatric evaluation, and endocrine, gastrointestinal and genitourinary studies prior to jejunio-ileal bypass surgery. At operation, biopsies of liver, jejunum and ileum were obtained for histologic evaluation and mucosal disaccharidase determinations.⁷ A 12 inch long segment of proximal jejunum, measured from the ligament of Treitz, was anastomosed end-to-end to a 6 inch long segment of distal ileum, measured from the ileocecal valve. The proximal end of the bypassed segment was oversewn and fixed to the transverse mesocolon, and the distal end was anastomosed end-to-side to the sigmoid colon (Fig. 1).

Four patients required a second operation 11 to 24 months post-bypass because of the development of a ventral hernia or failure to lose significant weight. The body weights of all four patients had stabilized prior to their second operation (Fig. 2). At operation (Fig. 1), intraluminal culture samples were collected, and biopsies were obtained at: (1) the jejunio-ileal anastomotic site; (2) the proximal bypassed jejunum; and (3) the distal bypassed ileum (12 inches from the ileo-colic anastomosis). Biopsy specimens were processed for histologic examination by light microscopy. Specimens were also assayed for mucosal disaccharidase content according to the method of Dahlquist.⁷ Intraluminal samples were cultured under aerobic and anaerobic conditions. Ventral herniorrhaphy was performed in three patients, while the

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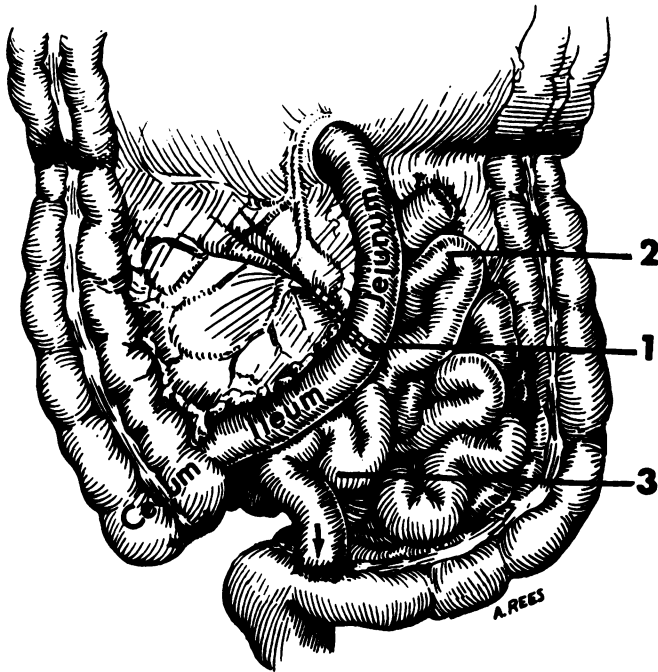


FIG. 1. At operation, intraluminal samples were collected, and biopsies were obtained at: (1) the jejunum-ileal anastomotic site; (2) the proximal bypassed jejunum; and (3) the distal bypassed ileum (12 inches from the ileo-colic anastomosis). Adapted from Scott, H. W., et al., *Ann. Surg.* 177:723, 1973.

fourth patient underwent resection of 6 inches of incontinuity small intestine to induce further weight loss.

Case Reports

Case 1. A 44-year-old female underwent jejunum-ileal bypass on 7/5/73. Prior to operation, the patient weighed 302 pounds and had normal gastrointestinal, genitourinary and endocrine studies except for a glucose tolerance test suggesting a mild pre-diabetes condition. Serum lipid and lipo-protein values were abnormally elevated. Postoperatively, a wound infection became evident and eventually resulted in an incisional hernia. She lost 110 pounds during the first 8 months, and although hepatomegaly developed, liver function tests remained normal. At this time, her glucose tolerance and serum lipid and lipoprotein levels had returned to normal. Barium enema demonstrated reflux into the blind intestinal loop. The incisional hernia was repaired on 11/13/74. At operation, the functioning in-continuity bowel showed marked hypertrophy in contrast to the atrophied bypassed segment (Fig. 3). Aerobic and anaerobic bacterial cultures were obtained from the proximal jejunal bypassed segment, the distal ileal bypassed segment and the jejunum-ileal anastomotic site. *E. coli* and *C. perfringens* were cultured from the latter specimen, while cultures from within the bypassed segment were negative for growth. Specimens of intestine were obtained from these same three areas for microscopic and mucosal enzyme studies (Tables 1, 3, 4 and Fig. 4). Twelve months after operation, the patient weighed 158 pounds and was having approximately 8 formed bowel movements per day.

