

The Role of Humoral Factors and the Ileocecal Valve in Pathological Changes Occurring after Distal Small Bowel Resection

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IMAMURA, M., TODA, M., SUZUKI, Y., SASAKI, I., SATO, T. and OHNEDA, A. *The Role of Humoral Factors and the Ileocecal Valve in Pathological Changes Occurring after Distal Small Bowel Resection.* Tohoku J. exp. Med., 1987, **151** (2), 155-168 — Experimental studies using dogs were performed to elucidate the participation of gastrointestinal hormones as well as the ileocecal valve in postoperative sequelae following massive small bowel resection. Although in both the ileal resection and the ileocecal resection groups the absorption of fat was reduced postoperatively, body weight tended to increase in the former, while it decreased gradually in the latter. In addition, watery diarrhea persisted after ileocecal resection. Plasma total bile acid concentrations in each group were lower than those before surgery, as were plasma levels of both total glucagon and neurotensin. Although differences were not significant, plasma neurotensin levels tended to be higher after ileocecal resection, but plasma total glucagon levels tended to be lower. Plasma gastric inhibitory polypeptide (GIP) response to butter ingestion was also lower after both ileal and ileocecal resection; especially in the latter case the decrease was significant. These results indicate that the diminished plasma levels of neurotensin, enteroglucagon and GIP may be related to the impairment of adaptive changes in the remaining small intestine. ——— distal small bowel resection; fat metabolism; total bile acid; gut hormones

Massive small bowel resection is often performed in the case of inflammatory bowel diseases, thrombosis of the mesenteric arteries, malignant tumors or adhesive obstruction of the small intestine. Following this procedure, many undesirable sequelae have been reported, such as malabsorption of nutrients (Kremen et al. 1954), disturbance in metabolism of bile acid (Heuman et al. 1982), changes in gastric acid secretion and pancreatic exocrine secretion (Santillana et al. 1969; Seal et al. 1982). The severity of these consequences seems to have a close

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relationship to the site and extent of the small intestine which is resected. Furthermore, the severity of these sequelae after small bowel resection is related to the ability of the retained small intestine to adapt to a new situation. Nygaard (1966) reported that the distal small intestine has a stronger ability for intestinal adaptation than the proximal small intestine.

In recent years, the pathological conditions accompanied by massive small bowel resection have been investigated by measuring gastrointestinal hormones. These hormones have regulatory actions on gastric acid secretion, pancreatic exocrine secretion, gastric emptying, and intestinal transit of nutrients (Junghanns et al. 1975; D'sa Barro and Buchanan 1977; Lilja et al. 1983; Sakamoto et al. 1984). Al-Mukhtar et al. (1983) reported that enteroglucagon plays a very important role in the adaptive changes of the remaining distal small intestine after proximal small bowel resection. Neurotensin is another peptide which is mainly released from the ileum into the circulation and has an effect on gastric acid secretion and pancreatic exocrine secretion (Skov Olsen et al. 1983; Sakamoto et al. 1984). Therefore, it is supposed that neurotensin may also be an essential hormone for intestinal adaptation after massive small bowel resection. Enteroglucagon and neurotensin are both released mainly from the distal small intestine in response to the digestive products of fat (D'sa Barro and Buchanan 1977; Reasbeck et al. 1984). Furthermore, it has been reported that gastric inhibitory polypeptide (GIP), another hormone released from the small intestine, plays an important role in the metabolism of fat as well as carbohydrate (Dupre et al. 1973; Eckel et al. 1979). GIP is also a well-known candidate for enterogastrone (Pederson and Brown 1972), which is released in response to digestive products of fat. In addition, it is well known that the ileum is the site of absorption of bile, which is necessary for the digestion of fat through micelle formation.

The purpose of the present study was to investigate experimentally the effect of the resection of the ileum, alone or together with the ileocecal valve, upon the absorption of fat, metabolism of bile acid, and the release of gastrointestinal hormone, and further to observe the intestinal adaptation resulting from the changes in these factors after distal small bowel resection.

