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Evolution of the restorative proctocolectomy and its effects on gastrointestinal hormones

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Abstract

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Gastrointestinal (GI) peptide hormones are chemical messengers that regulate secretory, mechanical, metabolic, and trophic functions of the gut. Restorative proctocolectomy (RPC) or resection of the colon and rectum with maintenance of intestinal continuity through the construction of an ileal pouch reservoir and preservation of the anal sphincters has become the standard of care for the surgical treatment of ulcerative colitis and familial adenomatous polyposis. The manipulation of the digestive system to create the ileal pouch involves altering gut-associated lymphoid tissue among other anatomic changes that lead to changes in GI peptides. In addition, the ileal pouch epithelium responds to a wide variety of stimuli by adjusting its cellularity and function. These adaptive mechanisms involve systemic factors, such as humoral and neural stimuli, as well as local factors, such as changes in intestinal peristalsis and intraluminal nutrients. There have been conflicting reports as to whether the alterations in GI hormones after RPC have actual clinical implications. What the studies on alterations of GI peptides' response and behavior after RPC have contributed, however, is a window into the possible etiology of complications after pouch surgery, such as pouchitis and malabsorption. Given the possibility of pharmacologically modifying GI peptides or select components of adaptation as a therapeutic strategy for patients with ileal pouch dysfunction or pouchitis, a clear understanding of human pouch mucosal adaptation is of paramount importance. In this review, we summarize the evolution of the RPC and its effects on the GI hormones as well as their possible clinical implications.

Keywords

Restorative proctocolectomy; Evolution of functional outcome; Complications; Gut hormones; Epithelial integrity; Quality of life

Introduction

Gastrointestinal (GI) peptide hormones are chemical messengers that regulate secretory, mechanical, metabolic, and trophic functions of the gut. In addition, they can lead to disease states through hyper- or hyposecretion or through anomalies of sensitivity and/or metabolism. These GI hormones are useful as diagnostic tools and may have therapeutic applications for disease states. Restorative proctocolectomy (RPC) or ileal pouch anal anastomosis (IPAA) preserves anal sphincters and has become the standard of care for the surgical treatment of ulcerative colitis (UC) and familial adenomatous polyposis (FAP). Plasma and gastric levels of GI hormones after RPC have been reported [1–14], suggesting that postoperative GI motility may have a period of relative hypomotility that is associated with random, disorganized bursts of electrical activity [15] and that the gut hormones are involved in mediating the adaptive response of the intestine after RPC. The manipulation of the digestive system to create the pouch in this procedure involves altering gut-associated lymphoid tissue that leads to adaptive changes in GI peptides. There have been conflicting reports on whether these alterations in fasting and meal-stimulated plasma levels of different intestinal hormones after RPC have actual clinical implications. What the studies on alterations of gut peptides' response and behavior after RPC have contributed, however, is a window into the possible etiology of complications after pouch surgery, such as pouchitis and malabsorption. In this review, we summarize the evolution of the RPC and its effects on the GI hormones and their possible clinical implications.

History

The surgical treatment for UC and FAP in the early 20th century required proctocolectomy and permanent end ileostomy despite poor stomal appliances and ileostomy techniques. Because of these stoma difficulties and the poor aesthetic and esteem issues associated with it, surgeons and patients wanted to attempt to maintain intestinal continuity. The evolution of the RPC, therefore, started with a direct anastomosis between the anus and the terminal ileum without a pouch being created. In 1933, Nissen [16] reported a successful result after an ileo–anal pull through procedure in a patient with familial adenomatous polyposis (FAP). In 1947, Ravitch and Sabiston [17] reported a proctocolectomy with rectal mucosal stripping followed by the distal ileum being passed through the remaining tube of rectal muscle and stitched to the anal skin as a straight ileo–anal anastomosis. In 1948, Ravitch followed the initial report with one of a proctocolectomy with mucosal proctectomy (excising the distal rectal wall as well) and straight ileo–anal anastomosis [18]. Later in 1951, Ravitch [19] claimed satisfactory functional and metabolic outcome with these procedures, but other researchers [20–22] reported frequent defecation, poor continence, and perineal pain (likely due to perineal irritation from frequent bowel function) with these methods. Moreover, mucosectomy was often technically difficult with a high rate of septic complications of about 70–80%, and therefore, the technique was essentially abandoned.

The return to intestinal continuity seemed even less necessary with the introduction by Brooke in 1952 [23] of an improved ileostomy technique through eversion and immediate mucocutaneous suturing (Fig. 1) and the development of better stoma appliances. Therefore, proctocolectomy and Brooke ileostomy became the first choice for the treatment of ulcerative colitis. During this period, several reports of animal studies [24–26] and human studies [17, 18] produced evidence that the incorporation of an ileal reservoir with ileoanal anastomosis improved functional results considerably as compared to a straight ileoanal (Fig. 2) and/or ileorectal (Fig. 3) technique. Despite initial concerns about preservation of normal bowel function, the operation was sporadically reported during the following decades until later studies showed that the presence of an ileal reservoir, physiologically, was consistent with normal intestinal function. In 1969, Kock [27] introduced the continent ileal reservoir through construction of an internal ileal pouch and creation of an ileostomy after complete proctocolectomy (Fig. 4).

In 1978, Parks and Nicholls [28] presented the first successful use in humans of the pelvic ileal pouch (Fig. 5). The functional results, in terms of stool frequency and anal continence, were very encouraging compared to those reported after straight ileo–anal anastomoses. However, 50% of the patients (with S-shaped reservoir) were not able to defecate spontaneously and therefore emptied the reservoir with a catheter [28–30]. Moreover, there was a high incidence of major complications with a reported pelvic sepsis rate of about 20% [31–35]. Parks et al. [28] advocated preservation of a long rectal muscle cuff almost enclosing the ileal pouch. The procedure then involved mucosal dissection performed via abdominal and transanal approaches with a long outlet between the pouch and the anal canal. The reason for such an approach was, firstly, to preserve rectal sensation considered essential for continence [31, 32], and secondly, to reduce disturbances in sexual function commonly encountered after conventional proctocolectomy [32]. Mucosal dissection of the

low muscular cuffs contributed to a high pelvic sepsis rate, and a long pouch outlet lead to functional imperfection [30]. Shortening of the efferent conduits and the muscle cuffs reduced these complications significantly [30], and postoperative continence was improved significantly after reduction of anal dilatation and preservation of the transitional zone.

The relative importance of the sphincter mechanism and distal rectum as a contributory factor to overall continence is not fully understood, and therefore, alternate different techniques have been employed for the proctectomy as well. The transanal approach with performing mucosectomy from below has been thought to cause direct sphincter damage due to stretch, so a different technique has been employed to avoid the stretch by performing the dissection entirely from above—both technically demanding procedures depending on the pelvic anatomy. Transection of the rectum just above the pelvic floor, e.g., omitting the tedious mucosal dissection from above or below and leaving only a short rectal muscle cuff, and thus, a short outlet eliminated the need for catheterization [33–35] without affecting continence adversely [36, 37]. Avoidance of the mucosectomy with low division of the rectum and maintenance of the most distal 2–3 cm of rectal mucosa (and utilization of a double-stapled technique for the ileal-pouch anastomosis) has shortened operative times with good functional results but need for continued mucosal surveillance. Unfortunately, results of mucosectomy vs double-stapled technique are contradictory in many reports and head-to-head comparative studies are scarce [38–41].

