How adaptable is the intestine in patients with short-bowel syndrome?1,2

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Several studies of animal models, mostly rodents but including other species as advanced as pigs, have shown that the intestine undergoes a variety of adaptive responses when shortened or deprived of nutrients. These responses include both hyperplasia and hypertrophy of either function or de novo expression of functional molecules (1). However, data documenting these responses in humans with short-bowel syndrome (SBS) are limited. The reasons for this lack of corroborating data are easy to enumerate. First, few humans have >75% of their small bowel resected, as was done in the animal models. Second, the ability to examine human small-intestinal tissue is limited, not only because the techniques necessary to accomplish this are invasive but also because the techniques are restricted to a small portion of the functionally inhomogeneous tissue (ie, those containing both crypts and villi). Finally, many patients with SBS continue to manifest conditions that may prevent adequate adaptive responses, most often chronic inflammation that requires surgical removal of the intestine (eg, Crohn disease), or develop altered bacterial flora (eg, bacterial overgrowth syndrome). Some data exist that allow one to judge whether the animal data are relevant to humans. The article by Ziegler et al (2) in this issue of the Journal makes another nice contribution to this small body of evidence.

Animal studies suggest that most adaptation is dependent on luminal nutrients, consistent with the observation that the outer two-thirds of the villus utilizes largely luminal amino acids. Most of these studies were carried out in rats, either after extensive removal of the small intestine or during treatment with total parenteral nutrition (TPN). In humans the data are largely derived from case studies of patients with SBS, most of whom were receiving TPN. Evidence for regeneration of the mucosa after extensive resection has been reported, but the mucosal thickness was no greater than that of unresected intestine (3). The fact that the mucosal thickness in the patients studied by Ziegler et al was no greater than what is considered normal may reflect either no loss of mucosa after the initial surgery or continued maintenance of normal mucosal thickness. The ability to produce hyperplastic mucosa may be limited in humans by luminal mechanisms that help to remove cells from the villus tip, by the presence of low-level apoptosis on the villus, or by the relatively short (2–3 d) cellular residence time on the villus that limits the time for regulatory response.

Evidence to support the role of luminal nutrients in small-bowel adaptation comes from animal models (mostly rats) in which mucosal atrophy produced by short-term TPN can be prevented by luminal nutrition (4). The mechanisms whereby this adaptation might occur are not known, but glutamine, short-chain fatty acids, and nucleotides have been suggested to be luminal stimuli (5). The colon utilizes short-chain fatty acids as its major fuel, and luminal short-chain fatty acids concentrations decrease after a left but not a right hemicolecotomy (6). Limited, inconclusive data suggest a role for glutamine as a specific small-intestinal nutrient in humans; however, these data were derived from studies performed in patients with acute critical illness rather than in patients with SBS (4). The argument relating the findings of the above-mentioned studies to SBS patients is that if atrophy occurs when luminal nutrition is limited, then hyperplasia with restoration of mucosal function should occur when luminal nutrients are given to such patients. However, rats develop mucosal atrophy within days of receiving TPN, which is not the case in humans during the usual treatment times and conditions of TPN (4). A few studies indicate modest mucosal atrophy (ie, ≤10% decrease in thickness) after short-term TPN in critically ill patients (7) or after long-term TPN (≥9–12 mo) in patients with inflammatory bowel disease (8). Thus, it seems possible that the small intestine in humans might become atrophic, but only if there is continuing or serious disease or if luminal nutrients are limited in the setting of acute or chronic illness. Under these circumstances, the atrophic effect appears to be modest, and the capacity of the small intestine to adapt via structural hyperplasia or improved function is similarly modest. It has not been shown that any of the reported mucosal changes produce a clinically significant effect.

Evidence of cellular hypertrophy or improved function of the small intestine in humans has been as hard to document as has that of structural hyperplasia. Increased permeability and bacterial translocation have been shown in animals, but these findings have not been supported by data from studies in humans (4). Recent studies have revived the concept that gut function is adaptable in response to hormonal regulation, which may account for some of the modest adaptation in humans. Glucagon-like peptide 2 (GLP-2) is expressed in the stomach, small bowel, and colon of humans. In patients with SBS and a preserved colon, plasma concentrations of GLP-2 are elevated (9). Moreover, in SBS patients without a

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colon, the provision of GLP-2 leads to improved intestinal absorption and nutritional status, although the response is modest (10). Total energy absorption increases by only 3.5%, largely because of improved protein absorption, and the 10% increase in villus height is not statistically significant. Thus, the functional capacity for recovery by the small intestine in humans also seems limited.

Ziegler et al showed that selective intestinal adaptation occurs in SBS patients, as evidenced by an elevated expression of colonic human PepT1, the oligopeptide transporter. This transporter can be anomalously expressed in the colon of patients with chronic inflammatory conditions, such as inflammatory bowel disease (11). Such ectopic expression may be a general feature of the gastrointestinal tract because chronic inflammatory conditions can result in an increase of other gastrointestinal proteins, such as intrinsic factor, into gastric cell lineages that normally show limited expression (12). The meaning of such ectopic expression in the SBS patients studied by Ziegler et al is uncertain. This phenomenon may represent molecular evidence for metaplasia in the setting of chronic inflammation, but no colonic inflammation was seen in these patients, at least in the lamina propria. If no inflammation were present in the deeper layers of the intestine, this change may represent molecular adaptation or hypertrophy. The expression of PepT1 in the colon of humans confirms the ability of the intestine to adapt under certain circumstances and strengthens the existing data that support a modest ability of the human intestine to undergo either atrophy or hyperplasia, unlike in the animal models that provide the basis for most of the hypotheses regarding intestinal adaptation. Thus, the further molecular characterization of SBS should be done in human studies, as exemplified by the study by Ziegler et al. Such studies may identify new mucosal functions in SBS patients that might lead to improved management of this condition.

REFERENCES