

# Intestinal Adaptation in Short Bowel Syndrome

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## ABSTRACT

Short bowel syndrome occurs when there is insufficient length of the small intestine to maintain adequate nutrition and/or hydration status without supplemental support. This syndrome most frequently occurs following extensive surgical resection of the intestine, and the extent of adaptation depends on the anatomy of the resected bowel and the amount of bowel remaining. Following resection, the intestinal tissue undergoes morphologic and functional changes to compensate for the lost function of the resected bowel. These changes are mediated by multiple interactive factors, including intraluminal and parenteral nutrients, gastrointestinal secretions, hormones, cytokines, and growth factors, many of which have been well characterized in animal models. The amount of small bowel remaining is the most important predictor of adaptive potential; neither structural nor functional adaptive changes have been demonstrated in humans or animal models with more extreme resections resulting in an end-jejunostomy. The current understanding of these processes has led to the recent use of supplemental hormones, such as growth hormone and glucagon-like peptide 2, in intestinal rehabilitation programs and may lead to the development of pharmacologic agents designed to augment the innate adaptive response.

**Key Words:** short bowel syndrome, growth factors, gastrin, growth hormone, glucagon-like peptide, neurotensin, epidermal growth factor, trefoil peptides, hepatocyte growth factor

Short bowel syndrome (SBS) occurs when there is insufficient length of the small bowel to maintain adequate nutrition and/or hydration without supplemental nutritional support. The syndrome is characterized by malabsorption and chronic diarrhea, with resultant fluid and electrolyte abnormalities, macro- and micronutrient deficiencies, and weight loss. The syndrome may result from congenital abnormalities (eg, intestinal atresia) but typically occurs following extensive surgical resection of the small intestine. A variety of pathologic insults may cause intestinal failure that requires extensive enterectomy for treatment. In the pediatric population, the most common

causes include necrotizing enterocolitis, congenital anomalies, gastroschisis, and midgut volvulus. The most common causes in adults are Crohn's disease and multiple small bowel resections, mesenteric infarction, radiation enteritis, and trauma.<sup>1</sup> Many patients with SBS require the intravenous supplementation of fluids and electrolytes or total parenteral nutritional (TPN), frequently for prolonged periods of time, even permanently. Small bowel transplant may be considered in selected patients with intestinal failure who fail to maintain adequate nutrition despite TPN.

Following extensive small bowel resection, several changes occur that allow the remaining bowel to compensate for lost function. Structural, hormonal, and metabolic changes occur to maximize intestinal function. These changes begin within days of resection and may continue to develop over the months that follow. The extent of intestinal adaptation depends on many factors, including patient age, the anatomy and extent of bowel remaining, the status of the underlying disease that leads to resection, patient nutrition and hydration status, the presence of intraluminal nutrients and gastrointestinal secretions, and a host of hormones and growth factors that promote adaptation by accelerating structural growth and enhanced function of the remaining bowel. Progressive adaptation may result in a decreased dependency on TPN, and eventually full enteral autonomy occurs in many patients, although others remain dependent on TPN for long periods of time. Understanding the specific mechanisms of adaptation is a crucial component in managing patients with SBS, and developing means of enhancing this process will, no doubt, influence pharmacologic and nutritional management of these patients in the future.

## STRUCTURAL ADAPTATION

Functional integrity of the small intestine depends to a significant degree on the amount of small bowel remaining following surgical resection. SBS typically occurs when there is  $\leq 200$  cm of small bowel remaining after surgical resection. In addition to preserving as much functional surface area as possible, it is important to maintain continuity of the alimentary canal as much as possible to maximize exposure of intestinal contents to the remaining bowel surface area.

The specific anatomic segments remaining have a distinct impact on adaptation. Three basic types of intestinal

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resection may result in SBS (Figure 1): limited ileal resection with ileocolonic anastomosis (often with right hemicolectomy), complete ileal resection with jejunocolonic anastomosis (with or without partial colectomy), and more extensive resection of small intestine with total colectomy and end-jejunostomy. The presence of intact ileum and colon is particularly important to the adaptation process. Ileal resection of  $\geq 60$  cm results in the loss of specialized transport mechanisms for bile salts and vitamin B<sub>12</sub>, although bile salt malabsorption may occur even if  $\leq 60$  cm of terminal ileum is resected. Transit time is also affected because the ileum has a slower rate of peristalsis compared with the jejunum.<sup>2</sup> Theoretically, the ileocecal valve also slows ileocolonic transit by acting as a physiologic sphincter; however, other data suggest that removal of the valve does not affect intestinal transit time.<sup>3</sup> Loss of the ileocecal valve may have other important implications, including the loss of a barrier to prevent reflux of colonic contents into the ileum, which may promote bacterial overgrowth in the small bowel.<sup>4</sup> The presence of intact colon in continuity with small bowel is clearly important in patients who have undergone resection of the small intestine. In addition to its ability to absorb water and electrolytes, the colon participates in a process called “carbohydrate salvage,” whereby malabsorbed carbohydrates are fermented by colonic bacteria to short-chain fatty acids (SCFAs). These SCFAs (principally butyrate) provide additional calories and stimulate sodium and water absorption.<sup>5</sup> Both the ileum and the colon are the primary sites of cells that secrete trophic hormones that stimulate intestinal growth; loss of these segments will have negative effects on the adaptive response.