The initial poor functional results of ileo–anal pouches led to a search for other techniques for the ileal pouch construction for which different pouch conformations were attempted (Fig. 6) [30, 42, 43]. In the original S-shaped reservoir design [28], the terminal ileum is folded into three loops 12–15 cm long, leaving a short segment of bowel projecting distally. The loop is sutured side-to-side and the lumina opened. The ileo–anal anastomosis is made end-to-end between the short projecting ileal segment and the anal canal. The J-shaped reservoir with a direct reservoir–anal anastomosis, introduced by Utsunomyia of Kyoto [29] (Fig. 7), soon became one of the most popular pouch configurations, partly due to its technical simplicity but also due to its favorable functional characteristics. It is constructed by folding the terminal ileum into two segments about 15–20 cm long which are sutured side-to-side, opened and joined together forming a pouch by a lateral anastomosis. The ileo–anal anastomosis is constructed side-to-end at the apex of the reservoir. Later, Nicholls [43] introduced the W-shaped or quadruple pouch, which is accomplished by adding another J to the first, which necessarily requires an additional length of ileum to be used in its construction. Attempts have been made to evaluate the functional merits of different pouch designs. Nicholls and Pezim [43] report superior results with the W-pouch compared to the S-pouch both with regard to defecation frequency and leakage. However, other studies fail to confirm this statement [44, 45]. There appear to be no major functional differences between the S- and J-shaped pouches [42, 45]. With its technically easier construction, especially with the advent of surgical stapling devices, the J-pouch has become the RPC pouch configuration of choice [29], and during the 1980s, the RPC became the first effectively functional continent alternative for the curative treatment of UC and FAP.

The functional outcome [1, 47–84] and patient quality of life [47, 50, 54, 63, 66–82] after RPC has been extensively reported. Although patient satisfaction is considered to be high,

results are not perfect regardless of technique. There are consistent reports on changes of enteric bacteriology [85–87], mucosal histological morphology [86–91], and absorption [84–87, 92, 53] of the acceptably functioning reservoir, however, regardless of the operative technique for ileal pouch construction. Studies regarding short- and long-term postoperative morbidity have been widely reported (Tables 1 and 2) [2, 23, 28, 34, 93–99]. The enigmatic syndrome of pouchitis (incidence range: 20–60%) caused by an unspecific inflammation of the reservoir mucosa seems to be the main cause of late morbidity [2, 93–99].

Gastrointestinal hormones

GI hormones are defined as peptides produced by endocrine cells located in the GI tract mucosa [100–111]. These hormones are released into the circulation under the influence of alimentary stimuli and are then involved in the regulation of secretion, motility, and growth of the digestive system [101–104]. A number of GI peptides are also produced by neurons in the central and peripheral nervous systems, particularly enteric neurons [111]. They are delivered locally (paracrine function) to their target cells, without entering the blood circulation, and/or exert biological effects outside the digestive system (endocrine function).

Cells producing GI hormones

Two types of cells synthesize and secrete peptides in the GI tract: endocrine cells [112, 113] found in the GI mucosa and pancreatic islets and neurons [114] located in all layers of the GI wall. Outside the digestive tract, only neurons produce GI peptides [114]. Together with the central and peripheral nervous systems, GI peptides influence (in a stimulatory or inhibitory manner) a number of GI functions, including other exocrine and endocrine secretions, motility, growth, and blood flow. Some peptides also affect secretion of other hormones and/or motility at extragastrointestinal sites, particularly in the circulatory, respiratory, and urogenital systems. They also control liver metabolism and exert various effects in the central nervous system, one of which is the regulation of appetite. Many of these effects result from a direct interaction of the peptides with epithelial, smooth muscle, or endocrine target cells, but some effects are hormonally and/or neurally mediated.

Exocrine secretions of the gastrointestinal tract—GI hormones regulate the secretion and/or absorption of water, electrolytes, enzymes, and mucus by epithelial cells of the GI, pancreatic, and biliary tracts. Thus, in glands of the gastric fundus, which consist of three morphologically and functionally distinct cell types, GI hormones affect the secretion of hydrogen ions by parietal (or oxyntic) cells [115], that of pepsinogen by chief cells, and the secretion of mucus by mucosal cells. Similarly, in the exocrine pancreas, which also shows cellular heterogeneity, GI hormones affect the secretion of water and bicarbonate ions by duct cells and that of enzymes by acinar cells. In intestinal epithelium, they regulate secretion in the crypts and absorption by the villi. Gastric acid secretion is stimulated primarily by gastrin and gastrin-releasing peptide (GRP)/bombesin. Gastric pepsin secretion is stimulated by gastrin, cholecystokinin (CCK), secretin, and vasoactive intestinal polypeptide (VIP). Intestinal secretion of water and electrolytes is also stimulated by VIP. Pancreatic secretion of enzymes is primarily stimulated by CCK but also by secretin,

VIP, substance P (SP), and bombesin. Bile secretion is stimulated by most peptides of the secretin/glucagons and gastrin/CCK families. Virtually, all GI secretions in the basal and hormone-stimulated state are inhibited by SS.

Endocrine secretions of the gastrointestinal tract—Most peptides of the gastrin/CCK and glucagons/secretin families stimulate the release of pancreatic hormones (especially insulin and SS). Bombesin and SS affect the secretion of virtually all peptides; the former is stimulatory, and the later inhibitory. Many of these effects occur via direct interaction of the peptides with endocrine effector cells, although the inhibitory effects of glucagons, VIP, and secretin on gastrin release are mediated by an increase in release of SS [105, 116].

Gastrointestinal motility

The effects of GI peptides on motor function of the GI tract are based on mechanical and/or myoelectrical activity in humans [117]. In general, gastrin, CCK, motilin, bombesin, and neurotensin are primarily stimulatory, whereas glucagon, VIP, gastric inhibitory peptide (GIP), secretin, and SS have mostly inhibitory affects on motility. Some peptides regulate the migrating motor complex (MMC) or myoelectric complex, a cyclical pattern of interdigestive motor activity that propagates from the stomach to the distal intestine [118]. Motilin initiates a fasting pattern (MMC propagation), in contrast to gastrin, CCK, bombesin, and neurotensin, which induce a fed pattern. The rate of gastric emptying and intestinal transit time are traditionally parameters affected by GI hormones in vivo, which in part, reflect changes in motor activity. The effects of GI peptides on GI motility observed in vitro are generally consistent with those observed in vivo [118, 119], although the type of smooth muscle affected and the mechanism of the response (direct and/or neurally mediated) varies depending on the particular peptide and GI region.

Gastrointestinal growth

GI hormones have effects on the growth of epithelial cells in the GI tract and pancreas [119–121]. Some peptides, such as gastrin, CCK, and bombesin, are stimulatory, whereas other peptides, such as VIP and SS, are inhibitory. Effects of GI hormones on the growth of GI epithelial cells can be functionally dissociated from the effects on secretion. GI hormones, especially gastrin, play an important role in the structural and functional changes of the GI mucosa, which occur in response to feeding, in neonatal development, and postoperatively, all of which reduce the amount or alter the position of absorbing mucosa.

Gastrointestinal blood flow

GI peptides regulate GI blood flow in association with the autonomic nervous system, biogenic amines (catecholamines, histamine), non-GI peptides (bradykinin, vasopressin, angiotensin), and intrinsic mechanisms (metabolic and myogenic) [121]. Thus, gastrin, CCK, secretin, glucagons, and neurotensin increase gastric, intestinal and/or pancreatic blood flow, as do VIP and SP (which also affect other vascular beds in the body). It has been suggested that endogenous CCK, secretin, and GIP play a part in the phenomenon of postprandial intestinal hyperemia, and neurotensin has been implicated as a mediator of the increased intestinal capillary permeability seen with the absorption of fat.

Non-gastrointestinal effects of GI peptides

A number of GI peptides, especially those produced by neurons, exert effects outside the GI tract [122]. These include: contraction or relaxation of various types of smooth muscle, especially vascular smooth muscle (VIP, SP, neurotensin), inotropic and chronotropic effects on the heart (VIP), stimulation of water and electrolyte secretion in various exocrine glands (VIP), and stimulation or inhibition of pituitary hormone release (CCK, VIP, SS, SP).

Colon as an endocrine organ

While the colon mainly functions to control propulsion of the fecal stream and to absorb fluids (and some nutrients), it is also considered an endocrine organ [123–131] by producing regulatory peptides via mucosal endocrine cells [128, 131, 132]. With the availability of radioimmunoassay and immunofluorescence techniques, it has been shown that not only are endocrine cells present in the colonic mucosa, but peptides could be identified in mucosal extract and the venous effluent from the colon. Among inhibitory peptides found in the human colonic mucosa are enteroglucagon, VIP, and neurotensin [128, 133].