MATERIALS AND METHODS

Ten adult beagle dogs (20–26 months) of both sexes, weighing 9.5–11.0 kg, were used for the experiments. After an 18-hr fast, the fully conscious dogs were given butter (2g/kg) orally for about a min. Blood samples were taken from the foreleg vein via an indwelling catheter. To measure the concentrations of triglyceride, total bile acid and gut hormones, blood was drawn into ice-chilled glass tubes containing EDTA (1.25 mg/ml blood) and aprotinin 500 KIU/ml blood) before and at regular intervals up to four hr after butter ingestion.

After these baseline experiments, the dogs were randomly divided into two groups. Five dogs were subjected to ileal resection; that is the distal half of the small intestine was resected, except for about 2 cm of the terminal ileum, and end-to-end jejunoileostomy was performed. For the other five dogs, the distal half of the small intestine was resected

together with the ileocecal valve and a small portion of the cecum, and end-to-end jejunocolostomy was performed. Each dog was treated with intravenous infusion of glucose solution and antibiotics for five days after surgery. The animals were then fed equal quantities of VITA-ONE® (Nippon Pet Food Co., Ltd., Tokyo) each morning. Three, 6 and 12 weeks after surgery, the experiment was performed on each dog in the same manner as in the baseline study.

Blood samples were centrifuged at 2800 rpm for 10 min at 4°C immediately after completion of the experiments, and plasma was stored at -20°C until the radioimmunoassays could be performed for neurotensin-like immunoreactivity (NLI), total glucagon-like immunoreactivity (total GLI) and immunoreactive gastric inhibitory polypeptide (IR-GIP). An aliquot of the plasma was used for the measurements of the concentrations of triglyceride and total bile acid.

The concentrations of neurotensin in plasma were measured by a radioimmunoassay kit (available from the Immunonuclear Corporation, Stillwater, MI, USA). Each assay tube was prepared with 200 μ l of plasma, 100 μ l of rabbit antineurotensin serum solution and 100 μ l of 125 I-labeled neurotensin (5500-5800 cpm). After incubation for 18 hr at 4°C, 500 μ l of goat anti-rabbit γ -globulin and polyethylene glycol complex were added to each tube, and the preparation was then incubated for 20 min at 20-25°C. The assay was terminated by centrifuging at 2500 rpm for 20 min at 4°C, followed by aspiration of the supernatant. Both the supernatant and the pellet of each sample were counted for 2 min in a gamma-counter. The sensitivity was 3.5-4.5 pg/ml. The intra-assay coefficients of variation were 2.2-6.4%. The interassay coefficient of variation was 6.5% at 45 pg/ml ($n=5$).

The plasma concentrations of total GLI were determined by the radioimmunoassay of Ohneda et al. (1979). The antiserum (G25) crossreacts with both pancreatic glucagon and gut GLI. Bound hormone was separated from free hormone using dextran-coated charcoal. The detection limit was 24 pg/ml. The interassay variation was 13.6%.

The concentration of GIP in plasma was measured by the radioimmunoassay reported previously (Sato et al. 1985). The antiserum (R65), which was generously supplied by Dr. A.J. Moody (Novo Institute, Copenhagen, Denmark), did not crossreact with natural porcine VIP, secretin, glucagon or gut GLI (Lauritsen and Moody 1978). The detection limit was 45 pg/ml. The intra-assay coefficients of variation were 7.3-10.1%. The interassay coefficient of variation was 18.9%.

The plasma concentrations of total bile acid were measured by an enzymatic method using a kit (Bile Acid Reagents from Kyokuto Pharmaceutical Ltd., Tokyo). Plasma triglyceride (TG) concentration was also measured by an enzymatic technique using a kit (Triglyceride G-Test, Wako Pure Chemical Industries, Osaka).

The results were expressed as mean \pm standard error of the mean (s.e.), and Student's *t*-test was used to evaluate statistical significance. Differences with a *p* value of less than 0.05 were considered statistically significant.

RESULTS

Body weight

In the ileal resection group, as shown in Fig. 1, body weight tended to increase postoperatively in each dog, and at 12 weeks after surgery no dogs showed any decrease of body weight. In contrast, in the ileocecal resection group, body weight decreased gradually after surgery, and at 12 weeks the mean weight was 87% of that before surgery. In fact, the weight of the latter group had decreased by 1.0-1.5 kg at 12 weeks. Furthermore, in the ileal resection group only one dog excreted watery stool, while four out of five dogs in the ileocecal resection group produced watery diarrhea, even at 12 weeks after surgery.

