Chapter 6: Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation

INTRODUCTION AND BACKGROUND

The collection of topics in this chapter is linked by a common interest in the physical integrity of the gut and strategies to promote natural repair and regeneration processes in response to loss of intestinal tissue function through surgery or disease.

Intestinal growth and differentiation. At birth, the human small intestine is typically 2-3 meters in length and grows to about 6-7 meters in adults. In addition, the epithelial lining of the intestine is continually renewed as new cells mature from the proliferating stem cells located at the base of the intestinal crypts. This lifelong capacity for growth and differentiation of the complex cellular structure of the intestine suggests the potential for development of regenerative cures for many digestive diseases as researchers learn how to identify, isolate and manipulate intestinal stem cells.

Short bowel syndrome and intestinal adaptation, repair and regeneration. Short bowel syndrome (SBS) can occur when half or more of the small intestine is missing or not functioning properly. Children can develop this condition for a variety of reasons including congenital defects and necrotizing enterocolitis (NEC). In adults, short bowel syndrome can result from surgical removal of the intestine for treatment of inflammatory, mechanical, and malignant processes including Crohn’s disease, tumors, volvulus (a twisting of the intestine that causes tissue death), bowel obstruction, traumatic injury, or other conditions. Patients with this syndrome develop diarrhea, dehydration and malnutrition due to the inability of the intestine to absorb sufficient water, vitamins, minerals, and other nutrients from ingested food.

Patients with SBS are treated with dietary modification (small frequent meals) with or without anti-motility and antisecretory medications. Patients with moderate to severe SBS often develop intestinal failure and require IV fluids and/or parenteral nutrition (TPN) - the delivery of nutrients and fluids by vein rather than by ingestion to sustain life. Unfortunately, with prolonged use, TPN is associated with life-threatening complications. Intestinal failure results when there is insufficient intestine to absorb adequate fluid to maintain hydration and/or to absorb 85 percent of required nutrients, thereby necessitating the likely use of intravenous fluids, electrolytes, or nutrients.

For fortunate patients without massive gut loss, short bowel syndrome is a temporary phenomenon. Intestinal adaptation can occur by enlargement of the intestinal villi, increase in crypt cell proliferation or an increase in the diameter of the small intestine—all of which augment surface area available for nutrient absorption. Alternatively, slowing of peristalsis—the movement of food through the digestive tract—can also help patients adapt to a shorter intestine. These processes can be stimulated with luminal nutrients and growth factors, although a much better understanding of these factors is needed to optimize this therapy. Finding ways to promote intestinal adaptation, repair, or regeneration could lead to new therapies for short bowel syndrome in both children and adults. TPN failure occurs in some patients due to loss of venous access due to central vein thrombosis, recurrent severe septicemias, and development of irreversible liver disease. These patients require small bowel transplantation. A combined liver/small bowel transplant is necessary when liver failure occurs in conjunction with intestinal failure.

Intestinal transplantation. For patients with irreversible intestinal failure or those with progressive complications of TPN, small intestine transplantation is the last therapeutic option. More than 100 intestinal transplantations, either alone or in combination with other abdominal organs, are performed each year in the U.S. The success of intestinal transplantation procedures is now similar to that for other solid organs (close to 90 percent 1-year survival for host and graft) due to recent advances in
immunosuppression, and recent studies suggest successful transplantation is associated with improved quality of life. Long term survival however remains suboptimal.

*Metabolic and nutritional consequences of surgically modified gut.* With the increasing prevalence of obesity in the U.S. and worldwide, bariatric surgical procedures are becoming more common in both adults and adolescents. Different surgical procedures are used, with the most frequent being a reduction in stomach size, bypass of a portion of the small intestine, or a combination of both strategies. Many patients achieve significant weight loss in response to the surgery, although serious complications at the time of surgery such as anastomotic leakage, pneumonia, deep vein thrombosis and embolism or death can occur in rare cases. Serious chronic side effects also may follow bariatric surgery procedures including intestinal infections, food intolerance, hernia, and the need for surgical revisions or surgery for treatment of complications, occasionally resulting in intestinal loss. Nutritional deficiencies can occur due to poor absorption of food and vitamins or minerals in the modified gut. Weight loss after bariatric surgery is not wholly explained by restricted food intake, but may also involve metabolic and hormonal changes resulting from the surgery that are not yet fully understood.