Case 2. A 49-year-old female weighing 250 pounds underwent jejunum-ileal bypass in February, 1974. Gastrointestinal, genito-

urinary, endocrine and liver function studies were normal. Her postoperative course was complicated by abdominal wound infection resulting in an incisional hernia. Despite counseling, she ingested ethanol in large amounts. Her weight decreased to 172 pounds over the ensuing 9 months. Liver function studies at that time included an elevated alkaline phosphatase of 193 IU (normal level = 40–100) and total bilirubin of 1.4 mg% (normal level = 0.4–1.0) with normal SGOT, SGPT, and arterial blood ammonia concentrations. Barium enema showed free reflux into the distal bypassed segment of bowel. At operation in November, 1975, the distal bypassed bowel appeared dilated without apparent obstruction. Aerobic and anaerobic cultures from the proximal jejunal bypassed segment, the distal ileal bypassed segment and the jejunum-ileal anastomotic site grew *E. coli* and *Bacteroides sp.* Specimens of intestine from these same three areas were obtained for microscopic and mucosal enzyme studies (Table 4 and Fig. 5). Postoperatively, her serum bilirubin concentration increased to 2.8 mg% but returned to normal levels after two and one-half weeks of intravenous hyperalimentation. Three months postoperatively, she had lost an additional 14 pounds and had normal liver function studies.

Case 3. A 33-year-old female weighed 280 pounds before jejunum-ileal bypass in January, 1974. Her preoperative evaluation was normal except for massive obesity. Liver function studies remained normal while she lost 113 pounds over 14 months. Intermittent abdominal pain occurred which was related to a small incisional hernia. In November, 1975, she weighed 138 pounds and had normal gastrointestinal and liver function studies prior to exploratory celiotomy and ventral herniorrhaphy. At operation, her distal bypassed bowel segment was dilated secondary to partial obstruction by adhesive bands. Cultures obtained from the proximal jejunal bypassed segment showed no growth, while specimens obtained from the distal bypassed segment and the jejunum-ileal anastomotic site grew *Bacteroides sp.* and *Peptostreptococcus*. Postoperatively, she has done well, has returned to responsible gainful employment and does volunteer work in our hospital.

Case 4. A 37-year-old female weighed 285 pounds prior to

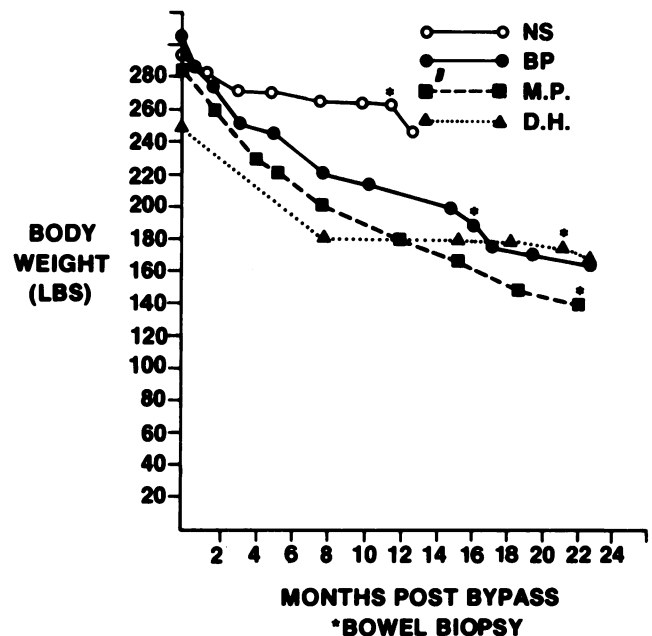


FIG. 2. The body weights of all four patients had virtually stabilized prior to their second operation.