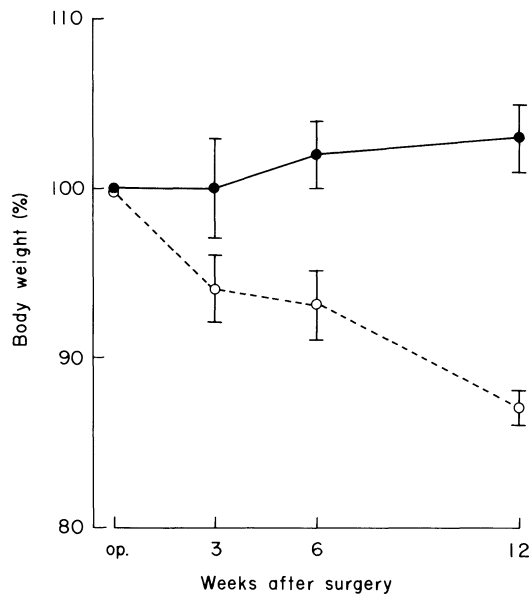


Fig. 1. Weight changes, shown as percentage of preoperative level (100%), following ileal resection (●—●; $n=5$) and ileocecal resection (○—○; $n=5$). Results are expressed as mean \pm S.E.

Plasma TG levels

As shown in Fig. 2, fasting plasma TG concentration was 32.5 ± 3.2 mg/100 ml. After oral butter loading, TG level steadily increased to a peak (76.4 ± 9.6

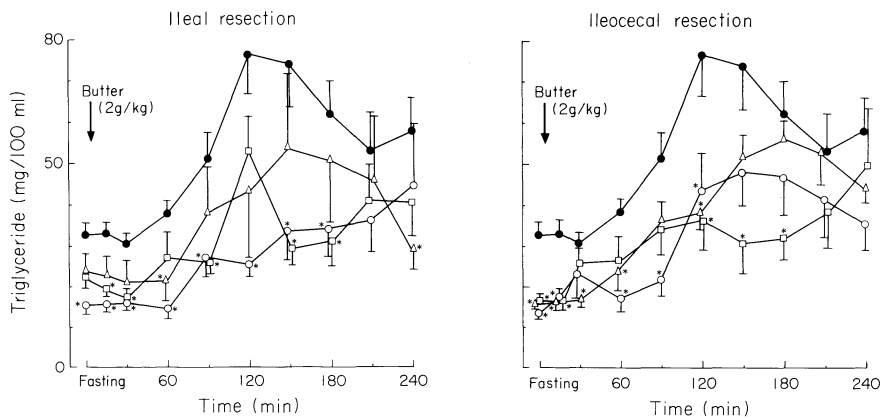


Fig. 2. Plasma concentrations of triglyceride in response to oral ingestion of butter (2 g/kg): before surgery (●—●; $n=10$), and at intervals after surgery of 3 weeks (○—○; $n=5$), 6 weeks (Δ — Δ ; $n=5$) and 12 weeks (\square — \square ; $n=5$). In Figs. 2 to 6, each point represents mean \pm S.E., and the asterisks indicate a significant difference ($p < 0.05$) compared to the preoperative value at the same point in time.

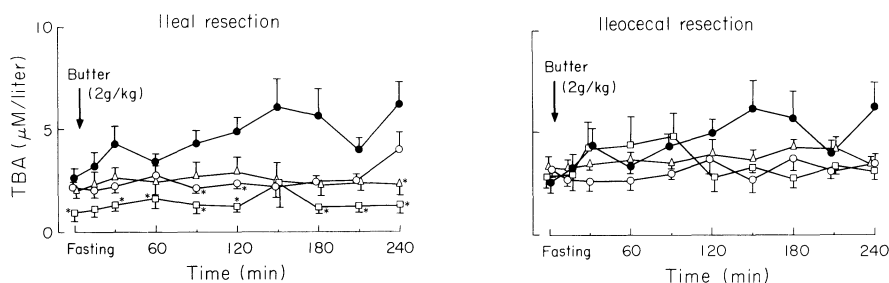


Fig. 3. Plasma concentrations of total bile acid (TBA) in response to oral ingestion of butter (for key to symbols, see legend in Fig. 2).

mg/100 ml) at 120 min, and decreased thereafter. Postoperative TG levels were reduced significantly compared to preoperative levels at several sampling points, and they did not show a tendency to recover to the preoperative levels during the observation period in either group. The integrated increments of plasma TG were slightly greater after ileocecal resection than after ileal resection, though there were no significant differences among the ileal resection, the ileocecal resection and the preoperative groups (Fig. 7).