It was not until the early to mid-20th century that there was an appreciation of the endocrine function of the colon. This was first noted in studies on the colon's effect on gastric function. In 1930, Kosaka and Lim [134] demonstrated that extracts from colonic mucosa that had been exposed to luminal fat were able to inhibit gastric acid secretion. Seal and Debas [123] later showed that colonic perfusion with several types of test substances was indeed a potent inhibitor of gastric acid secretion in animals. Soon-Shiong et al. [124] and Jian et al. [128] confirmed that such an inhibitory influence of the colon on gastric secretion was noted to occur similarly in humans.

Further observations on endocrine functions of the colon, has shown that the colon also influences pancreatic exocrine secretion [110, 111]. Hage et al. [125] noted that colonic perfusion with oleic acid markedly inhibited secretin-stimulated pancreatic secretion. In 1974, Harper et al. [126] demonstrated that colonic extracts given intravenously inhibited stimulated pancreatic secretion (see “Gastric Inhibitory Peptide” below).

Postoperative mucosal adaptation

With removal of the colon and rectum during RPC [28, 29, 44, 135], there is a resulting loss of endocrine cells and neurons in the enteric nervous system. The loss of the hormones produced by these cells, therefore, exerts an influence on the remaining bowel, including its proliferative adaptive abilities [136–138]. There are clear histological adaptive changes in the pouch epithelium both in animals [12] and in humans [87, 88] after RPC. The main features are chronic inflammatory infiltrate in the lamina propria, loss of villous length, and crypt hyperplasia making the pouch mucosa appear more like colorectal mucosa. Such changes were first reported by Senn et al. in 1888 [139] after surgical intestinal manipulations in patients with intestinal obstruction. Similar observations were noted by Flint et al. [140] confirming adaptive changes in patients with extensive resections of the small intestine. After these initial studies detailed the morphological and functional changes in the bowel, research is seeking to understand the basic science pathways underlying

this adaptive process, thought to be linked to changes in luminal nutrition, endogenous secretions, and GI peptides.

Effects of Restorative Proctocolectomy on Gastrointestinal Hormones

The Gastrin family

The gastrin family hormones include gastrin, ghrelin, and CCK (Table 3).

Gastrin

The main sites of gastrin synthesis are in the upper small intestine and in open-type G cells in the gastric antrum [104]. It is the most important peptide in the physiologic regulation of gastric acid secretion [141–143] in response to a meal [115, 142–144]. Excessive secretion of gastrin in humans may lead to basal acid hypersecretion and hyperplasia of the acid-secreting mucosa [145], peptic ulcers, and diarrhea [3, 146, 147].

Gastrin has been studied in UC [3, 148–152], FAP [153], and in RPC-patients [3, 8, 129]. In UC RPC-patients *without pouchitis*, a Swedish study [3] demonstrated no significant changes in serum gastrin levels compared to the pre-RPC values. Despite this, in the same subjects, a significant increase in gastric acid secretion (based on direct measurements and pH monitoring) vs pre-RPC levels was found in fasting retention, basal, and after-pentagastrin stimulation. Interestingly, in UC and FAP RPC-patients *with pouchitis*, a Canadian study [2] found a low level of gastric acid secretion. This may suggest a link between gastric acid reduction and pouchitis that does not appear to be linked to gastrin levels. Gastric hypoacidity in patients *with pouchitis* after RPC might reduce the sterilizing barrier of the gastric acidity [2], which may promote gut microbial proliferation and potentiation of the pouchitis. The microbial etiology of pouchitis is supported by the fact that it is often relieved by antibiotics such as metronidazole [63, 65]. The possible link between pouchitis and gastric hypoacidity may warrant clinical trials looking at the use of agents to increase gastric acidity (e.g., gastrin analogs) or avoiding antacids (e.g., proton pump inhibitors or H₂ receptor blockers) in RPC patients with pouchitis.

Ghrelin

Ghrelin is a novel gastrointestinal growth hormone-releasing peptide produced by P/D1 cells lining the fundus of the human stomach, with potential endogenous anti-inflammatory activities ameliorating some pathologic inflammatory conditions [154]. It is capable of down-regulating the production of proinflammatory cytokines (IL-1 β , IL-6, and TNF- α) and chemokines (IL-8) by activated monocytes and endothelial cells (Th1-mediated immune response). Newer data demonstrates novel therapeutic actions for ghrelin in a mouse model of colitis [154]. Ghrelin, also, stimulates gastric motility and emptying without affect on acid secretion and gastric endocrine cells [155] and acts as an appetite stimulant. Its role as a prokinetic is not well established in humans [154, 157].

There are no study reports on ghrelin in FAP or after RPC, but its levels have been noted to be elevated in the serum of UC patients [156]. A correlation between the severity of the inflammation and ghrelin levels has been suggested, although no association was found

with clinical disease activity. Patients with ileal Crohn's disease had higher ghrelin levels compared to colonic Crohn's disease [154–157]. Further research may lead to advances in the treatment of conditions such as inflammatory bowel disease, pouchitis, and postoperative ileus.

Cholecystokinin (CCK)

CCK is secreted by open-type cells (I cells), which are most densely located in the small intestine and gradually decrease in number toward the large intestine [158–160]. CCK has a wide range of effects on the GI tract. Three physiological effects on gut motility have been identified: contraction of the gallbladder [158], relaxation of the sphincter of Oddi [159], and inhibition of gastric emptying [158]. CCK also increases pancreatic enzyme secretion [158]. Its role on colonic motility is controversial. While Behar et al. [158] were able to demonstrate increased colonic contractions after CCK administration, Niederau et al. [160], Chijiwa et al. [161], and Makino et al. [162] could find no effect of CCK on colonic motility. Several studies in different species have reported that after colectomy, there are higher plasma concentrations of CCK, both basal and postprandial, compared to healthy controls [163–165]. It has been suggested that this is due to depletion of an inhibitory factor of CCK secretion which is released from the colon. It is not known if the elevated CCK levels observed in colectomy patients [163–165] have any impact on GI motility or health.

RPC is known to predispose patients to the formation of gallstones [165, 166]. Gallstones formed in proctocolectomy patients are mainly composed of cholesterol [162]. Harvey et al. [163] reported that 3 of 20 of his colectomy patients had gallstones classified as cholesterol stones. On the other hand, Galatola et al. [164] suggested that RPC did not predispose patients to the formation of cholesterol gallstones. Noshiro et al. [165] found pigment gallstones in seven of ten colectomized animals. The stones were composed mainly of sodium bilirubinate and proteins and differed from the black pigment stones formed in humans. These studies suggest that pigment gallstones may not be formed in colectomy patients. However, one case of pigment gallstone formation in animals after RPC has been reported [166]. The interrelationship between the colon, ileal pouch, CCK, and gallstone formation has yet to be clarified.

The Secretin family

The hormones in the secretin family include secretin, vasoactive intestinal polypeptide (VIP), peptide histidine methionine (PHM), enteroglucagon (GLP), and gastric inhibitory peptide (GIP) (Table 4).

Secretin

Secretin was the first hormone ever discovered. It is produced in the S cells of the duodenum in the crypts of Lieberkühn. Its primary effect is to regulate the pH of the duodenal contents via the control of gastric acid secretion through buffering with water and bicarbonate [167, 168]. There are no studies of secretin after colectomy and/or RPC.

Vasoactive Intestinal Polypeptide (VIP)

Initially, VIP was only considered to be a gut hormone, but it was later shown to be widely distributed throughout the central and peripheral nervous systems and to be associated exclusively with neurons [169]. The major effect of VIP is to inhibit absorption and stimulate the secretion of water and electrolytes (especially chloride) and to inhibit enzyme secretion in the small and large intestine [170, 171]. VIP also has a role in the relaxation of gut smooth muscle sphincters in response to certain stimulants [171].

VIP has been studied in RPC patients. The number and density of VIP-immunoreactive nerve fibers in the lamina propria were markedly increased in the pouch of RPC-patients *with pouchitis* when compared to the number of fibers in a normal RPC pouch, in the ileum of UC patients, and in the normal ileum [172]. This suggests that VIP may play a role in pouchitis perhaps by mediating inflammatory processes that may contribute to the regulation of intestinal motility [172, 173]. Hypothetically, increased VIP production could also lead to increased alkalization of the intestinal effluent (neutralizing the gastric acid bacterial barrier), thus, permitting further bacterial overgrowth in the ileal pouch and worsening pouchitis. This has not been scientifically confirmed.