*Nutritional support of patients with gastrointestinal disorders.* Patients with gastrointestinal disorders often develop nutritional deficiencies due to interference with the normal digestion and absorption of food, ranging from mild deficiencies due to poor absorption of micronutrients to dehydration and starvation in extreme cases. Some patients, such as those with anorexia or dysfunction of the upper GI tract can be treated by enteral feeding through a tube placed directly into the gastrointestinal tract. If all gut function is lost, as for patients with moderate to severe SBS and intestinal failure or in premature infants with NEC, TPN supports survival. Specialized enteral diets and gut peptide analogues such as GLP-2 and growth hormone, are capable of maximizing mucosal adaptation and regeneration. However, complications of TPN, for patients needing long-term nutritional support, can include infections, chronic liver failure, loss of kidney function, metabolic bone disease, and blood clots.

**RECENT RESEARCH ADVANCES**

*Mechanisms regulating mucosal function and growth have been clarified at the cellular and molecular level allowing manipulation of the intestinal milieu to augment intestinal adaptation*  

Growth factors enhance villus growth, stimulate enterocyte proliferation, and attenuate enterocyte apoptosis in the remnant gut following massive intestinal resection. Animal investigations as well as preliminary studies in humans suggest that growth factors, including glucagon-like peptide II, insulin-like growth factor I (IGF I) and epidermal growth factor may help stimulate intestinal growth and development and lead to improved fluid and nutrient absorption. Collectively, these growth-stimulating phenomena in animal models are termed post-resectional adaptation. Work over the last two decades has demonstrated that this process is influenced by a number of factors including specific luminal nutrients, such as fiber, as well as a variety of gastrointestinal and systemic hormones and peptides. These studies have identified that luminal nutrients and bacteria are capable of altering gene expression profiles and absorption and digestion in enterocytes. The availability and study of isolated enterocytes and enterocyte cell lines have allowed clarification of the specific role of peptides, hormones and matrix factors on these growth and differentiation processes.

The chronology of intestinal adaptation has demonstrated that the gut is most responsive to stimulation and augmented growth immediately following the loss of intestinal surface area. Both animal and human models demonstrate that growth hormone, but not glutamine may enhance intestinal adaptation and improve fluid and nutrient absorption leading to the ability to reduce parenteral nutrition requirements. Recent translational studies in patients with SBS-intestinal failure have shown promise for novel agents and efficacy of medications not originally developed for GI conditions. The adaptive processes of villus
hypertrophy and improved fluid absorption, with the reduced need for TPN, can be enhanced with GLP-2 and GLP-2 analogues. Improved chloride and fluid absorption has been reported with orally-administered or transdermal clonidine.

The identification of a stem cell niche with specific responsiveness to growth factors, gut peptides, and paracrine factors has enhanced our understanding of specific molecular features of this growth adaptive process.

*Surgical modification of the small intestine*

Intestinal lengthening procedures have led to improved management of infants and children with refractory short-gut syndrome. Intestinal dilation, bacterial overgrowth, and luminal stasis are hallmarks of chronic short-gut syndrome in infants and children. Refractory to medical strategies to minimize malabsorption, it has been demonstrated that intestinal lengthening procedures, including serial transverse enteroplasty (STEP) and the Bianchi procedure to remove non-functional and dilated loops of the intestine, lead to improved intestinal function including absorption of nutrients and liquids.