Total bile acid levels

Fig. 3 shows that in the preoperative studies the fasting plasma total bile acid concentration ($2.6 \pm 0.5 \mu\text{M/liter}$) increased significantly after butter ingestion, with peaks at 30 min ($4.3 \pm 0.9 \mu\text{M/liter}$) and 150 min ($6.1 \pm 1.4 \mu\text{M/liter}$). Following the ileal resection, the fasting total bile acid level was below the preoperative level and there was only a slight increase after butter loading throughout the observation period. In the ileocecal resection group, plasma fasting concentration of total bile acid remained at almost the same level as that before surgery and it tended to rise after butter loading in proportion to the length

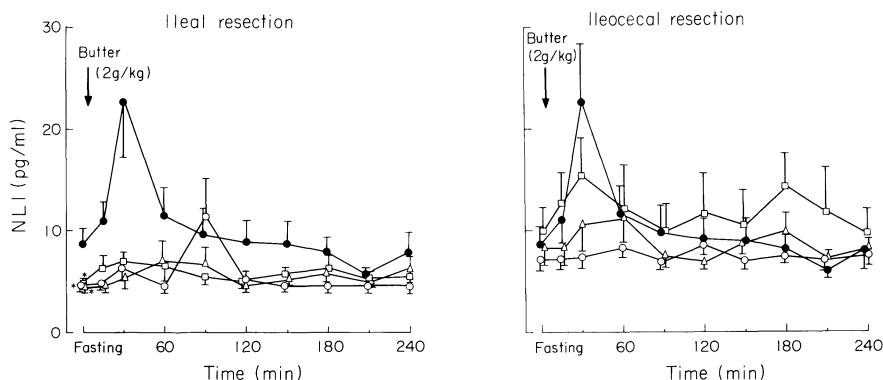


Fig. 4. Plasma concentrations of neurotensin-like immunoreactivity (NLI) in response to oral ingestion of butter (for key to symbols, see legend in Fig. 2).

of the postoperative period. As shown in Fig. 7, the integrated increments of total bile acid concentrations were significantly reduced in both groups, compared with the value before surgery, except for 12 weeks after the ileocecal resection when a slight increase in total bile acid concentration was observed during the first 120 min. There were no significant differences between the ileal resection and the ileocecal resection groups.

Plasma neurotensin levels

Preoperative plasma neurotensin concentration, as shown in Fig. 4, was 8.0 ± 2.3 pg/ml in the fasting state and increased promptly after butter ingestion, reaching a peak (22.6 ± 5.7 pg/ml) at 30 min and decreasing rapidly thereafter to the fasting level. In the ileal resection group, fasting plasma concentrations of neurotensin were significantly lower than those in preoperative studies, and the neurotensin levels rose slightly after butter loading throughout the period of experiments. On the other hand, in the ileocecal resection group, plasma neurotensin concentrations were slightly lower than those before surgery, and they showed a tendency to rise and to form two peaks, especially at 6 and 12 weeks. The integrated incremental responses of NLI (Fig. 7) after butter ingestion showed a tendency to increase postoperatively in the ileocecal resection group, although in fact there were no significant differences between either ileal or ileocecal resection groups and preoperative levels.