Peptide Histidine Methionine

Peptide histidine methionine (PHM) is structurally related to VIP [169, 174] and shares many of its biological activities, just less potent. It was first identified as part of the sequence of the VIP precursor, and it was later isolated from the colon [175, 176]. The mucosal–submucosal concentrations of PHM in UC show a significant decrease when compared to normal colon [177]. These results indicated that PHM, like VIP, is localized within the same neural structures that have been altered in idiopathic inflammatory bowel diseases. There are no studies regarding the effects of RPC on PHM.

Enteroglucagon

Enteroglucagon is produced by endocrine cells of the colonic mucosa and from L-cells in the distal small intestine [178–180]. It is immunochemically related to pancreatic glucagon but heterogeneous as to molecular size, charge, and nature of the glucagon-like peptides (GLP) [181–183]. Enteroglucagon stimulates liver glycogenolysis [184] and insulin release from the pancreas [185], albeit with lesser potency than pancreatic glucagons. Under both normal and pathologic conditions, enteroglucagon is an important regulator of intestinal epithelial proliferation [123, 124] by inhibiting gastric acid secretion and intestinal motility. There are at least two subtypes of enteroglucagon [186–188]: GLP-1 which stimulates the release of insulin in response to glucose and inhibits the release of pancreatic glucagon; and GLP-2 which shows a direct proliferative action on human intestinal epithelial cells suggesting that it can be a regulator of proliferation, depending on the target cell type. Most of the stimuli for the secretion of enteroglucagon are luminal [183, 185, 189] and include glucose, triglycerides, or the ingestion of a mixed meal. Two regulatory peptides known to influence the rate of enteroglucagon release are SS, which inhibits it, and bombesin, which stimulates its release.

Enteroglucagon has been noted to be increased in RPC-patients [4, 5, 13]. In contrast, Palnaes Hansen et al. [122] found a lower concentration of GLP-1 in patients after RPC than in controls or patients after proctocolectomy and end ileostomy. Therefore, increasing the circulating and tissue levels of enteroglucagon could be important in patients with intractable diarrhea by decreasing intestinal secretion, slowing intestinal transit and increasing small bowel absorption [4, 5]. Hypothetically, when the colon is resected, the production and release of enteroglucagon would increase in the remaining small bowel, suggesting that L-type endocrine cells may participate in adaptive responses that improve intestinal function after colonic surgery.

Gastric Inhibitory Peptide

In the human GI tract, gastric inhibitory peptide (GIP) is released from endocrine K-cells, which are present at highest concentration in the duodenum and jejunum [190]. GIP is a GI hormone whose major effects are to inhibit gastric acid secretion through gastric motor activity and stimulation of intestinal secretion of water and electrolytes. GIP also enhances insulin secretion in the presence of elevated glucose concentrations [122, 191]. Glucose metabolism by the β -cell is a prerequisite for GIP-stimulated insulin secretion to occur. At supraphysiological concentrations, GIP inhibits gastric acid secretion in humans.

Studies on GIP have shown how normal colon is capable of influencing pancreatic and gastric function [3, 122, 127]. Palnaes Hansen et al. [122] concluded from patients undergoing RPC for UC that the effects of the proctocolectomy on the “enteroinsular axis” may be due to adaptive changes in the small intestine and the absence of endocrine factors from the colon. This study on the enteroinsular axis in patients with UC after colectomy included patients with a conventional ileostomy, patients with an ileo–anal reservoir, and normal controls. The concentrations of GIP were measured in plasma during an oral glucose test with peak levels of GIP being significantly higher in RPC patients vs end ileostomy patients and controls [122]. The peak level was four times higher in RPC patients compared to controls... Patients with an ileo–anal reservoir in this study showed a slower GLP-1 response after intake of glucose. These results suggest that the colon, with its physiologic role as an endocrine organ, affects the enteroinsular axis through GIP release, perhaps leading to hyperinsulinemia and an impaired glucose tolerance. The clinical relevance of this is yet unclear.

The Pancreatic Polypeptide Family

The three hormones in the pancreatic polypeptide family include pancreatic polypeptide (PP), peptide tyrosine–tyrosine (PYY) and neuropeptide Y (NPY) (Table 5).

Pancreatic Polypeptide

PP is a CCK antagonist polypeptide secreted by PP cells in the endocrine pancreas, predominantly in the head of the pancreas. It suppresses pancreatic secretion and stimulates gastric secretion, GI motility, and pancreatic growth [192]. The release of PP into the blood is stimulated by luminal nutrients, especially lipids and proteins. Studies after RPC and/or colonic resection showed an elevation in the levels of PP [8, 143, 193–196]. After intestinal resection, PP was the most elevated hormone observed [197]. This may also be due to

the presence of inflammatory bowel disease as this condition alone is also associated with elevated levels of PP [196, 197]

Peptide tyrosine–tyrosine

Highest tissue concentrations of PYY are seen in the rectum, sigmoid colon, ascending colon, and ileum [198–201]. PYY is regulated by luminal stimulants, paracrine factors, and vagal influence. The peptide is released in response to the ingestion of a meal, particularly fat and proteins [198, 202]. PYY mediates the inhibitory effect of oleic acid on gastric and pancreatic secretion, and thus, corresponds to the so-called “enterogastrone”, “pancreatone”, and “anti-CCK hormone”. In the small intestine, PYY reduces jejunal contractility and increases small intestinal transit times. Furthermore, PYY is a potent inhibitor of water and chloride ion secretion from jejunal crypt cells and a trophic hormone that may be important in both the development of the intestinal mucosa and dietary adaptation.

There are conflicting reports on the effects of RPC on PYY [1, 4–14]. Some authors noted decreased PYY levels [1, 6–8], while others noted increased PYY levels [4, 5, 10–14] after RPC. Armstrong et al. [4] and Pietroletti et al. [5] observed significant increases in basal and postprandial plasma PYY concentrations after RPC for both UC and FAP patients compared to healthy controls. These increases in the release of PYY seems to be involved in the “ileal brake” [13], a physiologic phenomenon that mediates the adaptive response of the GI tract and is related to a compensatory increase in L-cell density in the mucosa of the ileal pouch, perhaps affecting functional results [1, 4, 5, 10, 11, 14, 118, 119, 149, 202–204]. These results include pouch volume, evacuation, and compliance along with sphincter function and volume of the stool reaching the pouch. PYY also inhibits gastric acid, pancreatic exocrine, and pepsin secretions, along with retention of gallbladder contents [122, 204]. It also acts as a potent intestinal vasoconstrictor and slows gastric and intestinal transit [198, 199, 204]. Thus, increased basal and meal-stimulated release of PYY after RPC might lead to improved pouch function by decreasing the volume of fluid reaching the pouch and its evacuation. Basal plasma PYY concentration and PYY response in RPC patients with pouchitis did not differ from those in patients without a history of pouchitis [4–7, 10]

Neuropeptide Y

NPY is a neurotransmitter peptide found in the brain and autonomic nervous system. It is a powerful vasoconstrictor and exerts numerous inhibitory effects on the GI tract, particularly on gut motility. In patients with slow transit chronic constipation (e.g., Arbuthnot Lane’s syndrome) that underwent surgery with subtotal colectomy and ileo–rectal anastomosis, NPY immunoreactivity was increased in the myenteric plexus [205] demonstrating that NPY acts as an autocrine neurotrophic factor for enteric neurons [206]. The NPY has also been associated with a number of physiologic processes in the brain, including the regulation of energy balance, memory, and learning [201, 204]. It also forms part of the “lipostat” system along with leptin and corticotrophin releasing hormone. NPY has not been studied in connection with RPC.

Miscellaneous

The miscellaneous group of hormones includes motilin, neurotensin, SS, gastric releasing peptide, bombesin, SP, galanin, thyrotropin-releasing hormone, and calcitonin gene-related hormone (CGRP) (Table 6). Of these, only motilin, neurotensin, SS, and SP has been studied in connection with RPC.