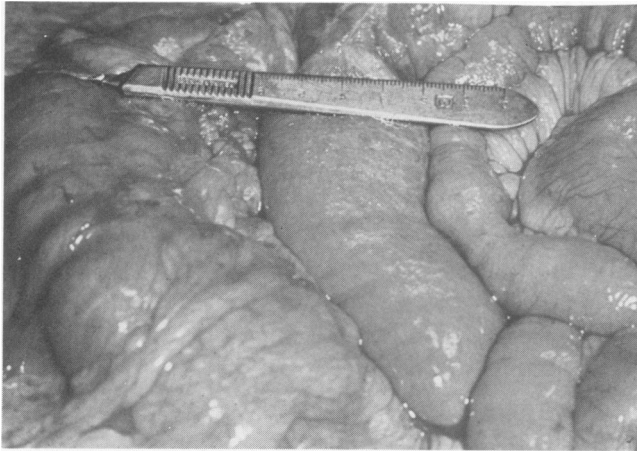


FIG. 3. At operation, the bypassed jejunum was atrophied (right), while the functioning in-continuity bowel was markedly hypertrophied (center), appearing similar in size to the colon (left).

jejuno-ileal bypass in April, 1975. Postoperatively, she had minimal diarrhea with normal oral intake and rapidly adapted her residual in-continuity bowel to the degree that she had only one to three formed bowel movements per day. By July, 1975, she had lost only 14 pounds and had no evidence of liver dysfunction. She continued to maintain her body weight and was re-admitted in February, 1976 for resection of several inches of in-continuity intestine. At operation, marked thickening and hypertrophy of the in-continuity bowel were noted; her ileum measured 7 inches from the anastomosis to the ileo-cecal valve, while the jejunum measured 15 inches from the ligament of Treitz to the jejuno-ileal anastomosis. A segment measuring 6 inches was resected at the anastomotic site (three inches of jejunum and three inches of ileum), and intraluminal cultures were obtained. Biopsies and cultures of the proximal bypassed jejunum and distal bypassed ileum were also obtained. *Candida albicans* and *Clostridium sp.* were grown from all three sites. Seven months after operation she weighed 237 pounds and had approximately three to five formed bowel movements per day.

Results

At operation, the functioning in-continuity small intestine in all patients was obviously hypertrophied

compared with the bypassed bowel (Fig. 3). Histologically, the villi had increased significantly in length in the in-continuity jejunum and ileum, and the crypts had appreciably increased in depth in the ileum compared with the normal pre-bypass specimens (Figs. 4 and 5). On the other hand, villus atrophy was evident in the bypassed jejunum and ileum microscopically, and decreased crypt depth was apparent in the jejunum (Table 1).

Mucosal disaccharidase levels at the time of jejuno-ileal bypass in five control obese patients were significantly elevated in the jejunum compared with the ileum (Table 2). At reoperation, in-continuity jejunal mucosal enzyme activity was similar to that of the bypassed jejunum (Table 3) and to pre-bypass levels in the five obese controls. Specific enzyme activity was elevated, however, in in-continuity ileum compared with levels in bypassed ileum (Table 4) and in pre-bypass ileum (Table 2).

Results of aerobic and anaerobic cultures varied among the four patients and were unrelated to the degree of hepatic fatty metamorphosis. Positive cultures were obtained from the jejuno-ileal anastomotic sites in all patients. Three patients had positive cultures from the distal bypassed ileum, while two patients had positive cultures from the proximal bypassed jejunum. *E. coli*, *Bacteroides sp.* and *Clostridium sp.* usually grew from these cultures.