Morphologic adaptation of the intestinal mucosa occurs following extensive resection. Much of our understanding of the histologic changes that occur come from animal models with a colon in continuity following jejunal resections; data derived from human subjects are scarce. There may be several reasons for this. Comparisons of intestinal mucosa before and after an insult are nearly impossible because these extensive resections are frequently either the

result of multiple less extensive surgeries of chronically diseased mucosa or following an unpredictable acute abdominal catastrophe. Human subjects frequently have persistence of the underlying disease that led to the enterectomy (eg, Crohn’s disease), which, depending on the natural history of the disease process, may limit subsequent adaptation. In addition, in some cases, sites undergoing the greatest degree of adaptation may be difficult to access with minimally invasive techniques.

Nonetheless, objective evidence is available from both human and animal data indicating that structural changes do occur in the remaining bowel. The morphologic changes seen are hyperplastic rather than hypertrophic, and these changes appear to correlate with enhanced function. For example, canine studies have correlated increased intestinal mass with improved absorption.<sup>6</sup> Studies in rodents have shown increased villus height and intestinal cellularity with increased crypt cell proliferation following resection, which correlated with improved absorption of fat, protein, glucose, sodium, water, bile acids, vitamin B<sub>12</sub>, calcium, and zinc.<sup>7</sup> In humans, the bowel dilates and becomes somewhat elongated. Alterations in cell turnover have been demonstrated, including villous cell hyperplasia at the level of the crypts and cellular migration with elongation of the villi. This process is regulated by a concomitant increased rate of apoptosis.<sup>8</sup> Genes involved in the development and homeostasis of the gastrointestinal tract may play a key role in regulating the balance between proliferation and apoptosis. Recent studies by Juno and colleagues examined the role of the *bax* gene, which codes for a peptide with proapoptotic function.<sup>9</sup> Increased expression of *bax* messenger ribonucleic acid (mRNA) appears to be correlated with increased apoptosis postresection, with decreased rates of apoptosis found in *bax*-null mice.<sup>10</sup> Increased apoptosis in the setting of intestinal adaptation appears to be *bax* dependent, in contrast to spontaneous apoptosis in unresected small intestine. In theory, blunting this effect on apoptosis would result in promotion of the proliferative response, but more recent studies failed to demonstrate an increase

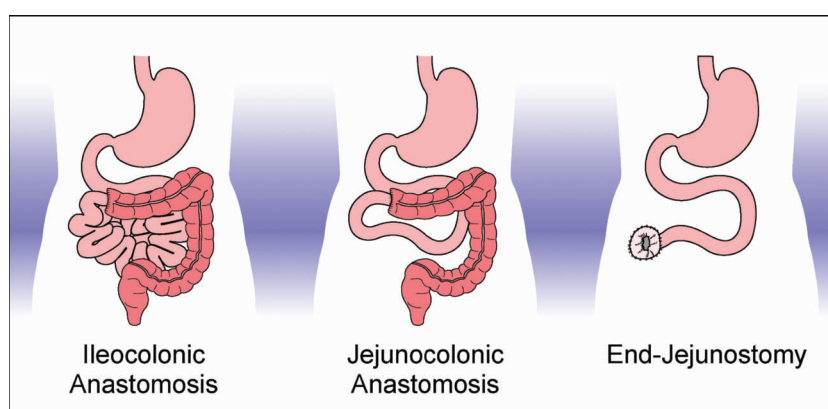


FIGURE 1 Postresection anatomic variations that may result in short bowel syndrome.

in intestinal proliferation in *bax*-null mice in the early postresection period.<sup>10</sup> A recent study by Tang and colleagues showed a similar decreased rate of apoptosis and decreased crypt proliferation in *bax*<sup>-/-</sup> mice 7 days after resection of 50% of the small intestine.<sup>11</sup> Despite the lack of cellular proliferation, the *bax*<sup>-/-</sup> mice in this study did have a modest increase in villus height compared with the *bax*<sup>+/+</sup> mice.

The degree of morphologic change in the intestine depends on the anatomic identity of the remaining bowel. For example, human and animal data suggest that the jejunum does not appear to have as much capacity for growth and functional adaptation compared with the ileum, where the most marked adaptive changes occur.<sup>12,13</sup> These morphologic changes have not been demonstrated in humans and in animal models. Evidence for structural adaptation of the jejunum in humans is scarce. Data in human subjects with ileal resection with a jejunocolonic anastomosis have been inconsistent, with two reports showing epithelial hyperplasia of the jejunum and a larger study showing jejunal atrophy.<sup>14-16</sup> No hyperplastic changes have been demonstrated in patients with an end-jejunosomy.<sup>17</sup> In contrast, following resection of the jejunum, the ileum will undergo morphologic changes typical for the jejunum with taller villi and deeper crypts.<sup>18</sup> Human subjects who had jejunoileal bypass surgery for obesity showed mucosal hyperplasia in the ileum that remains in continuity compared with hypoplasia in the bypassed jejunum, although this may represent the effect of luminal nutrients and pancreatobiliary secretions rather than the hyperplastic potential of these segments.<sup>19</sup> Segmental adaptability may be related to multiple factors, including loss of site-specific cells that produce trophic hormones, such as L cells, which are located in the ileum and colon.