Motilin

Motilin is found in open-type M cells of the epithelium throughout the small intestine, most dense in the duodenum and proximal jejunum [207]. Motilin regulates the interdigestive motility of the stomach and small intestine [208–220]. The release of motilin into the blood is stimulated by, among other things, luminal acid and pancreatico-biliary secretions and by circulatory bombesin [210, 215, 216]. Acidification of the duodenum produces a prompt increase in plasma motilin, whereas alkalization produces a decrease [215, 216].

Basal plasma motilin levels were noted to be elevated after RPC when compared to patients with a continent ileostomy, end ileostomy, active ulcerative colitis, and healthy controls. Similar changes also occurred in ulcerative colitis patients and those with conventional ileostomy [8]. These changes in motilin levels are difficult to interpret, but may be due to alterations in luminal acidification associated with UC or after RPC, but this has not been fully elucidated.

Neurotensin

Neurotensin causes vasodilatation and hypotension, but affects several GI functions as well [221, 222]. In the GI tract, neurotensin predominates in the epithelium of the distal jejunum and ileum where it is synthesized and released by endocrine N-cells. It inhibits basal and stimulated acid and pepsin secretion, pancreatic exocrine secretion, and GI motility. Hallgren et al. [223] reported effects of RPC on neurotensin in both RPC-patients with a diverting loop ileostomy and in those without. The neurotensin levels were noted to be identical. It seems therefore that maintenance of bowel continuity has no effect on the secretion physiology of neurotensin.

Somatostatin

In the human GI tract, SS reaches highest concentrations in the stomach and duodenum [116, 224] and is associated predominantly with the mucosa and submucosa. SS is released from GI and pancreatic endocrine D-cells. In humans, all major classes of nutrients and a number of GI peptides stimulate SS release. Inhibitors of its secretion include endorphins and SS itself. SS is the predominant inhibitory hormone of the GI tract and has also been shown to inhibit the growth of the GI mucosa and normal pancreas [225]. The mechanism by which it inhibits acid secretion may involve release of prostaglandins [226], but this has been disputed [227, 228].

SS's inhibitory effects have been beneficially used in clinical trials [229–231], including reducing complications after RPC [230, 232–234]. Because of its anti-secretory effect (or its octapeptide analogue, octreotide), SS has been used in the treatment of pouch dysfunction [230, 232] and in the reduction of the effluent volume associated with high ileostomy output

or post-RPC diarrhea [233]. Long-acting SS has been shown to be effective for prolonged diarrhea in patients who have undergone RPC and have not responded to conventional medications [232–234]. Gullichsen [235] observed that approximately 72% of post-RPC-patients with diarrhea, who were treated with long-acting octreotide, experienced a marked reduction in bowel movement frequency. The active peptide analogue of SS has also been effectively used as an agent to ameliorate symptoms after RPC from bowel and anastomotic strictures, pouchitis, or cuffitis [234–236].

Bombesin and Gastric Releasing Peptide

Bombesin/GRP has been identified in the GI tract associated with neurons and is found predominantly in the mucosa of the gastric fundus and the muscular layer of the antrum and intestine [237]. Bombesin, like GRP, stimulates the release of gastric acid secretion, gastrin, and a variety of other GI peptides [237]. Bombesin has been used in studies to stimulate plasma CCK levels and decrease gallbladder volume. In patients, after RPC was compared to normal controls, bombesin had a significantly greater effect on CCK levels [156]. These findings suggest that the colon may contain a factor that inhibits the release of CCK and that colectomy may have an impact on the formation of the reported cholelithiasis after RPC [158–163].

Substance P

In the GI tract, SP is found predominantly in the muscular layer of the intestine and is also present in a subpopulation of endocrine enterochromaffin cells [174, 238]. The biological action of SP is as a potent stimulator of GI motility, and it affects numerous other GI functions. In the circulatory system, SP causes potent vasodilatation.

The SP distribution in RPC patients has been documented by Keranen et al. [172, 173]. The number and intensity of SP immunoreactive nerve fibers were markedly increased in pouches of patients with pouchitis as compared to normal pouches, the ileum of UC patients, and to normal ileum. The results suggest that SP may play a role in mediating inflammatory processes in patients with pouchitis.

Galanin, thyroid releasing hormone, and calcitonin gene-related hormone

There are no studies on the effects of RPC on galanin, thyroid releasing hormone (TRH), and CGRP.

Effects of galanin on GI function have been widely reported [238–243]. Investigations show that galanin suppresses gastric emptying [239], increases gastric motility [240], and induces hyperphagia [228, 242–244]. Galanin is known to be involved in the regulation of feeding and gastric motility [239–242], and therefore, colectomy and RPC procedures alone may not negatively affect the physiological function of galanin.

TRH was the first hypothalamic-releasing factor to be isolated [244]. TRH is widely distributed throughout the GI tract with concentrations in the pancreas, stomach, and colon [245–248]. Secretion of TRH, and hence, thyroid-stimulating hormone (TSH), is inhibited by high blood levels of thyroid hormones in a classical negative feedback loop. Loss of TRH

secretion cells from the colon, after colectomy, is compensated for by other sources of TRH secreting cells in the GI tract.

CGRP is a mediator of gastric mucosa and produces splanchnic and peripheral vasodilatation [249]. As CGRP release is stimulated by glucose, a role for CGRP in producing postprandial hypotension has been suggested. It regulates food intake at both peripheral sites and within the central nervous system. CGRP release is also stimulated by acid in the gastric mucosa. The CGRP released from primary afferent sensory nerves stimulates the release of SS, thus, decreasing gastric acid secretion.

Conclusions

Restorative proctocolectomy has become the standard of care for the surgical treatment of most UC and FAP patients. The RPC results in a series of adaptive responses by the GI tract, including morphologic changes and proliferation of enteroendocrine cells in the ileal pouch. Basal and postprandial plasma gastrin, enteroglucagon, neurotensin, VIP, CCK, GIP, PYY, motilin, SS, SP, and PP levels in RPC-patients have been studied. Observations on digestive function and circulating and morphologic gut endocrine responses after RPC are often contradicting and with unclear clinical implications. After an ileal reservoir, sufficient reserve apparently remains for the majority of GI hormones to maintain adequate release into the circulation, suggesting compensation for the presence of an ileal reservoir and the absence of a colon and rectum. Further studies of the ileal pouch after RPC for FAP vs UC should clarify whether the underlying disease process is responsible for some of the hormone changes noted after RPC. Reservoirs may show neuromorphologic and histologic alterations that appear to be related to mucosal inflammation but may be due to adaptive changes alone. Therapeutic strategies to improve intestinal function and enhance repair and regeneration of the intestinal epithelial integrity have been inadequate and remain the goal of future research into the GI peptide changes after RPC.

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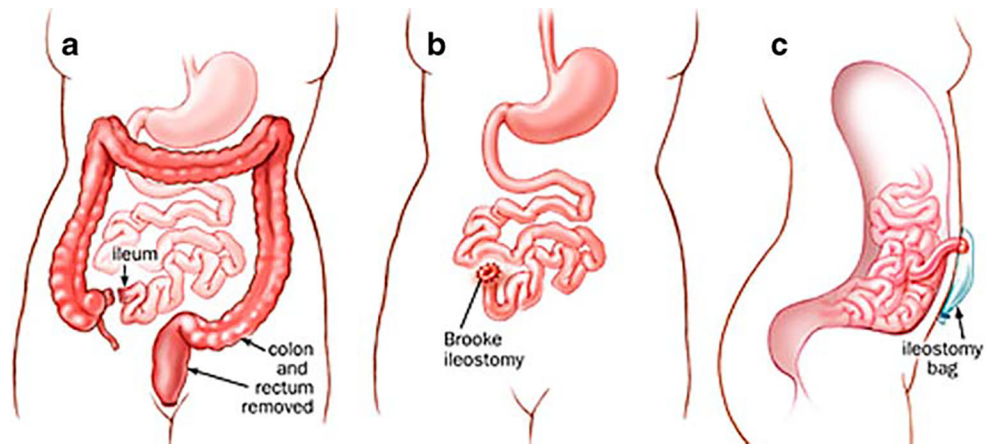