Plasma total GLI levels

As shown in Fig. 5, preoperative levels of plasma total GLI at fasting were 1302 ± 86 pg/ml, and they rose significantly after butter ingestion, reaching a peak (2627 ± 430 pg/ml) at 90 min and decreasing gradually thereafter. Throughout the observation period, after ileal resection the fasting plasma total GLI levels were lower than those before surgery. In this group, the GLI responses to butter

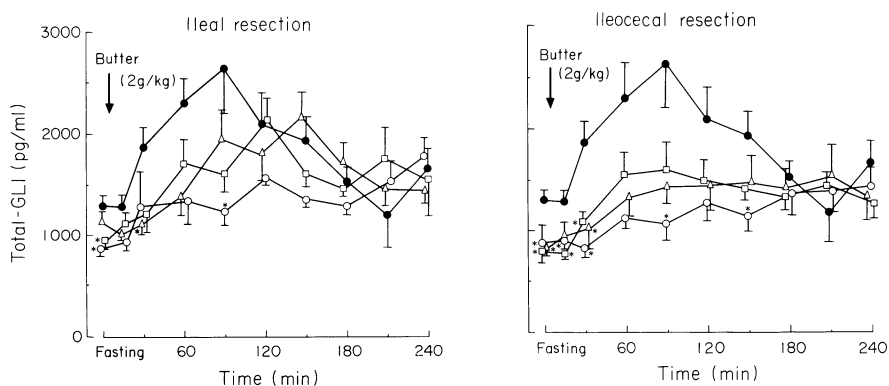


Fig. 5. Plasma concentrations of total glucagon-like immunoreactivity (Total-GLI) in response to butter ingestion (for key to symbols, see legend in Fig. 2).

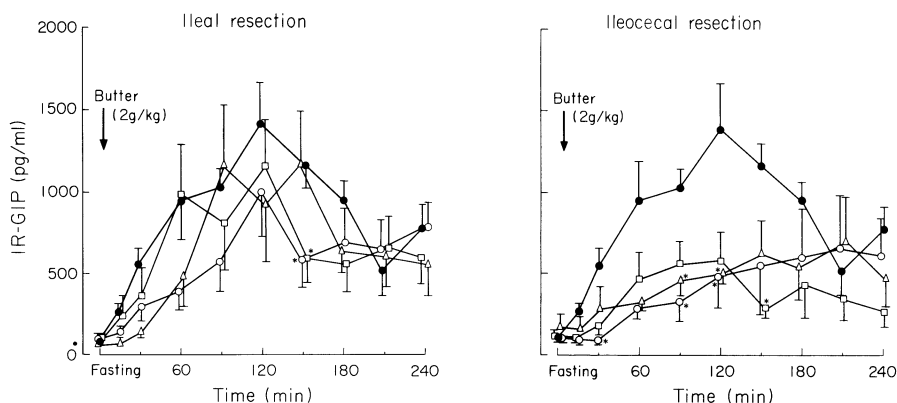


Fig. 6. Plasma concentrations of gastric inhibitory polypeptide (GIP) in response or oral ingestion of butter (for key to symbols, see legend in Fig. 2).

loading recovered to levels near to those before surgery, especially at 6 and 12 weeks. On the other hand, in the ileocecal resection group the fasting levels of plasma total GLI were significantly lower than those in the preoperative studies, and the plasma GLI levels in response to butter tended to be lower than those before surgery throughout the observation period, especially at 3 weeks. The incremental responses of plasma total GLI (Fig. 7) after butter loading tended to be augmented in the ileal resection group in comparison with the ileocecal resection group, though compared to preoperative levels they declined in both groups. With time, these responses tended to regain preoperative levels.

Plasma GIP levels

Fig. 6 shows the changes in plasma GIP concentrations. Before surgery the fasting plasma GIP concentrations were 97 ± 8 pg/ml. Plasma GIP levels increased after butter loading and reached peak levels (1417 ± 840 pg/ml) at 120 min, after which they decreased gradually. In the ileal resection group, the fasting plasma GIP levels were similar to those before surgery, and the GIP levels in response to butter approached those before surgery as postoperative time increased. The incremental responses of plasma GIP were also reduced after ileal resection, as shown in Fig. 7, though there were no statistical differences between pre- and postoperative levels. On the other hand, in the ileocecal resection group, although plasma GIP levels in the fasting state were close to those before surgery, the increase of GIP concentrations in response to butter was markedly reduced and the integrated increments were significantly lower than those before surgery throughout the observation period (Fig. 7). Comparing the incremental responses between the ileal resection and the ileocecal resection groups, the differences failed to achieve statistical significance at any observation period.