Discussion

The deleterious effects of jejuno-ileal bypass on hepatic structure and function have been extensively studied clinically and in the laboratory, but little is known about gastrointestinal adaptive changes following jejuno-ileal bypass in man. The exact mechanism responsible for mucosal changes after small bowel bypass are unknown. Intestinal adaptation may occur as a result of several interacting factors. During the

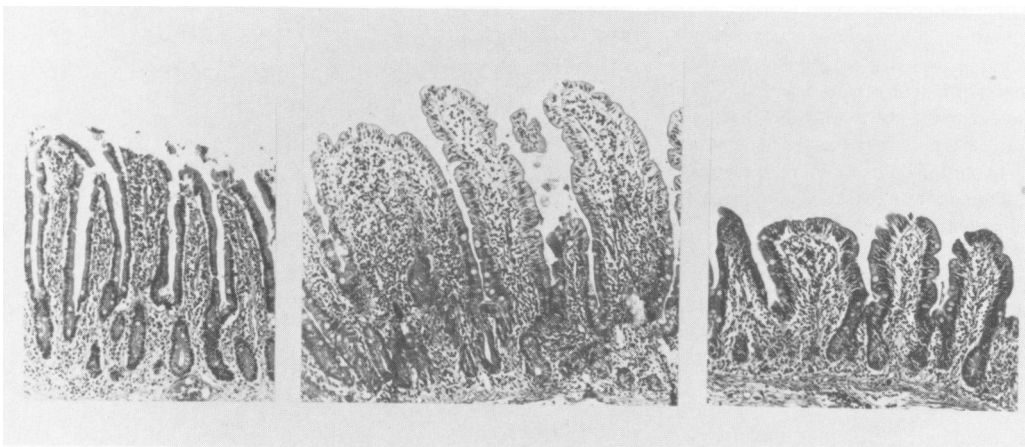


FIG. 4. Microscopic sections of jejunum at the same magnification show the degree of villus hypertrophy in the functioning in-continuity jejunum (center), compared with pre-bypass normal jejunum (left), and the bypassed jejunum (right).

FIG. 5. Marked mucosal villus hypertrophy of functioning in-continuity ileum (center) is evident 21 months post-jejuno-ileal bypass compared with specimens of pre-bypass ileum (left) and bypassed ileum (right).



process of cell transport, nutrients derived from the intestinal lumen might be used by the cell and thereby influence cell turnover and migration. In the ileum, the nutrient content of intraluminal chyme is normally low, villi are normally short, and the rate of cell migration is slow.² In experimental animals, after proximal jejunal resection or when the ileum has been surgically transplanted to a more proximal position in the intestinal tract, marked cellular hyperplasia and more rapid cell migration rates are noted in the ileal segments.⁸ In both of these situations, the ileum is exposed to a greater than normal nutrient load, and seems to have the capacity to increase its surface area and absorptive capacity to jejunal levels. In our patients, greater adaptation, morphologically and biochemically, occurred in the ileum compared with the jejunum after small bowel bypass. Gleeson, et al.¹² demonstrated that when luminal nutrition is excluded from an intestinal segment as in Thiry-Vella bypassed loops of jejunum, mucosal atrophy and diminished absorption occur. These atrophic changes in bypassed bowel correlate with reduced mucosal protein and RNA content and with decreased epithelial-cell migration rate.¹³ Intravenous hyperalimentation in animals has also been demonstrated to result in moderate mucosal atrophy when oral intake is excluded.¹⁴ These changes, however, are prevented when oral nutrition is provided along with intravenous nutritional support.²³ In fact, after massive intestinal resection, intravenous hyperalimentation maintained nutritional status while intestinal adaptation progressed.

While a relative increase in luminal nutrition might explain the greater ileal hyperplasia seen after proximal jejunal resection, it cannot account for the more

modest adaptation which occurs in the jejunum after ileal resection or bypass.¹³ Tilson, et al. found that mucosal villus length and villus cell counts in bypassed segments were similar to those of normal bowel, but were reduced compared with functioning in-continuity bowel.²¹ These findings suggest the presence of a systemic (hormonal) stimulus for intestinal epithelial growth. Gleeson, et al.¹¹ described a patient with diffuse small intestinal mucosal hyperplasia associated with a polypeptide hormone-secreting renal tumor. The intestinal hyperplasia promptly disappeared on removal of the tumor, which was shown to contain large amounts of a polypeptide hormone with characteristics of enteroglucagon. Further support for the systemic hormonal hypothesis was gained when Johnson, et al.¹⁴ demonstrated that parenteral administration of pentagastrin prevented intestinal atrophy in animals fed exclusively by vein.