### FUNCTIONAL ADAPTATION

The physiologic mechanisms of intestinal adaptation are complex and involve a variety of interactions between the intestinal tissue and intraluminal nutrients, pancreatobiliary secretions, growth factors, cytokines, and other cell-signaling molecules (Figure 2). This process begins immediately following enterectomy and continues over time. The time required for maximal adaptation is variable and dependent on many interactive factors. Whereas structural responses appear to be maximal within several weeks, functional adaptation appears to continue for months to years before full adaptation is achieved. Maximal digestive adaptation is thought to be reached by 1 to 3 years in adults and 1 to 4 years in children.<sup>20,21</sup> Messing and colleagues reported long-term data from 124 patients showing that the probability of TPN dependence at 2 and 5 years was 49 and 45%, respectively.<sup>22</sup> The probability of permanent intestinal failure was 94% for those patients who remained TPN dependent at 2 years.

### Fluid and Electrolyte Absorption

In the period immediately following resection, patients with SBS experience severe loss of fluid and electrolytes, resulting in complete dependency on parenteral nutrition. One of the earliest changes seen in the adaptation process is an improved ability to absorb fluid and electrolytes, as demonstrated by decreased stool volume over time. This is most pronounced in the first 1 to 3 months following resection, although the process is ongoing over time.<sup>23</sup> This appears to be mediated, at least in part, by up-regulation of the Na<sup>+</sup>/glucose cotransporter, the Na<sup>+</sup>/H<sup>+</sup> exchanger, and other enzymes involved in intestinal fluid absorption.<sup>24</sup> Oral or enteral nutrition and weaning or discontinuation of TPN are titrated accordingly during this time.

### Role of Nutrition

Dietary constituents likely regulate multiple pathways involved in intestinal adaptation. Although achieving enteral autonomy obviously depends on receiving nutrition via oral or enteral means and these routes are clearly more physiologic, some of the adaptive mechanisms influenced by nutrition likely occur independent of the route of

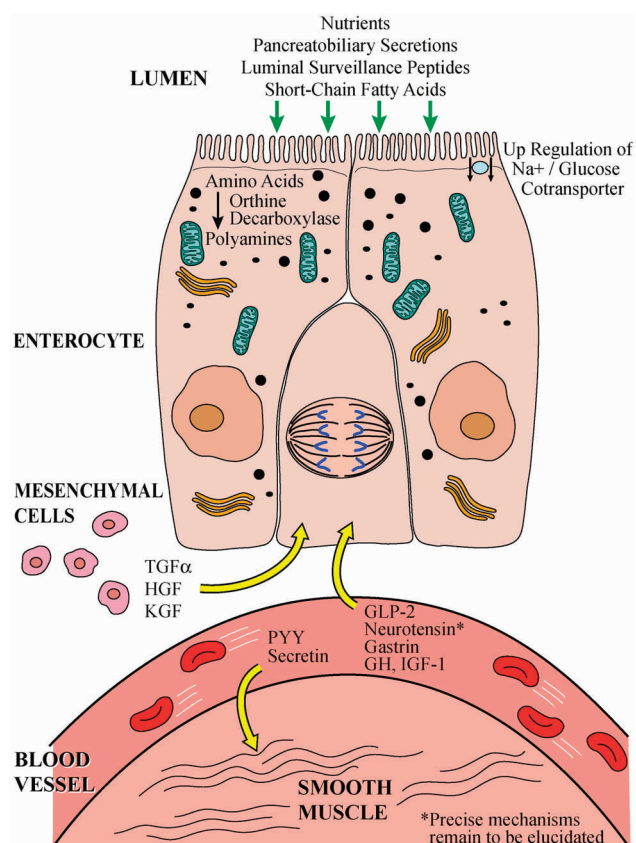


FIGURE 2 Putative interactions of factors influencing the intestinal adaptation process (the precise mechanisms remain to be elucidated). GH = growth hormone; GLP = glucagon-like peptide; HGF = hepatocyte growth factor; IGF = insulin-like growth factor; KGF = keratinocyte growth factor; PYY = peptide YY; TGF = transforming growth factor.

administration. Multiple studies demonstrate a positive effect of various nutrients supplemented in TPN.

Pectin and other soluble fibers have been shown to promote intestinal adaptation. The beneficial effects of fiber may be related to prolonged intestinal transit or the fact that soluble fibers act as a substrate for “carbohydrate salvage.”<sup>25</sup> Pectin has also been shown to decrease body weight loss in rat models of SBS.<sup>26</sup> Lack of dietary fiber results in atrophy of colonic mucosa, which can be reversed with fiber supplementation.<sup>27</sup>