*Intestinal transplant registry*

Advances in intestinal transplantation have been documented by establishment of a voluntary international intestinal transplant registry. The registry includes virtually all intestinal, intestine/liver and multivisceral transplants performed around the world. Expansion of the registry has allowed accurate appraisal of patient survival, graft survival, impact of survival on parenteral nutrition use and other outcome data. This registry has allowed the early development of a network of international centers with expertise in management of patients with critical short gut syndrome although consensus on data points, consistency and data entry and fostering of collaborative research programs has not yet been achieved.

*Intestinal transplantation*

Intestinal transplantation, with or without the liver, has become progressively more successful in the major centers with first year survival rates similar to orthotopic liver transplantation alone. The improvement in quality of life is substantial for IF patients dependent on permanent TPN. This occurs in the majority, but not in all graft recipients. Definition of factors contributing to graft survival, optimal management of immunosuppressive regimens, improved methods to monitor rejection, and factors contributing to adaptation of the transplanted gut remain areas of active investigation. It has also been observed that intestinal transplantation can not only prevent, but also reverse early TPN-induced liver dysfunction, thus avoiding the eventual need for combined small bowel/liver transplantation.

Candidate markers for intestinal rejection without the need for tissue biopsy have been identified including 3-0-methyl glucose absorption, serum citrulline, and calprotectin. Each may potentially serve as a surrogate for intestinal mass and/or rejection and thus avoid the need for frequent intestinal biopsies to identify early reversible rejection. Tolerance to the intestinal grafts develops in some patients allowing a reduction in immune suppression to a few times per week. Factors responsible for the development of tolerance are unclear and are being investigated.

*Regenerative medicine for treatment of intestinal failure*

Mucosal plugs from the intestinal stem cell niche have been successfully grown on bio-artificial scaffolds. Placed in continuity with the native intestinal tract, these mucosal plugs have demonstrated normal proliferative patterns and the capacity to expand to occupy defects in the intestinal mucosal surface area. Given the dense lymphatic tissue burden in intestinal allografts, the ideal long-term solution for patients
with intestinal failure will be a regenerative medicine approach in which native intestinal tissue is expanded on a suitable scaffold and grown to a size and surface area sufficient to support enteral nutrition when placed in continuity in the gastrointestinal tract. Identification of the stem cell niche and expansion of this population into a mature and differentiated mucosal surface is an important first step in this process. Identification of appropriate matrix, manipulation of the growth and differentiated environment and strategies to induce vascularization sufficient to incorporate the tissue into the native gastrointestinal tract will be required to achieve a tissue engineered solution.

Effect of parenteral nutrition on gastrointestinal development

Several strategies to reduce the negative impact of parenteral nutrition on developing gastrointestinal organs have been identified. Parenteral nutrition may cause choline deficiency which has been implicated in fatty liver, an early step in liver disease. Intravenous choline supplementation may ameliorate this process. Fish-based emulsions, tumor necrosis factor blockade, cycling of parenteral nutrition, and ursodeoxycholic acid administration have been reported to possibly be of benefit in the treatment of parenteral nutrition-associated liver disease. The timing of introduction of enteral feedings, initiation of parenteral nutrition in neonates and premature infants has demonstrated that there are critical windows to optimally introduce these factors to maximize gastrointestinal development and infant weight gain and growth.

Prevention and treatment of necrotizing enterocolitis

Necrotizing enterocolitis remains one of the most lethal perinatal conditions of premature low birth weight infants. Prevention is the key objective, for once established this condition is the lead cause of intestinal failure in children. Preliminary data from trials in premature infants suggest that probiotics may be beneficial in the prevention of necrotizing enterocolitis and granulocyte stimulating factor may reduce the progression to more severe necrotizing enterocolitis. Surgical approaches have also been introduced to minimize the role of resection in the management of these patients while ensuring adequate management of abdominal sepsis in these critically ill infants.

Intestinal Microbiota

The application of DNA methodology to assess the resident bacteria of the gut has revealed tremendous diversity and mass of the microbiota. These studies have opened up the investigation of the role of bacteria in the prevention and causation of intestinal disorders, including those that may lead to SBS-IF.