Fig. 1. Total proctocolectomy with Brooke ileostomy. **a** Proctocolectomy; **b** Brooke ileostomy; **c** side view with ileostomy bag

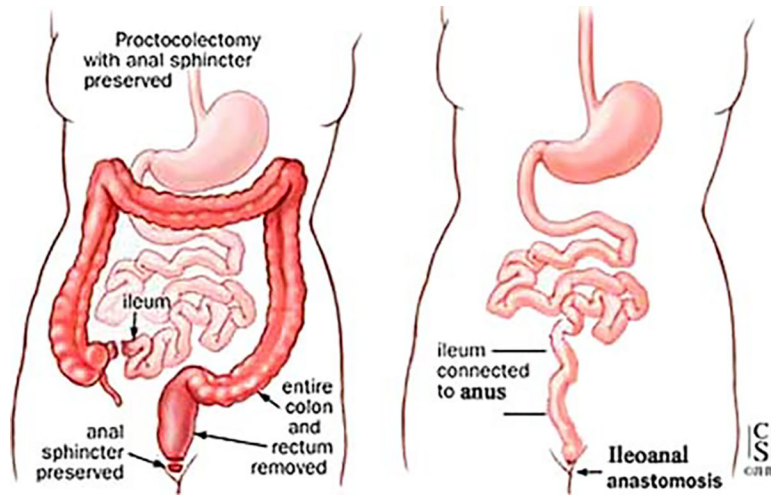


Fig. 2.
Proctocolectomy with straight ileoanal anastomosis

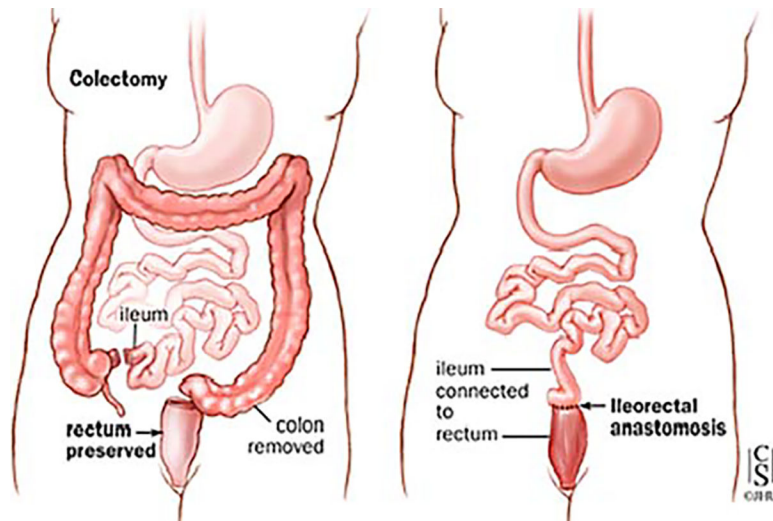


Fig. 3.
Colectomy with straight ileorectal anastomosis (ileorectostomy)

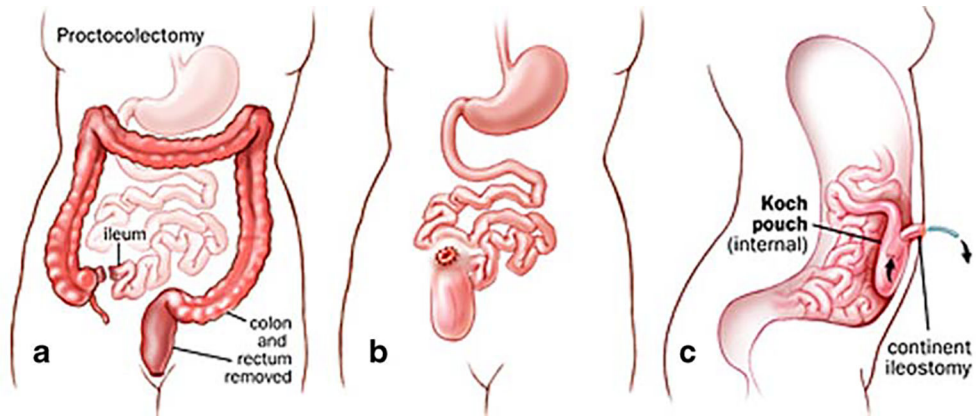


Fig. 4. Total proctocolectomy with Koch pouch (continent ileostomy). **a** Proctocolectomy; **b** with internal Koch ileostomy; **c** side view

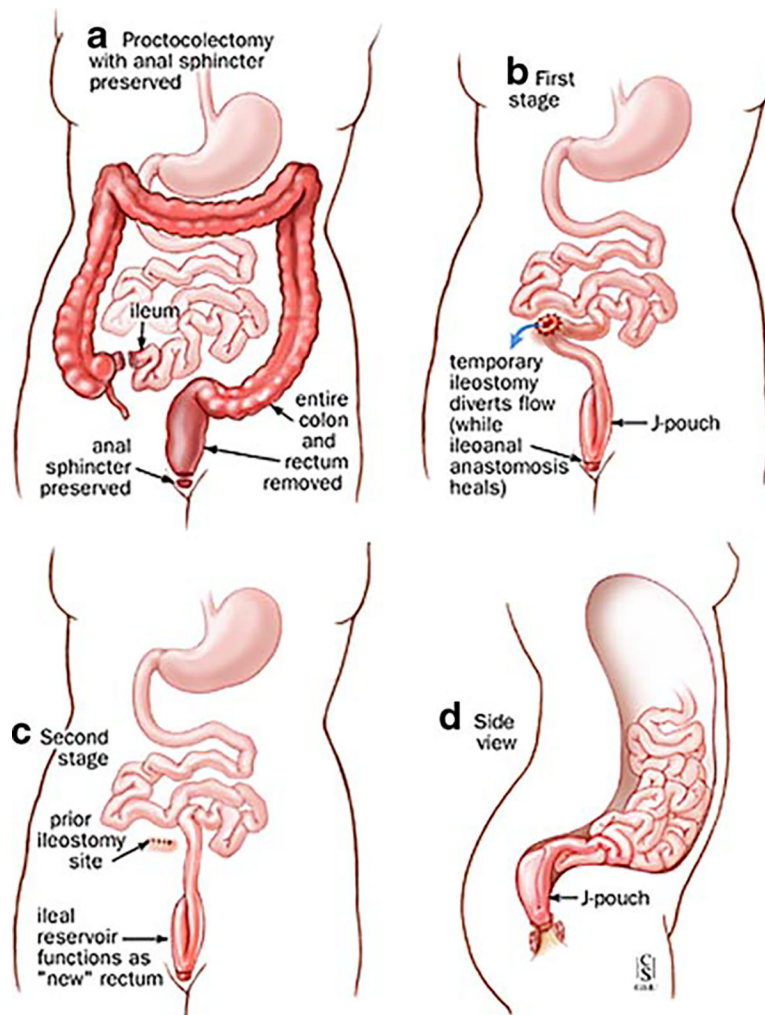


Fig. 5. Restorative proctocolectomy (ileoanal pouch anastomosis, two stages procedure). **a–d** Two stages of restorative proctocolectomy. **a** Proctocolectomy with anal sphincter preserved. **b** First stage. **c** Second stage. **d** Side view

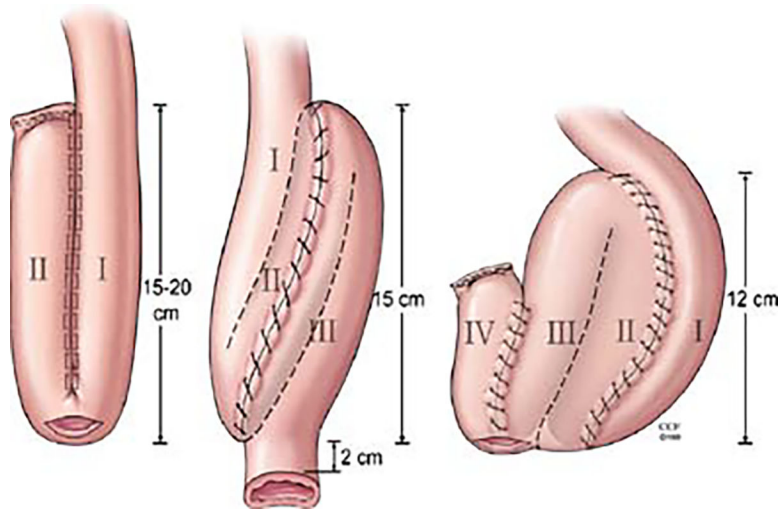


Fig. 6.
Different pouch conformations (J-, S- and W-shaped reservoirs)