Fiber fermentation by anaerobic bacteria in the colon results in the production of short-chain fatty acids. SCFAs appear to have a particularly important role in SBS patients with an intact colon in continuity with the small bowel. These patients appear to have enhanced energy absorption by “carbohydrate salvage.” This refers to the fermentation of malabsorbed carbohydrates to SCFAs by anaerobic bacteria in the colon.<sup>28</sup> SCFAs appear to have multiple effects in the intestine, including enhanced colonic sodium and water absorption and stimulant effects on bowel growth.<sup>29</sup> Studies by Tappenden and colleagues demonstrated an increased concentration of glucose transporter 2 mRNA in adult rats given SCFA-supplemented TPN with a resected and intact bowel, as well as an increase in the concentration of mRNA of serum glutamic pyruvic transferase 1, a sodium-glucose cotransporter found in the brush border of the enterocyte.<sup>30</sup> Administration of SCFAs in TPN-fed rodents with an intact bowel and in rodent models of SBS also results in higher levels of other growth markers, such as proglucagon and ornithine decarboxylase.<sup>31</sup>

Polyamines may be derived from nutrients or synthesized within epithelial tissues. They are involved in stimulating the proliferation of rapidly dividing tissues, including intestinal epithelium. Endogenous polyamines, such as putrescine, spermidine, and spermine, are found in enterocytes. Polyamine synthesis is regulated by ornithine decarboxylase; levels of this enzyme are high in dividing tissues and low in quiescent tissue. Increased intracellular concentrations of polyamines are seen following small bowel resection. Inhibition of polyamine synthesis by blocking ornithine decarboxylase results in decreased structural adaptation in rats following jejunectomy.<sup>32</sup> Rokkas and colleagues demonstrated increased epithelial hyperplasia and nutrient absorption in rats given aminoguanidine to block polyamine degradation.<sup>33</sup> The effect that dietary polyamines have on the regulation of endogenous polyamine synthesis is unclear, but intraluminal infusion of putrescine has been shown to promote the growth of ileal mucosa in rats.<sup>34</sup>

Numerous investigators have studied the role of the amino acids arginine and glutamine in the adaptation process. Rats given arginine-deficient diets after massive small bowel resection had more weight loss than rats given a normal diet.<sup>35</sup> In addition to being a precursor to polyamines, arginine is converted to nitric oxide and cit-

rulline by nitric oxide synthetase. Nitric oxide may play an important role in maintaining the barrier function of the intestinal mucosa. Welters and colleagues demonstrated a reduction in intestinal permeability in rats given parenteral arginine supplementation after massive small bowel resection.<sup>36</sup> Glutamine is considered a “conditionally essential” amino acid. It is normally nonessential, except in times of severe stress, such as critical illness. Fasting rats on standard TPN develop intestinal hypoplasia, which is reversed with supplementation of parenteral glutamine.<sup>37</sup> Rats that have had extensive intestinal resection have improved adaptation when glutamine is included in their TPN solution.<sup>38,39</sup> These effects have not been shown to occur when glutamine is supplemented into diets given orally or enterally, although rat models have been shown to have improved absorption of glucose and sodium when given enteral glutamine.<sup>40–45</sup> Data on glutamine supplementation in humans with SBS have failed to show improvement in intestinal adaptation. No morphologic changes have been demonstrated with glutamine supplementation in humans with SBS. Several studies have shown improvement in body weight and nitrogen, sodium, and water absorption with glutamine supplementation.<sup>46–48</sup> Patients in these studies were all supplemented with growth hormone (GH) as well. The individual contributions of each of these supplements in humans with SBS are yet to be determined.

Other dietary components that appear to promote adaptation include long-chain triglycerides, which were shown to have more pronounced effects on adaptation than proteins and polysaccharides in rat models.<sup>49</sup> Free fatty acids appear to have an even more pronounced effect than long-chain triglycerides.<sup>50–52</sup> Medium-chain triglycerides also appear to be beneficial, but with less pronounced effects.<sup>53</sup>

The importance of enteral nutrition to the process of intestinal adaptation has been well demonstrated. Even in normal bowel, the presence of food in the gut lumen provides a major stimulant to mucosal proliferation, whereas fasting and parenteral nutrition lead to hypoplasia and atrophy, disproportionate to the weight loss seen in other tissues in the fasting state. Intraluminal nutrition may be beneficial for several reasons, including stimulation of pancreaticobiliary secretions into the alimentary tract, stimulation of trophic hormones and growth factors, and direct mucosal stimulatory effects of enterocyte contact with specific nutrients (eg, glutamine and SCFA). Many of the adaptive changes discussed above, particularly the morphologic changes, appear to be dependent on the presence of food and pancreaticobiliary secretions in the gut lumen. Jejunectomized animals given TPN fail to develop the adaptive changes seen in the ileum of control animals fed enterally. Thus, reinstating enteral nutrition early is critical to optimizing the adaptive response.

The composition of the diet is clearly important. Elemental diets have been used in the past with the intent of



introducing a diet that would not require as much digestion as more complex diets and would give the highest yield of absorption over a given length of bowel. Studies proving the efficacy of this have been limited, particularly in adults.<sup>54–56</sup> More complex diets actually appear to have greater effects on intestinal adaptation. For example, intestinal infusion of disaccharides results in greater mucosal growth than monosaccharides, and rats given polymeric diets have more pronounced mucosal regeneration following massive small bowel resection compared with rats given monomeric diets.<sup>57,58</sup> This enhanced adaptation through stimulation by the “functional workload” of more complex diets likely occurs because of greater stimulation of pancreaticobiliary and other gastrointestinal secretions and the release of local factors that promote adaptation.