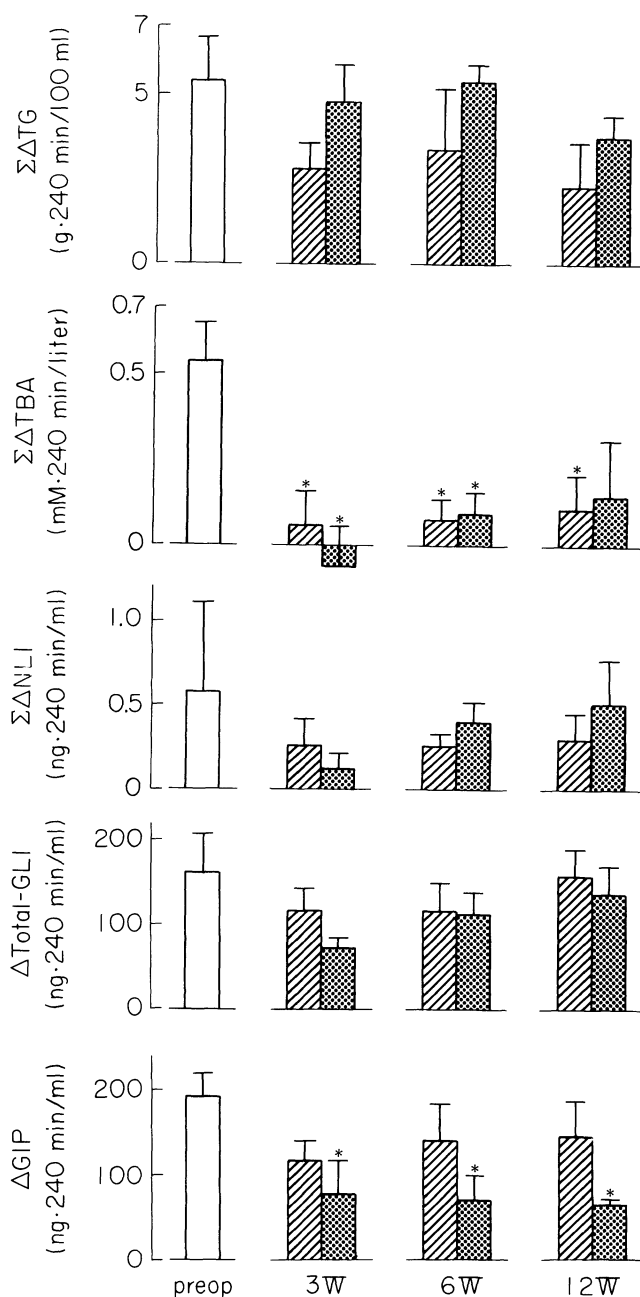


Fig. 7. Integrated increments of plasma triglyceride (TG), total bile acid (TBA), neurotensin-like immunoreactivity (NLI), total glucagon-like immunoreactivity (Total-GLI) and gastric inhibitory polypeptide (GIP) after oral butter loading. \square , before surgery ($n=10$); hatched , ileal resection ($n=5$); dotted , ileocecal resection ($n=5$). Each value represents mean \pm s.e.. The asterisk indicates a significant difference ($p < 0.05$) compared to the preoperative value. There were no significant differences between the two operated groups.