Animal models of bariatric surgery

A rat model of gastric banding has been developed and bariatric surgical mouse models have also been developed. While mechanical mechanisms were once considered the primary modality of weight loss, recent advances in measurement of gut hormones including ghrelin polypeptide Y and others indicate that substantial changes in metabolic and gastrointestinal hormones occur. Identification of the mechanisms underlying surgically induced weight loss in animal models could result in development of medical means to produce significant and durable weight loss, which is currently achievable only through surgery. Animal models may also allow better understanding of the long-term metabolic sequelae of bariatric procedures including specific nutrient deficiencies, metabolic and bone disorders, management of by passed segments, and other issues.

GOALS FOR RESEARCH

Research Goal: Define mechanisms of intestinal growth and differentiation.
The intestine has the capacity to grow during childhood, renew its lining throughout life, and adapt to loss of surface area due to surgical resection or disease. By understanding these processes at a molecular and cellular level, it might be possible to develop new pharmaceutical or cell-based therapies to enhance these natural phenomena to effect total remission or cure of disease by replacing sections of the intestine with functional tissue or to promote recovery from surgery or injury by stimulating endogenous repair pathways. Researchers are focused on characterizing the mechanisms that govern lineage selection of cell phenotypes from intestinal stem cells and understanding the molecular pathways involved in intestinal adaptation.

Objectives:
- Isolate, characterize, manipulate, and expand human intestinal stem cells in vitro.
- Define optimal factors—growth factors, nutrients, extracellular matrix or milieu—to enhance post-resectional adaptation in human patients.
- Develop an optimal bioartificial scaffold for neomucosal growth.
- Develop artificial intestinal constructs for replacement of diseased bowel.
- Conduct a clinical trial of exogenous factors to optimize post-resectional adaptation.

Research Goal: Develop new strategies to treat short bowel syndrome and intestinal failure.

Surgical bowel resection for conditions such as Crohn’s disease or injury can lead to the development of short bowel syndrome or intestinal failure, although some adaptation of the remaining tissue is possible. Studying the nutritional, hormonal, or other factors that promote adaptation could reveal new strategies for enhancing bowel recovery from surgical resection. Avoidance of short bowel syndrome and failure would represent a significant therapeutic advance and relieve the significant medical and economic burden of these conditions. Further research is needed to understand why TPN complications arise and how they can be prevented and/or treated.

Objectives:
- Evaluate the effect of specific micronutrients and diet on postoperative intestinal adaptation.
- Develop and validate non-invasive markers of intestinal growth and adaptation in short gut models.
- Develop reliable non-invasive methods to measure intestinal growth and adaptation in patients.
- Develop more effective techniques and strategies to reduce septic, metabolic, and hepatic complications of parenteral nutrition and intestinal failure.
- Define the molecular basis of radiation enteritis and prevent and treat radiation enteritis and proctitis.
- Conduct a clinical trial of optimal growth factor (or synergistic combination) therapy following massive intestinal resection.
- Reduce the thrombotic, infective, hepatic and metabolic complication of PN to prevent PN-failure.
- Develop prognostic indicators for PN failure to guide the timing of intestinal transplant evaluation in optimal candidates.

Research Goal: Improve the success of intestinal transplantation.

Intestinal transplantation can be a life-saving treatment for some patients with intestinal failure who have developed potentially life-threatening complications of intestinal failure. The success of this procedure could be improved by developing novel immunosuppressive drugs that are tailored for the unique immunological milieu of the intestine, or optimizing organ selection and preparation to minimize the risk
of rejection and infection. Moreover, new techniques are needed to monitor organ rejection that would be less invasive than conventional endoscopy biopsy.

**Objectives:**
- Determine the role of exogenous growth factors and micronutrients post-transplantation.
- Improve methods for donor bowel preservation pre-transplant.
- Identify new targeted pathways for novel immunosuppressive therapies.
- Develop artificial intestinal conduits from native tissues and cells for autotransplantation.
- Identify biomarkers for non-invasive diagnosis of intestinal transplant rejection.
- Identify factors that diminish long-term post transplant survival and appropriate countermeasures.