Hyperphagia often occurs spontaneously as oral nutrition is reintroduced. The appetite appears to be stimulated to compensate for malabsorption of nutrients. This frequently occurs early in the course of SBS and is believed to lead to increased epithelial cell renewal and increased small bowel mass. Development of hyperphagia is encouraged during this time to attenuate the rapid weight loss seen immediately following resection.<sup>59</sup> Increased calorie intake also helps compensate for malabsorption. There may be other benefits of oral nutrition: oral feedings may stimulate the release of epidermal growth factor (EGF) and other growth factors in saliva that are not stimulated by nasoenteral feedings. Intraluminal nutrients also result in stimulation of bile and pancreatic secretions, which are enterotrophic<sup>60</sup> and correlate with the size of intestinal villi in rats following diversion of pancreaticobiliary secretions to the distal intestine.<sup>61,62</sup>

The use of TPN has had a dramatic impact on improving the overall prognosis in patients with SBS, but the extent of adaptation in the remaining intestine will be limited if nutrition is provided exclusively via intravenous routes. Fasting rats on TPN develop mucosal hypoplasia and decreased weight of the small and large intestine, both of which reverse rapidly following reintroduction of enteral feedings.<sup>63,64</sup> Studies in fasting humans on TPN demonstrated similar results, although less striking than the morphologic changes shown in animal models,<sup>65</sup> and are probably not clinically significant. The presence of nutrients within the lumen of the intestine is considered one of the most potent stimuli of mucosal proliferation in the intestine. Thus, resumption of oral or enteral feedings is usually done as early as possible in the postoperative period.

### Hormones and Growth Factors

Multiple peptides and hormones have been shown to promote the adaptive response in animal models and patients with SBS (Table 1). Whereas many of these clearly influence the cellular proliferation and subsequent tissue

growth, others may result in enhanced cellular function independent of enhanced tissue structure.

### Gastrin

Hypergastrinemia occurs transiently following extensive resection of small intestine, but the effects of this are unclear. It is possible that the increased gastric secretion that results may impair absorption by inactivating pancreatic lipase and deconjugating intraluminal bile salts.<sup>66</sup> In addition, the increased volume delivered to the remaining bowel may increase flow rates, limiting time for contact with the mucosa, and dilute nutrients and electrolytes, with resultant impaired processing and absorption. Providing acid suppression with pharmacologic agents may blunt this effect. Gastric hyperplasia is seen in rats with hypergastrinemia in the setting of acid suppression, and at one time, gastrin itself was thought to stimulate hyperplasia throughout the intestinal tract.<sup>67</sup> Evidence to support this theory has failed to demonstrate such an effect. Infusion of gastrin into animal models causes trophic effects in the stomach and proximal small intestine, particularly in gastric endocrine cells, but this did not result in trophic effects in the majority of the small intestine.<sup>68,69</sup> Administration of H<sub>2</sub> receptor antagonists improved intraluminal digestion and intestinal absorption in a patient with SBS, presumably by decreasing acidity and flow rates.<sup>70</sup> Data using proton pump inhibitors are limited but suggest that improved water absorption may occur with the use of these agents.<sup>71</sup>

### GH and IGF-1 and -2

GH is secreted by the anterior pituitary and is recognized by a receptor that is expressed throughout the small intestine, particularly on mesenchymal cells in the lamina propria.<sup>72</sup> Administration of GH to rodents following enterectomy results in intestinal hypertrophy and weight gain.<sup>73,74</sup> In vitro studies of human duodenal mucosa showed a trophic response to the addition of GH.<sup>75</sup> GH is also thought to result in specific functional changes. Increased water, sodium, and amino acid absorption has been shown in rats.<sup>76,77</sup> Administration of GH to humans with SBS has produced conflicting data, partly owing to heterogeneity in study design, with various combinations of GH dose and glutamine supplementation.<sup>46–48,78–81</sup> The available data do suggest a trend toward a beneficial effect, particularly on fluid and energy absorption.

The effects of GH are primarily mediated through insulin-like growth factor I (IGF-I); exogenous administration of GH in rodents results in an increase in the concentration of IGF-I in serum and in the small intestine.<sup>82</sup> IGF-I and IGF-II are single-chain polypeptide growth factors with an amino acid structure similar to insulin, which plays a key role in normal growth and development. The effects of these growth factors appear to be more direct and pronounced than GH; this has been well demon-