DISCUSSION

It has been suggested that, after massive small bowel resection, a compensatory mechanism involving adaptation of the residual intestine is induced by nutrients, biliary and pancreatic secretions, and/or gastrointestinal hormones (Al-Mukhtar et al. 1983; Sagor et al. 1983; Grey et al. 1984). In the present study, we investigated the adaptation of intestinal function to malabsorption induced by distal small bowel resection by measuring body weight and plasma triglyceride levels in response to butter ingestion. Regarding plasma triglyceride levels, malabsorption of fat was presented in both the ileal resection and the ileocecal resection groups, even at 12 weeks after surgery. Booth et al. (1961) reported that the jejunum is a major site of fat absorption and that increasing amounts of fat reach further into the distal part of the small intestine as the dietary load increases. Regarding the change of intestinal motility, Nygaard (1967) reported that intestinal transit was more rapid after distal resection than after proximal resection. Therefore, it is suggested that as long as 12 weeks after distal intestinal resection, large quantities of fat may escape from the upper small intestine, resulting in the relatively low levels of plasma triglyceride observed following fat ingestion, and that such malabsorption of fat is not related to the presence or absence of the ileocecal valve. On the other hand, as shown in Fig. 1, there was a definite difference in the postoperative change of body weight between the two groups in this study. If a greater amount of butter were loaded than the 2 g/kg which was used in the present study, differences in the impairment of fat absorption after ileal or ileocecal resection might become more apparent. Moreover, there may be severe malabsorption of protein or carbohydrate after ileal resection together with the ileocecal valve throughout the observation period. Hence, the impaired absorption of nutrients may explain the loss of body weight following ileocecal resection. Judging the postoperative nutritional state by change of body weight, therefore, the preservation of the ileocecal valve would seem to be essential. In this respect, Gazet and Kopp (1964) also reported that preservation of the ileocecal junction plays an important role in preventing loss of weight. In other words, if the ileocecal valve is preserved, maintenance of body weight is expected even after massive resection of the distal small bowel.

It is well known that bile, as well as pancreatic enzyme, enhances the digestion of fat by micelle formation. According to the report of Cooper et al. (1982), at least 25 cm of terminal ileum is required for the absorption of bile salts, and in the present study the plasma concentrations of total bile acid were generally lower after both ileal and ileocecal resections than those before surgery. These results are in agreement with the suggestion of Neal et al. (1984) that fat malabsorption, following resection of the distal ileum, is most likely to be due to the impairment of absorption of bile salts and subsequent depletion of the bile salt pool. Regarding the tendency of a gradual rise in total bile acid concentrations

during the observation period in the ileocecal resection group, the participation of bacterial flora in this procedure must be considered as Gazet and Kopp (1964) reported. Accordingly, it is speculated that, in the case of the deficiency of the ileocecal valve, primary bile acids may easily become dehydrated in the upper small intestine by the increased intestinal bacteria, resulting in the increase of absorption of dehydrated bile acids in the jejunum. In this respect, Heuman et al. (1982) indicated that considerable absorption of dihydroxy bile acid occurred from the jejunum in their study of patients with Crohn's disease who had been submitted to ileal resection.

The present study shows that the plasma neurotensin level in response to butter ingestion rose rapidly and reached a peak at 30 min, and that only a small rise in plasma neurotensin concentration was observed after ileal resection, whereas a biphasic response was detected after ileocecal resection especially at the later observation times. These results suggest that neurotensin may be released into the circulation shortly after the ingestion of fat. The response pattern of neurotensin conflicts with the fact that the main locating site of neurotensin-containing cells (N cells) is the distal small intestine (Polak et al. 1977; Iwasaki et al. 1980). However, Rosell and Rokaeus (1979) and Sakamoto et al. (1984) reported similar results to ours; circulating neurotensin concentration reached a peak level at 30–90 min following oral or intraduodenal administration of fat. In relation to this pattern of neurotensin release, they postulated that the proximal part of the gastrointestinal tract is the site of origin of a nervous reflex pathway and/or a neurotensin-releasing hormone. According to Iwasaki et al. (1980), 72.5% of gastrointestinal neurotensin is distributed in the ileum, 21.8% in the jejunum, 5.2% in the duodenum and 0.5% in the large intestine in dogs. Therefore, it is probable that intestinal neurotensin may be released sufficiently from the proximal small intestine as well as the distal small intestine in response to direct luminal stimulation. Furthermore, neurotensin from the large intestine may partly contribute to the biphasic release of neurotensin. This may have a close relationship with the rapid flow of intestinal contents into the large intestine in the ileocecal resection group of the present study.