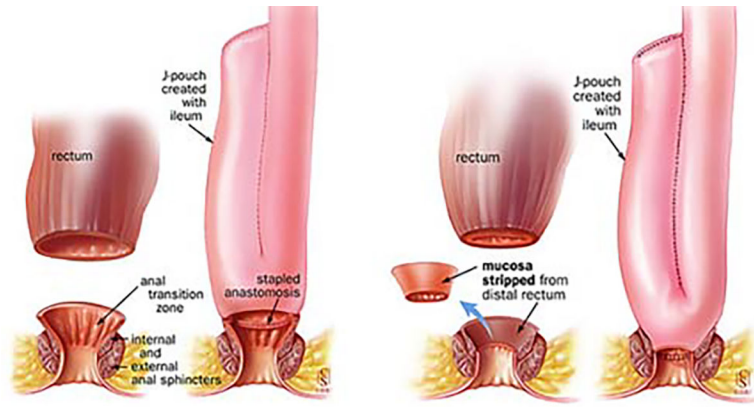


Fig. 7. J-shaped reservoir (Utsunomyia). Ileal pouch anal anastomosis without stripping (double-stapled technique, *left*) and with rectal stripping (mucosectomy, *right*)

Short- and long-term postoperative classification of complications of the restorative proctocolectomy and ileal pouch–anal anastomosis

Table 1

Complication	Percentage (%)	Cited references
Pouchitis	30–59	Sandborn et al. 1994, Hurst et al. 1996, Meagher et al. 1998, Simchuk et al. 2000, Trainen and Matikainen 2000, Heuschen et al. 2001
Pelvic sepsis	3–18.6	Meagher et al. 1998, Johnson et al. 2001
Anastomotic stricture/stenosis	4–11	Dayton et al. 2002, Prudhomme et al. 2003, Machelassi et al. 2003
Fistulae	1.6–9	Lee et al. 1997, Belliveau et al. 1999, Dayton et al. 2002, Breen et al. 1998, Dayton et al. 2002, Zimicola et al. 2004, Gorfine et al. 2004, Tekkis et al. 2005
Dysplasia/neoplasia/cancer	0.5–15	Baker et al. 1978, Grudfest et al. 1981, Johnson et al. 1983, Puthu et al. 1992, Hocenner et al. 1994, Ziv et al. 1994, von Herbay et al. 1996, Sequens et al. 1997, Sarigol et al. 1999, Vuilleumier et al. 2000, Thompson-Fawcett et al. 2001, Heuschen et al. 2001b, Gorfine et al. 2004, Borjesson et al. 2004, Rutter et al. 2004
Pouch failure	0.3–15	Heppel et al. 1983, Pemberton et al. 1987, Keränen et al. 1997, Dayton et al. 2002, Fazio et al. 1995, Lepistö et al. 2002, Öresland et al. 2006
Cholelithiasis	2–5	Harvey et al. 1991, Makino et al. 194, Mibu et al. 1995, Mibu et al. 2001
Iron deficiency anemia	6–20.8	M'Koma et al. 1994a, M'Koma et al. 1994b, Trainen et al. 2000, Kuisma et al. 2001, M'Koma et al. 2006
Vitamin B ₁₂ deficiency anemia	3–9	Jagenburg et al. 1975, Nilsson et al. 1984, Bayat et al. 1994, M'Koma et al. 1994a, M'Koma et al. 1994b, M'Koma et al. 2006
Crohn's disease	2.7–13	Gemlo et al. 1992, Goldstein et al. 1997, Deutch et al. 1991, Neille et al. 1999, Yu et al. 2000, Keighley et al. 2000, Peyregne et al. 2000, Fazio et al. 2003, Shen et al. 2005, Fukushima et al. 2006
Cuffitis	2–7	Schmitt et al. 1992, Shen et al. 2002, Shen et al. 2004, Mattioli et al. 2005, Abdelrazek et al. 2005
Osteoporosis	2.3–5.0	Sher et al. 1996, Abitbol et al. 1997, Teixeira et al. 1999, Valentine et al. 1999, Kuisma et al. 2002
Sinuses	2.1–12	Beck et al. 2001, Prudhomme et al. 2003, Swain et al. 2004, Gorfine et al. 2004, Mehdi et al. 2004
Leaks	13–20	Shen et al. 2005, M'Koma et al. 2006
Abscess	1.3–6	Belliveau et al. 1999, Bursics et al. 1999, Rossi et al. 2002, Heuschen 2002, Banerjee et al. 2004
Adhesion	5–23	Van de Pavoorst et al. 1987, Edwards et al. 1998, Ikeuchi et al. 2004, Parc et al. 2004, Patel et al. 1995, Parker et al. 2005, Wong et al. 2005
Prolapsy	0.4–2	Moskowitz et al. 1986, Sheperd et al. 1987, Nicholls et al. 1989, Blazebay 1994, Belliveau et al. 1999, Ehsan et al. 2002, Williams et al. 2003, Williams et al. 2004
Bacterial overgrowth	–	Stryker 1985, Nasmyth et al. 1989, Natori, et al. 1992, Natori et al. 1992, Salemans et al. 1993, Taylor et al. 1998, Gionchetti et al. 1999, Whinerary et al. 2000, Kelly et al. 2004, Gionchetti et al. 2004, Gosselink et al. 2004
CMV infection	0.5–1	Moskowitz et al. 1986, Mooka et al. 1998, Munoz-Juarez et al. 1999, Munoz-Juarez et al. 2000, Pfau et al. 2005
<i>Clostridium difficile</i> infection	1–5	LaMont et al. 1980, Bolton et al. 1986, Fekety et al. 1997, Cleary et al. 1998, Heuschen et al. 2001, Mann et al. 2003, Shen et al. 2003
Inflammatory polyps	0.5–2	Keighley et al. 1987, Thompson et al. 1998, Freeman et al. 2001, Saigusa et al. 2003, Polese et al. 2003, Watanabe et al. 2006
Adenoma	7–15	Malassagne et al. 1995, Enriquez et al. 1998, van Duijvendijk et al. 1999, Parcy et al. 2001, Renzi et al. 2001, Tulchinsky et al. 2005

Includes: surgical/mechanical, inflammatory/infectious, dysplasia/neoplasia/cancer, and systemic/metabolic

Table 2

Short- and long-term postoperative classification of functional outcome complications of the restorative proctocolectomy and ileal pouch–anal anastomosis

Function	Percentage (%)	Cited references
Number of stools/24 h	5–7	Keränen et al. 1997, Meagher et al. 1998, Johnson et al. 2001
Need for night evacuation	40–80	Romanos et al. 1997, Keränen et al. 1997
Urgency	6–10	Romanos et al. 1997
Incontinence		
Occasional	10–39	Meagher et al. 1998, Tiainen and Maitkainen 2000
Frequent	3–7	Pemberton et al. 1987, Tuckson et al. 1991, Michelassi et al. 1993
Use of retarding drugs	29–75	Keränen et al. 1997, Romanos et al. 1997, Johnson et al. 2001
Protective pads	17–30	Meagher et al. 1998, Johnson et al. 2001
Perianal soreness	30–48	Meagher et al. 1998, Johnson et al. 2001
Irritable pouch syndrome	43–46	Camiller et al. 1999, Shen et al. 2002, Hahnloser et al. 2004, Shen et al. 2004
Liver dysfunction	7–19	Nicholls et al. 1981, Max et al. 1987, Fiorentini et al. 1987, Jensen et al. 1992, M'Koma et al. 1994, 2006 and 2007
Pelvic floor dysfunction	8–40	Öresland et al. 1989, Gemlo et al. 1992, Björk et al. 2001, Kraugz et al. 2005, Öresland et al. 2006, Arberg et al. 2006, Tilney et al. 2006, Prete et al. 2006, Baig et al. 2006, Strong et al. 2006, Kartheuser et al. 2006, Börjesson et al. 2006
Poor pouch compliance		Groom et al. 1994, Goldberg et al. 2006
Pseudo-obstruction	3–11.7	Stabile et al. 1992, Stewart et al. 1994, Suilleabhain et al. 2001, Machelassi et al. 2003, Stabile et al. 2005