**TABLE 1 Peptides and Hormones with Demonstrated Effects on Intestinal Adaptation Following Resection**

<i>Hormones</i>	<i>Source</i>	<i>Receptor/Location</i>	<i>Action/Effects</i>
Gastrin	G cells (predominantly antrum of stomach)	CCK-B receptor on ECL cells	Increased gastric acid secretion* Gastric hyperplasia†
Growth hormone	Anterior pituitary	GHR expressed in stomach, small intestine, colon	Increased cellular proliferation* Increased absorption of water, sodium, amino acids†
Secretin	Duodenum, jejunum	Multiple (stomach, colon, pancreas)	Decreased gastric emptying†
Putative hormones			
Peptide YY	L cells of ileum, colon	Y receptor family/diffuse, including small and large intestine, CNS	Decreased gastric emptying* Prolonged intestinal transit†
GLP-2	L cells of ileum, colon	GLP-2 receptor	Increased cellular proliferation, enhanced absorption*
Neurotensin	N cells of small and large intestine, CNS	Receptors on multiple target cells	Increased proliferation, increased weight†
Growth factors			
IGF-I	Liver	IGF-IR (ubiquitous receptor)	Increased cellular proliferation, weight gain† Glucose and amino acid uptake (in vitro)
Hepatocyte growth factor	Intestinal fibroblasts	c-Met receptors (intestinal epithelial cells)	Increased cellular proliferation, differentiation†
Epidermal growth factor	Brunner's glands of duodenum, salivary glands, PB secretions	TGF- $\alpha$ /EGFR (shared receptor found throughout the intestinal epithelium)	Increased cellular proliferation†
TGF- $\alpha$	Epithelial cell throughout the gastrointestinal tract	TGF- $\alpha$ /EGFR (shared receptor found throughout the intestinal epithelium)	Increased cellular proliferation†
Keratinocyte growth factor	Stromal cells	KGFR (intestinal epithelial cells)	Increased cellular proliferation†
Cytokines			
IL-11	Stromal cells	IL-11R $\alpha$ (intestinal epithelial cells)	Increased intestinal mass, enhanced absorption†

CCK-B = cholecystokinin B; CNS = central nervous system; ECL = enterochromaffin-like cells; EGFR = epidermal growth factor receptor; GHR = growth hormone receptor; GLP = glucagon-like peptide; IGF = insulin-like growth factor; IL = interleukin; KGFR = keratinocyte growth factor receptor; PB = pancreaticobiliary; TGF = transforming growth factor.

\*Human and animal data.

†Animal data.

strated in animal models.<sup>83</sup> Activation of the IGF receptor by IGF-I results in activation of multiple pathways, including many directly involved in cellular proliferation. Activation of phosphatidylinositol-3 kinase appears to be a major target of IGF-I and appears to influence the mitogenic and antiapoptotic effects of IGF-I.<sup>84</sup> IGFs clearly stimulate cell growth, as well as glucose and amino acid uptake in vitro.<sup>75</sup> IGF-I is also believed to cause an increase in nutrient transport in the enterocyte. Rat models of SBS administered IGF-I had improved weight gain that correlated with increased villus size and an increase in nutrient transport at the cellular level.<sup>85</sup> Concomitant administration of growth hormone and IGF-I appears to produce greater anabolic effects than administration of either

alone. Improved anabolic parameters have been demonstrated in human and animal models.<sup>86–88</sup>

### **Neurotensin**

Neurotensin (NT) is a 13-amino acid peptide found primarily in the central nervous system but is also found throughout the small and large intestine. It is found in particularly high concentrations in the ileum. Plasma concentrations increase in response to meals, and intraluminal fat is considered the most potent stimulus.<sup>89,90</sup> It is thought to have effects on intestinal motility and growth. Trophic effects on the small intestine have been demonstrated in rats given NT, including increased weight,

deoxyribonucleic acid (DNA) and protein content in the small bowel, and higher concentrations of the brush border enzymes sucrase, maltase, and leucine aminopeptidase.<sup>91</sup> Reversal of hypoplasia in rats given NT and fed elemental diets has also been demonstrated.<sup>92</sup> Exogenous NT administration has been shown to induce intestinal growth in rats after extensive intestinal resection, particularly in the jejunum, suggesting that the trophic effects of NT may be selective.<sup>93</sup> Enteroglucagon levels were increased in these rats, suggesting that some of the trophic effects of NT may be mediated by the effects of other hormones. Whether NT itself acts primarily by paracrine or neuroendocrine effects also remains unknown.

### Peptide YY

Similar to glucagon-like peptide 2 (GLP-2), peptide YY (PYY) is secreted by L cells located in the ileum and colon. This peptide is thought to promote adaptation by decreasing the motility of the gastrointestinal tract and thus increasing nutrient contact time; it has not been demonstrated to have a role in directly promoting proliferation or hyperplasia. Specifically, PYY acts as the hormonal “brake,” increasing gastric emptying times and small bowel transit, allowing increased contact time between intraluminal contents and the intestinal mucosa, which may subsequently affect functional adaptation. Serum concentrations of PYY are high in SBS patients with retained colon and low in those with a jejunostomy.<sup>94</sup> Similar trends are seen in the levels of GLP-2 and NT; these patterns may suggest another mechanism for the lack of adaptation seen in patients with ileocollectomy and jejunostomy.<sup>94,95</sup>