TABLE 1. Microscopic Mucosal Changes in the Jejunum and Ileum of Four Patients 11 to 22 Months after Jejunum-Ileal Bypass

	Pre-Bypass Jejunum	In-continuity Jejunum	Bypassed Jejunum
Villous Height (μ)	350 \pm 13	490 \pm 10**	240 \pm 15**
Villous Width (μ)	120 \pm 6	134 \pm 20	118 \pm 7
Crypt Depth (μ)	165 \pm 10	170 \pm 6	102 \pm 8**
	Pre-Bypass Ileum	In-continuity Ileum	Bypassed Ileum
Villous Height (μ)	333 \pm 19	500 \pm 22**	310 \pm 26
Villous Width (μ)	130 \pm 10	140 \pm 8	120 \pm 9
Crypt Depth (μ)	155 \pm 16	203 \pm 10*	188 \pm 8

* P < 0.05 as determined by Student's t-test.

** P < 0.001 as determined by Student's t-test.

TABLE 2. *Mucosal Enzyme Activity in Five Control Obese Patients at the Time of Jejunio-Ileal Bypass*

	Disaccharidases (units/mg Protein) \pm S.E.	
	Jejunum	Ileum
Maltase	3.14 \pm 0.51	1.44 \pm 0.48*
Sucrase	1.08 \pm 0.24	0.36 \pm 0.11*
Trehalase	0.23 \pm 0.07	0.08 \pm 0.02*
Palatinase	0.36 \pm 0.08	0.07 \pm 0.01*
Lactase	0.16 \pm 0.06	0.03 \pm 0.01*

* $P < 0.05$ using unpaired Student's t-test.

A third proposed mechanism for the stimulation of intestinal adaptation following intestinal resection postulates undefined factors normally present in bile and pancreatic juice. Altmann¹ transplanted the duodenal papilla together with the biliary and pancreatic ducts, or anastomosed the bile duct alone, to self-emptying ileal segments in the rat. He showed that while bile within the ileal segment produced a mild decrease in villus size, pancreatic secretions stimulated marked villus enlargement. Hormonal factors which may be present in exocrine secretions or may be released from the intestine by pancreatic juice may be responsible for the villus hypertrophy. While controversy exists over the etiology of intestinal changes in bypassed bowel segments, experimental studies uniformly demonstrate villus hypertrophy in the functioning in-continuity bowel. Moreover, these findings are consistent with results reported after massive small bowel resection in animals and man.^{3,8,15,22,23}

Histologic studies in our patients demonstrated increased villus length and mucosal cell hyperplasia in in-continuity jejunum compared with the patient's normal pre-bypass jejunum. Biopsy specimens from bypassed jejunum showed mucosal villus atrophy and decreased crypt depth. Maltase, sucrase and trehalase activity per milligram protein (specific activity) were not significantly different in in-continuity jejunum and bypassed jejunum compared with pre-bypass jejunal mucosal enzyme activity. Lactate activity, however,

TABLE 3. *Mucosal Enzyme Activity in the Jejunum of Four Patients 11 to 22 Months after Jejunio-Ileal Bypass*

	Disaccharidases (units/mg Protein) \pm S.E.	
	Jejunum (In-continuity)	Jejunum (Bypass)
Maltase	3.07 \pm 0.36	4.34 \pm 1.35
Sucrase	0.78 \pm 0.16	0.82 \pm 0.29
Trehalase	0.27 \pm 0.05	0.77 \pm 0.39
Lactase	0.22 \pm 0.09	0.51 \pm 0.12*

* $P < 0.05$ using unpaired Student's t-test.