We measured plasma total GLI concentrations but not glucagon immunoreactivity, which mainly represents the immunoreactivity of pancreatic glucagon. Ohneda et al. (1984) reported that the level of plasma glucagon was less than 150 pg/ml at fasting in both normal and pancreatectomized dogs and did not change significantly following the administration of triglyceride. In contrast, mean plasma total GLI levels ranged from 786 to 1302 pg/ml at fasting and reached the levels of 1445 to 2627 pg/ml after butter ingestion in the present study. Consequently, the changes in plasma total GLI could be assumed to represent those in gut GLI. The fasting levels of plasma total GLI were significantly lower after both ileal and ileocecal resection (except after 6 weeks in the former group) than the preoperative levels. This is expected since the highest numbers of

enteroglucagon-containing cells are located in the ileum (Ghatei and Bloom 1981). In this study, plasma total GLI response to butter ingestion was greater in the ileal than in the ileocecal resection group. This may be explained by a shorter intestinal transit time after ileocecal resection, in the absence of the ileocecal valve. As a result, the time period during which jejunal enteroglucagon-containing cells make contact with the luminal nutrients would be shorter in the case of ileocecal resection. In addition, the fact that in the ileal resection group about 2 cm of the terminal ileum is preserved might be in part the cause of the relatively high response of total GLI. Moreover, in both groups plasma total GLI response to fat ingestion tended to augment at 12 weeks compared to the response at 3 weeks. This may imply that adaptive changes of the retained small intestine are progressing by an augmented release of enteroglucagon.

The decrease of GIP release after ileal or ileocecal resection is explained by the impaired micelle formation of ingested fat, due to the declining bile salt pool and rapid intestinal transit of food. This is conceivable from the following facts: first, GIP-secreting cells (K cells) are distributed mainly in the upper small intestine, rather than the distal small intestine (Polak et al. 1973); secondly, the decrease of GIP release was more marked after ileocecal resection than after ileal resection; and thirdly, the hydrolysis of fat is essential for the release of GIP (Ross and Shaffer 1981). Moreover, Eckel et al. (1979) reported that GIP enhanced lipoprotein lipase activity in cultured preadipocytes and Wasada et al. (1981) showed that in GIP-infused dogs the rise in plasma triglyceride during infusion of chylomicrons was significantly below that of the control animals. Therefore, it should be considered that the impairment of GIP release may result in the disturbance of fat metabolism as well as a change in gastric acid secretion.

There still remains much controversy about the physiological role of neurotensin, enteroglucagon and GIP. Regarding the biological activity of neurotensin, inhibition of gastric acid secretion (Andersson et al. 1976; Skov Olsen et al. 1983) and stimulation of pancreatic exocrine secretion (Sakamoto et al. 1984) have been reported. Similarly, it is known that both enteroglucagon and GIP inhibit gastric acid secretion (Pederson and Brown 1972; D'sa Barro and Buchanan 1977; Christiansen et al. 1979). Therefore, it is speculated that, in addition to GIP, both neurotensin and enteroglucagon may be good candidates for enterogasttrone, the existence of which was first demonstrated by Kosaka and Lim (1930). These same gut hormones may play an important role in the regulatory mechanism of the small intestine, i.e. the ileal brake (Neal et al. 1984). From the experience of enteroglucagonoma (Gleeson et al. 1971), Sagor et al. (1983) reported that after massive small bowel resection, enteroglucagon has a slowing action on small intestinal transit and a hypertrophic action on the intestinal mucosa. Accordingly, the decrease of body weight and prolonged watery diarrhea following the ileocecal resection in the present study, may be brought about by the deficit of the regulatory activity of gut glucagon.

In conclusion, although there were no noticeable differences in the impairment of fat absorption (as estimated here by the changes in plasma triglyceride levels after butter ingestion) between the ileal and the ileocecal resection groups, the body weight tended to increase in the former, while it decreased gradually in the latter. Plasma total bile acid concentrations in both groups were lower than those before surgery. Although plasma neurotensin levels in the ileocecal resection group tended to return to the preoperative levels during the observation period, both the ileal and the ileocecal resections resulted in diminution of fat-stimulated neurotensin release. On the other hand, although both groups showed lower total GLI levels than before surgery, the levels in the ileocecal resection group declined even further than those in the ileal resection group. Plasma GIP responses to butter ingestion in each group were lower than those before surgery, especially in the ileocecal resection group. Therefore, we conclude that malabsorption of fat has a close relationship with decreased plasma total bile acid levels following massive distal small bowel resection, and that the ileocecal valve plays an important role in maintaining a good nutritional state. It is also suggested that diminished plasma levels of neurotensin, enteroglucagon and GIP may be responsible for a reduction in adaptive changes to the remaining small intestine.

Acknowledgments

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