### Proglucagon-Derived Peptides

Of all of the humoral factors that contribute to intestinal adaptation, it is the proglucagon-derived peptides (PGDPs) that have generated a particular amount of interest in recent years. Included in this group are glucagon-like peptides 1 and 2 (GLP-1 and GLP-2), glicentin, oxynomodulin, and glicentin-related pancreatic polypeptide. Interest in these peptides as enterotrophic modulators began with findings noted in patients with glucagon-secreting endocrine tumors noted to have thickened mucosal folds with enlarged villi. Enterocyte hypertrophy resolved following removal of the tumors, correlating with a fall in plasma glucagons concentration.<sup>96</sup> These observations correlated with immunopositivity for glucagons in tumor extracts, which confirmed that the findings seen on small bowel histology in these patients were related to the effect of glucagon or a related substance.<sup>96</sup> Subsequent rodent investigations showed an association between increased concentrations of PGDPs and small bowel resection or injury, with up-regulation of intestinal proglucagon mRNA transcripts in the remaining bowel.<sup>19,97–103</sup> Similar

observations have been reported in humans. Intestinal hyperplasia and increased serum enteroglucagon have been shown in patients following jejunoileal bypass and in patients with small bowel resection.<sup>104,105</sup> Patients with colonic resection did not have increased levels of circulating enteroglucagons, and patients with ileostomies had decreased enteroglucagon concentration.<sup>105,106</sup> Therefore, at one time, enteroglucagon was believed to be one of the primary mediators of intestinal adaptation.

However, more recent investigations that examined this relationship were less convincing. Purified glicentin was produced and administered to rats receiving TPN. Little effect on intestinal hyperplasia was induced.<sup>107</sup> Attention then shifted to GLP-1 and GLP-2. Based on the observation of small intestinal hypertrophy in mice with subcutaneous glucagonomas, Drucker and colleagues performed a series of experiments to evaluate the role of PGDPs in intestinal growth.<sup>108</sup> Mice given GLP-1 had no increase in small bowel mass, whereas mice given glicentin or GLP-2 had increased small bowel mass; GLP-2 mice exhibited the strongest effect.

Multiple studies in rodents have since demonstrated the trophic effects of GLP-2. Rodents given exogenous GLP-2 had increased jejunal and ileal wet weight, prolonged intestinal transit, increased intestinal crypt proliferation, increased mucosal protein and DNA content, increased thickness of the epithelial mucosa, and reduced apoptosis in the enterocyte and crypt compartments.<sup>108–111</sup> Rat models of 75 to 80% small bowel resection had increased GLP-2 concentration following resection,<sup>112</sup> and rats given h[Gly<sup>2</sup>]-GLP-2 treatment had increased jejunal crypt–villus height and increased mucosal sucrase activity following jejunal resection.<sup>113</sup>

GLP-2 appears to be one of the most influential growth factors involved in intestinal adaptation. GLP-2 is produced and secreted from L cells, enteroendocrine cells of the small and large intestine. The circulating form of GLP-2 in humans consists of a 33–amino acid peptide that is secreted in response to nutrients in the gastrointestinal tract. The amino acid sequence is highly conserved among mammalian species. The actions of GLP-2 are mediated by a recently identified G protein–coupled receptor expressed in endocrine cells and enteric neurons of the stomach, small bowel, and colon.<sup>114</sup>

In addition to its trophic effects, GLP-2 appears to enhance function. Rodent data suggest that GLP-2 is a key regulator of mucosal permeability, promoting energy absorption and decreased fluid losses.<sup>113</sup> GLP-2 also appears to promote energy absorption and decreases gastric acid secretion.<sup>115,116</sup> Parenteral GLP-2 administered to mice enhanced absorption of monosaccharides (galactose) and glycine.<sup>117,118</sup> GLP-2 also delays antral emptying<sup>119</sup> and prolongs intestinal transit, thus increasing the contact time of intraluminal nutrients with the intestinal mucosa.<sup>115</sup>

Plasma concentration of GLP-2 in patients with SBS depends on the remaining anatomy. Given that it is pro-

duced in the L cells of the ileum and colon, it is not surprising that patients who have had ileal or colonic resection have lower levels. Studies in SBS patients with a preserved colon have shown markedly increased levels of circulating GLP-2, whereas patients with a jejunostomy had normal basal levels of GLP-2 but significantly impaired postprandial response levels.<sup>120</sup> This may be a major reason why patients with an end-jejunostomy have limited structural and functional adaptation compared with patients with an intact ileum.<sup>105,106</sup> Exogenous administration of GLP-2 has been shown to promote the growth of colonic epithelium in unresected animals.<sup>121</sup> A study by Jeppesen and colleagues of patients with SBS administered GLP-2 subcutaneously showed a statistically significant improvement in nutrient absorption and body weight with increased crypt depth and villus height demonstrated on jejunal and ileal biopsies.<sup>116</sup>

GLP-1 does not appear to have the same magnitude of effect on the adaptive process as GLP-2, but it does promote efficient nutrient assimilation via effects on food intake, gastric emptying, stimulation of insulin secretion, and control of islet proliferation.<sup>66</sup> GLP-1 also appears to inhibit gastric secretion and motility by inhibiting central parasympathetic outflow.<sup>122</sup>