TABLE 4. *Mucosal Enzyme Activity in the Ileum of Four Patients 11 to 22 Months after Jejunio-Ileal Bypass*

	Disaccharidases (units/mg Protein) \pm S.E.	
	Ileum (In-continuity)	Ileum (Bypass)
Maltase	2.23 \pm 0.48	1.73 \pm 0.77
Sucrase	0.56 \pm 0.19	0.25 \pm 0.14
Trehalase	0.37 \pm 0.28	0.11 \pm 0.02
Lactase	0.23 \pm 0.17	0.04 \pm 0.01

was actually highest in bypassed jejunum. Mucosal hypertrophy in functioning incontinuity jejunum results in markedly increased mucosal surface area per unit length of intestine. This results in increased mucosal enzyme activity per unit length of functioning bowel even though specific activity (enzyme activity per milligram protein) remains unchanged. Our findings correspond to the experimental results of Gleeson, et al.¹³ who studied intestinal adaptation following small bowel bypass in rats. They found decreased mucosal enzyme activity per mg of protein or DNA, but noted increased mucosal enzyme activity per unit length of functioning jejunum. One may postulate that an increased epithelial cell migration rate in functioning bowel mucosa after bypass surgery leads to a less mature mucosal cell with a corresponding decrease in enzyme content. Villus hyperplasia, however, results in increased enzyme activity per unit length of bowel. A relatively slow epithelial cell migration rate in bypassed bowel can result in an increased density of more mature cells with greater enzyme content per cell, but villus atrophy results in diminished total absorptive capacity and surface area.

While the biochemical adaptive changes found in the jejunum after small bowel bypass may be explained by the preceding hypothesis, it does not reflect the changes found in the ileum. Villus height and crypt depth were significantly increased in the in-continuity ileum compared with normal pre-bypass ileum. Biopsy specimens from bypassed ileum, however, were similar to prebypass ileum. Mucosal specific enzyme activities were slightly, but not significantly, greater in the in-continuity ileum compared with the pre-bypass ileum and the bypassed ileum. These findings indicate that, after small bowel bypass, the in-continuity ileum undergoes greater biochemical and morphologic adaptation than the jejunum. Moreover, intraluminal nutrients and chyme seem to be essential to maximal intestinal adaptation.

Our patients demonstrated the expected weight loss characteristic of jejunio-ileal bypass surgery. In the absence of serum enzyme and bilirubin abnormalities, hepatic fatty infiltration was prominent 16 months after

bypass surgery in Case 1. Massive hepatic fatty metamorphosis with early cirrhotic changes at 21 months post-bypass occurred in Case 2, while the liver appeared normal at 22 months post-bypass in Case 3. While many investigators feel that protein-calorie malnutrition accounts for hepatic steatosis, O'Leary, et al.¹⁸ suggest that hepatic fatty infiltration may be secondary to portal venous toxemia as a result of bacterial overgrowth in the bypassed segment. Negative aerobic and anaerobic cultures, however, were obtained from two levels of the bypassed bowel in Case 1, while positive cultures were grown from the in-continuity anastomotic site. Cases 2 and 4 had positive cultures from both proximal and distal sites in the bypassed segment, while Case 3 had positive cultures only from the distal bypassed bowel. In this small series of patients, no correlation was found between bacterial growth in the bypassed intestine and hepatic fatty metamorphosis.

The characteristic weight changes after jejunio-ileal bypass procedures may be explained by alterations in dietary intake and intestinal adaptation. Initially, because of malabsorption, diarrhea and intestinal cramping, there is decreased food intake and absorption which lead to rapid weight loss, protein-calorie malnutrition and hepatic dysfunction. Intestinal adaptation followed by more normal bowel function may then allow improved dietary intake and nutrient assimilation with subsequent weight stabilization.

Further studies in man are needed to describe more specifically the intestinal adaptive responses which follow bypass operations and to clarify the mechanisms responsible for these changes. Such information is essential to assure maximum efficacy and safety in the surgical treatment of massively obese patients.

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DISCUSSION

DR. H. WILLIAM SCOTT, JR. (Nashville, Tennessee): I'm much impressed by the fact that the histologic changes of hypertrophy were more impressive in the shortened ileum than in the jejunum. I would have thought it would have been just the reverse.

(Slide) Let me review with you a bit of clinical data about adaptation. In a series of just under 200 massively obese patients submitted to jejunioileal bypass over the last ten years, we have used the Payne procedure in 11 patients and the end-to-end anastomotic procedure in 186. End-to-end anastomosis of the proximal jejunum to the distal ileum was used with the idea of avoiding the reflux of nutritious