**Research Goal:** Understand and treat the metabolic and nutritional consequences of bariatric procedures and other surgical modifications of the gut.

Bariatric surgery for weight loss and other surgical modifications of the gut have metabolic and hormonal consequences that were not originally predicted based on simple resection of tissue. Researchers are working to understand the molecular bases for these phenomena and use these insights to develop non-surgical interventions to achieve the same result. Further, knowledge of these pathways could aid in the identification of biological markers that predict which patients are most likely to benefit or not from bariatric or other surgeries.

**Objectives:**
- Identify pre-operative biomarkers to predict weight loss and metabolic correction.
- Characterize the neuroendocrine, hormonal, cytokine, proteomic response to bariatric procedures in animal models and humans.
- Characterize the long-term metabolic (vitamins, calcium, minerals, other) sequelae and changes in anorexic and orexigenic hormones in bariatric surgical patients.
- Develop non-surgical therapy that “mimics” neurohumoral sequelae of bariatric procedures.

**Research Goal:** Optimize nutritional support of patients with gastrointestinal disorders.

Many patients with severe gastrointestinal dysfunction, including premature infants, rely on enteral or parenteral nutritional support to sustain life. Although these procedures are indispensable for many patients, they carry the risk of severe side effects and do not perfectly replicate normal digestion and absorption of nutrients. Further research is warranted to understand the impact of nutritional support protocols on patients’ daily lives, to improve the nutritional value of these treatments, and to reduce the risks of adverse events.

**Objectives:**
- Develop and validate quality-of-life measures for patients with chronic GI dysfunction to allow assessment of efficacy of different treatments.
- Evaluate the effect of specific micronutrients and diet on GI absorption, motility and immunity.
- Investigate the importance of the gut microbiome in the prevention and causation of GI diseases
- Assess the safety and potential efficacy of probiotics, probiotics, and symbiotics in the prevention of necrotizing enterocolitis and catheter-related sepsis.
- Design and test diet formulations to prevent neonatal feeding intolerance and necrotizing enterocolitis.

**MAJOR CHALLENGES AND STEPS TO ACHIEVE THE GOALS**
National research resources: Translational and clinical research on intestinal failure and regeneration and related issues is hampered by the small numbers of patients at any single institution. In addition, many investigators have difficulty in accessing human intestinal tissue at the time of resection or at regular intervals after adaptation. The establishment of multi-center clinical and basic research networks would promote progress in the field by fostering collaboration and sharing of resources. A national registry for intestinal failure/short bowel syndrome patients and for those with small intestine allografts would facilitate recruitment of patients for clinical research and intervention trials. Finally, centralized tissue banks of biosamples from patients with different gastrointestinal disorders or who are undergoing bariatric surgery and follow-up would enable researchers to readily access human tissues for research regardless of the location of the patients.

Standardized clinical definitions: Development of a standardized system to characterize short gut and intestinal failure in terms of anatomy, nutritional support, and complications is an important challenge for the field. Having such a system would enable researchers to directly compare data and outcomes across studies and patient groups. Achieving consensus on data points, definitions, and outcome measures would facilitate understanding of the relative effectiveness of medical, nutritional, and surgical intervention strategies. ICD-9 codes should be created and implemented to assist in the tracking of afflicted patients. Creation of a health outcomes research consortium is one step that could be taken to promote standardization.

Advanced technologies: The difficulty in accessing the small bowel with repetitive surgical or endoscopic procedures hampers clinical research as well as patient care. The development of novel, less invasive technologies to access the intestinal lumen would stimulate research on human disease. Furthermore, identification of serum or other surveillance markers would enhance the ability to care for patients with small intestinal disorders, including short gut syndrome, intestinal failure and other with intestinal transplants.