### **Epidermal Growth Factor**

EGF is a 53-amino acid peptide with receptors found on the basolateral and brush border membranes of cells throughout the intestinal tract. In normal physiology, EGF is thought to play a prominent role in the repair of damaged intestinal mucosa. The highest concentrations are found in the submandibular glands and the Brunner's glands of the duodenum. It is also present in a variety of other bodily fluids that are found within the alimentary tract and thus bathe the intestinal mucosa, including saliva, breast milk, and pancreatobiliary secretions.<sup>123</sup> EGF plays a key role in the maintenance of mucosal integrity, in part by the stimulation of enterocyte proliferation and migration.<sup>124</sup> In addition to promotion of the proliferative response, EGF may play a role in mediating cell turnover by regulating apoptosis. EGF has been shown to induce the transport and synthesis of polyamines, which have been suggested to play a role in modulating apoptosis.<sup>7</sup> This appears to be mediated by stimulation of ornithine decarboxylase, leading to polyamine synthesis. Polyamines are believed to play a role in promoting mucosal proliferation by attenuating apoptosis.<sup>125,126</sup> Administration of intravenous recombinant EGF to TPN-fed rats reverses intestinal hypoplasia.<sup>127</sup> Studies examining the role of EGF administered systemically to rodents and rabbits with intestinal resection have shown a trophic effect, including induction of mucosal hyperplasia and proliferation, increased intestinal length and weight, mucosal thickness, crypt depth, and villus height.<sup>128–130</sup> Studies by Goodlad and colleagues demonstrated that in addition to increasing colonic weight, the pancreatic weight was also

increased, suggesting that some of the trophic effects noted may be related to stimulation of the pancreas (ie, increased pancreatic secretions).<sup>131</sup>

### **Trefoil Peptides**

Trefoil peptides (pS2, human spasmolytic polypeptide, intestinal trefoil factor) constitute a group of peptides secreted by mucin-secreting epithelial cells throughout the gut that appear to stimulate the mucosal repair process.<sup>132</sup> The characteristic three-loop structural motif that gives the group its name also gives these peptides a compact structure that prevents proteolytic digestion.<sup>133,134</sup> Under normal circumstances, these proteins are thought to play a role in mucus stabilization. They also appear to influence mucosal defense and repair, particularly in ulcerative disease of the gastrointestinal epithelium, such as peptic ulcer disease and inflammatory bowel disease. The mechanism of action appears to be stimulation of lateral migration of intact cells at the site of injury without stimulating proliferation *per se*,<sup>134,135</sup> although there does appear to be a correlation between spasmolytic polypeptide gene expression and expansion of the proliferative zone of the mucosa, suggesting that increased proliferation of epithelial cells may contribute to the repair process.<sup>136</sup> Whether trefoil peptides play a role in the intact epithelium of SBS patients remains to be elucidated.

### **Hepatocyte Growth Factor**

Hepatocyte growth factor (HGF) was initially described as a stimulant for hepatocyte DNA synthesis in the setting of acute liver failure. Subsequent studies showed that HGF binds to a transmembrane tyrosine kinase receptor that is found in many other tissues, including the gastrointestinal tract.<sup>137</sup> This peptide appears to have multiple effects, including influencing cell proliferation, differentiation, and morphogenesis. Like trefoil peptides and EGF, HGF appears to play a prominent role in the repair of damaged mucosal tissue. HGF appears to be active in the adaptation process as well. Studies in rats with 80% intestinal resection demonstrated increased intestinal epithelial mass and function when the rats were given parenteral HGF.<sup>138</sup>

### **Other Growth Promoters**

Multiple other proteins are likely involved in the adaptation process. Transforming growth factor  $\alpha$  (TGF- $\alpha$ ) is a 50-amino acid EGF analogue that is found in mucosal cells and, like EGF, binds and activates the EGF receptor. This peptide has also been shown to stimulate gut growth when given parenterally to rodents.<sup>132</sup> Fibroblast-derived keratinocyte growth factor (KGF) is a peptide that is known to stimulate proliferation in multiple types of epithelium, including skin, the lung, and the intestine. Recombinant



KGF administered to rat models of short bowel has also been shown to enhance intestinal mucosal proliferation.<sup>139</sup> Interleukin-11 (IL-11) is a multifunctional cytokine that has trophic effects on small bowel mucosa in rats<sup>140,141</sup> and appears to have antiapoptotic effects on human colonic cells in vitro.<sup>142</sup> Enhanced absorptive function has also been demonstrated with parenteral administration of IL-11 in rat SBS models.<sup>143</sup>

## CONCLUSION

Intestinal adaptation is a complex process, dependent on the anatomy remaining after resection and the expression and function of growth factors and hormones to promote mucosal growth and function. Examination of the contribution of each of these factors and how they interact with each other will be crucial. Enhancing adaptation is key to giving patients with SBS autonomy.

Given the costs, complications, and decreased quality of life associated with TPN, regaining enteral autonomy is the most desirable outcome in the patient with SBS. For this to occur, the function of the remaining bowel must compensate for the bowel that is lost. The adaptation process is complex and dependent on the status of the underlying disease that led to loss of bowel, the existing surface area, the anatomic identity and functional integrity of the remaining bowel, and multiple physiologic substrates that promote the growth and function of the remaining bowel. Further understanding of the role of each of these factors and how we may manipulate them will allow us to augment this process. Extensive research in the molecular mechanisms involved in the stimulation and regulation of intestinal growth will be needed to develop more refined techniques to promote this process. In so doing, we may hope to improve the quality of life for patients with SBS and intestinal failure.

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