Table 3

Gut hormones: gastrin family: their mode of delivery, site of action, their physiologic effects, and the levels post-RPC surgery and cited references

Hormone	Modes of delivery	Site of action	Effects	Levels in RPC	Cited references
Gastrin	Endocrine	Stomach (parietal cells)	↑ Gastric acid secretion	Identical	Inoue et al. 1982, Greenberg et al. 1989, M'Koma et al. 1999
Ghrelin	Endocrine Paracrine	Stomach (A-like cells)	↑ Gastric emptying ↑ Gastric motility	No study in RPC ↑ in modulating immune response inflammatory colitis	– Chang et al. 2003, Brzozowski et al. 2004, Dixit et al. 2004, Korbonits et al. 2004, Granado et al. 2205
Cholecystokinin	Endocrine	Gall bladder Small intestine	↑ Contraction of gallbladder ↓ Gastric emptying ↑ Pancreatic enzyme secretion ↑ Memory enhancement Satiation	↑ in RPC	Salemans et al. 1995, Hallgren et al.1995, van Battum et al. 1999

RPC Restorative proctocolectomy, *IPAA* ileal pouch anal anastomosis

Table 4

Gut hormones: secretin family: their mode of delivery, site of action, their physiologic effects, and the levels post-RPC surgery and cited references

Hormone	Modes of delivery	Site of action	Effects	Levels in RPC	Cited references
Secretin	Endocrine	Pancreatic acini Liver	↑ HCO ₃ -rich secretion ↑ Bile secretion	No study in RPC	
Vasoactive intestinal peptide (VIP)	Neurocrine	Stomach Liver Pancreas	↓ Gastric acid secretion ↑ Glucose release ↑ Insulin release ↑ HCO ₃ -rich secretion ↓ Absorption of water and sodium (inhibitor)	↑ in RPC with pouchitis	Keränen et al. 1996a, Keränen et al. 1996b
Peptide histidine methionine (PHM)	Neurocrine	Ileum Colon Trachea Stomach Gallbladder Blood vessels	↑ Intestinal secretion of water and electrolytes (stimulatory) ↑ Pancreatic secretion of water and bicarbonate in vivo and of amylase in isolated acini (stimulatory). Relaxation of tracheal, gastric and gallbladder smooth muscle and vasodilation ↑ Insulin, glucagon and prolactin secretion (stimulatory).	No study in RPC	
Glucagon like peptide	Endocrine	Lower Ileum Colon	↑ Gastric emptying ↑ Small bowel absorption ↑ Growth of small bowel mucosa ↓ Small bowel transit ↓ Gastric acid secretion ↓ Intestinal motility	↑ in RPC	Pietroletti et al. 1990, Armstrong et al. 1991, Pironi et al. 1993, Palnaes Hansen et al. 1997
Gastric inhibitor peptide (GIP)	Endocrine	Duodenum Jejunum Stomach Ileum	↓ Gastric acid secretion ↑ Insulin release ↓ Water and electrolyte absorption in ileum	↑ in RPC	Palnaes Hansen et al. 1997

Table 5

Gut hormones: pancreatic polypeptide family

Hormone	Modes of delivery	Site of action	Effects	Levels in RPC	Cited references
Pancreatic polypeptide (PP)	Endocrine	Pancreas	<ul style="list-style-type: none"> ↑ Gastric acid secretion ↓ Stimulated pancreatic & pentagastrin secretion ↑ Stomach and intestine motility 	↑ in colonic resection	Besterman et al. 1982, Flaten et al. 1982, Yamamura et al. 1985, Greenberg et al. 1989, Sharkey et al. 1990, Yanagi et al. 1991
Peptide tyrosine-tyrosine (PYY)	Endocrine	Lower ileum	<ul style="list-style-type: none"> ↓ Gastric acid secretion (inhibitory) 	↑ in RPC	Adrian et al. 1987, Pietroletti et al. 1990, Armstrong et al. 1991, Pironi et al. 1993, Tsukamoto et al. 1994, Imamura et al. 1999, Teixeira et al. 2001
		Colon	<ul style="list-style-type: none"> ↓ Pepsin secretion (inhibitory) 		
			<ul style="list-style-type: none"> ↓ Pancreatic exocrine secretion (inhibitory) ↓ GI motility (inhibitory) ↑ Potent intestinal vasoconstriction 	↓ in RPC	Greenberg et al. 1989, Falk et al. 1998, Terment et al. 1998, van Battum et al. 1999
Neuropeptide Y (NPY)	Neurocrine	GI tract	<ul style="list-style-type: none"> Acts on various smooth muscles 	No study in RPC	
		CNS	<ul style="list-style-type: none"> ↓ Local blood flow ↑ Adrenergic vasoconstriction 		
		PNS			

Their mode of delivery, site of action, their physiologic effects, and the levels post-RPC surgery and cited references

GI Gastrointestinal, CNS central nervous system, PNS peripheral nervous system, IPAA ileal pouch anal anastomosis, RPC restorative proctocolectomy

Table 6

Gut hormones: miscellaneous: their mode of delivery, site of action, their physiologic effects, and the levels post-RPC surgery and cited references

Hormone	Modes of delivery	Site of action	Effects	Levels in RPC	Cited references
Motilin	Endocrine	Stomach Duodenum Jejunum Esophagus	↑ Smooth-muscle contraction	↑ in RPC and in end ileotomy than control	Greenberg et al. 1989
Neurotensin	Endocrine Neurocrine	Stomach Jejunum Ileum	↓ Gastric secretion and/or emptying ↓ Pepsin secretion ↓ Pancreatic exocrine secretion ↓ Smooth muscle motility ↑ Pancreatic secretion ↑ Intestinal fluid secretion	Identical	Hallgren et al. 1995
Somatostatin	Endocrine Paracrine	Stomach Ileum Pancreas and neurocrine normal pancreas	↓ Gastric acid secretion ↓ Mucosal growth of the GI tract	Used in clinical trials for difficult pouch dysfunction	Kusuhara et al. 1992, Sagar et al. 1994, Rabau et al. 1995, Spiliotis et al. 2003
Gastric releasing peptide (GRP)	Neurocrine	Stomach Ileum	↑ Release of gastrin and Somatostatin ↑ Gastric acid secretion ↑ Pancreatic enzyme secretion	No study in RPC	
Bombesin	Neurocrine Endocrine	Stomach Ileum CNS	↑ Release of gastrin and Somatostatin ↑ Gastric acid secretion ↑ Pancreatic enzyme secretion	Used to study CCK levels and gallbladder volume in RPC; CCK was increased in RPC patients and gallbladder volume decreased	Salemans et al. 1995
Substance P	Endocrine Paracrine	CNS Intestine	↑ Nitric oxide synthesis ↑ GI motility ↑ Potent vasodilatation ↑ Salivary flow (stimulatory)	↑ in RPC with pouchitis	Keränen et al. 1996a, Keränen et al. 1996b
Galanin	Neurocrine	CNS Stomach Small intestine	↓ Gastric motility ↑ Gastric emptying Induce hyperphagia ↓ Gut-related NST and DMNV neurons ↓ Gut-related DVC neurons	No study in RPC	
Thyrotropin-releasing hormone	Endocrine	Pancreas Stomach Enteric nerves	↓ Gastric secretion ↓ Amylase and lipase (inhibitory) Stimulates intestinal smooth muscle Inhibits cholesterol synthesis in intestinal mucosa	No study in RPC	
Calcitonin gene-related hormone	Endocrine	Sensory nerves	Vasodilation Enteric nerves	No study in RPC	

DMNV Dorsal motor nucleus of the vagus nerve, *DVC* dorsal vagal complex, *NST* nucleus of the solitary tract, *RPC* restorative proctocolectomy, *CNS* central nervous system