Illustration showing the proposed origin of various small bowel epithelial cell types from possible stem cells located at the base of the crypts. Stem cells play an important role in regenerating the intestinal epithelium.

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

SUMMARY OF RESEARCH GOALS

Loss of intestinal function can occur through surgical removal of tissue or diseases that impair digestion or cause tissue death. The Commission recommends research goals that, if pursued, would increase understanding of the natural mechanisms of growth, differentiation, and adaptation in the gastrointestinal (GI) tract and use that information to better treat patients with GI diseases. Research is needed on the development of new treatment strategies for short bowel syndrome (SBS) and intestinal failure, including innovative approaches to optimizing intestinal transplantation and post-transplant survival. GI tract surgeries, including bariatric surgeries for weight loss, are frequently associated with nutritional or hormonal complications. An important research focus is improving nutritional support for surgical patients and others with digestive diseases who rely on parenteral or enteral nutrition to sustain life, including premature infants with necrotizing enterocolitis (NEC). Achieving these research goals would markedly enhance the quality of life and health of many patients with digestive diseases or injury who are unable to properly absorb nutrients through their GI tract.

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 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: SBS can occur when half or more of the small intestine is missing or not functioning properly. Infants and children can develop this condition for a variety of reasons, including congenital defects and NEC. In adults, SBS 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 mild SBS are treated with dietary modification (small frequent meals), with or without anti-motility and anti-secretory medications. Patients with moderate to severe SBS often develop intestinal failure, which results when there is insufficient intestine to absorb adequate fluid to maintain hydration and/or to absorb 85 percent of required nutrients. These patients require intravenous fluids, electrolytes, or nutrients through such means as parenteral nutrition (PN)—the delivery of nutrients and fluids by vein rather than by ingestion to sustain life. Unfortunately, with prolonged use, PN is associated with life-threatening complications.

For fortunate patients without massive gut loss, SBS is a temporary phenomenon. Intestinal adaptation can occur by enlargement of the intestinal villi, an increase in crypt cell proliferation, or an increase in the diameter of the small intestine—all of which augment the 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 facilitated 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 SBS in both children and adults. PN failure occurs in some patients from loss of venous access as a result of central vein thrombosis, recurrent severe septicemias, or 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 PN, small intestine transplantation is the last therapeutic option. Close to 200 intestinal transplantations, either alone or in combination with other abdominal organs, are performed each year in the U.S. The short-term success of intestinal

transplantation procedures is now similar to that for other solid organs (close to 80 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 GI disorders:[12] Patients with GI disorders often develop nutritional deficiencies due to interference with the normal digestion and absorption of food, ranging from mild deficiencies resulting from 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 GI tract. If all gut function is lost, as for patients with moderate to severe SBS and intestinal failure or in premature infants with NEC, PN supports survival. Specialized enteral diets and gut peptide analogues, such as glucagon-like peptide-2 (GLP-2) and growth hormone, can maximize mucosal adaptation and regeneration. However, complications of PN 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

The mechanisms responsible for regulating mucosal function and growth have been clarified at the cellular and molecular levels, allowing for manipulation of the intestinal milieu in order to augment intestinal adaptation. For example, growth factors have been shown to 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 GLP-2, insulin-like growth factor-1 (IGF-1), 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

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[12] The Commission considered the issue of nutritional support and its consequences for patients with gastrointestinal diseases. However, the broader topic of nu-tritional research planning is overseen by an existing group, the NIH Nutrition Coordinating Committee within the Division of Nutrition Research Coordination.

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 GI and systemic hormones and peptides. These studies have demonstrated 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 clarified 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 PN requirements. Recent translational studies in patients with SBS-intestinal failure have shown promise for efficacy of novel agents and medications not originally developed for GI conditions. The adaptive processes of villus hypertrophy and improved fluid absorption, with the reduced need for PN, 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 SBS. Intestinal dilation, bacterial overgrowth, and luminal stasis are hallmarks of chronic SBS 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 data from 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 on survival of PN use, and other outcome data. The collaborations that contribute to the ongoing registry project have facilitated improved management of patients and development of new collaborative research projects by international centers of excellence in intestinal transplantation.

Intestinal transplantation

Intestinal transplantation, with or without the liver, has become progressively more successful in the major transplant centers, with first-year survival rates similar to orthotopic liver transplantation alone. The improvement in quality of life is substantial for patients with intestinal failure who are dependent on permanent PN. This occurs in the majority of, but not 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 PN-induced liver

dysfunction, thus avoiding the eventual need for combined small bowel/liver transplantation.

Candidate markers for intestinal transplant 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 graft 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 bioartificial scaffolds. Placed in continuity with the native intestinal tract, these mucosal plugs have demonstrated normal proliferative patterns and the capacity to expand to fill gaps in the intestinal mucosal surface. 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 GI 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 GI tract will be required to achieve a tissue-engineered solution.

Effect of parenteral nutrition on GI development

Several strategies to reduce the negative impact of PN on developing GI organs have been identified. PN 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 (TNF) blockade, cycling of PN, and ursodeoxycholic acid administration have been reported to possibly be of benefit in the treatment of PN-associated liver disease. The timing of introduction of enteral feedings or PN in neonates and premature infants has demonstrated that there are critical windows to optimally introduce these factors to maximize GI development, infant weight gain, and growth.

Prevention and treatment of NEC

NEC 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 NEC, and granulocyte stimulating factor may reduce progression to more severe NEC. 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 microflora

The application of DNA methodology to assess the resident bacteria of the gut has revealed tremendous diversity and mass of the microflora. These studies have opened

up research on the role of bacteria in the prevention and causation of intestinal disorders, including those that may lead to SBS-intestinal failure.

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 GI 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 bypassed segments, and other issues.

GOALS FOR RESEARCH [13]

Research Goal 6.1: Define mechanisms of intestinal growth and differentiation. (See also Goal 1.6.)

The intestine has the capacity to grow during childhood, renew its lining throughout life, and adapt to loss of mucosal 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, either to (1) effect total remission or cure of disease by replacing sections of the intestine with functional tissue; or (2) 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 growth factors, nutrients, extracellular matrix, and 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 6.2: 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 SBS or intestinal failure, although some adaptation of the remaining tissue is possible.

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[13] Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.

Studying the nutritional, hormonal, or other factors that promote adaptation could reveal new strategies for enhancing bowel recovery from surgical resection. Avoidance of SBS and intestinal 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 PN complications arise and how they can be prevented and/or treated.

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

Research Goal 6.3: 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. 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 by 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 endoscopic 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 noninvasive diagnosis of intestinal transplant rejection.
- Identify factors that diminish long-term post-transplant survival and develop appropriate countermeasures.

Research Goal 6.4: 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 biologic markers that predict which patients are most likely to benefit from bariatric or other surgeries.

Objectives:
- Identify pre-operative biomarkers to predict weight loss and metabolic correction.
- Characterize the neuroendocrine, hormonal, cytokine, and proteomic responses 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.
- Develop specific dietary guidelines for patients undergoing bariatric and other surgical modifications of the gut that can effectively prevent adverse metabolic and nutritional consequences based on newly identified hormonal and absorptive abnormalities.

Research Goal 6.5: Optimize nutritional support of patients with GI disorders.

Many patients with severe GI 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 the efficacy of different treatments.
- Evaluate the effect of specific micronutrients and diet on GI absorption, motility, and immunity.
- Evaluate the importance of the gut microflora in the prevention and causation of GI diseases.
- Determine optimal micronutrient requirements for patients that require long-term PN, as well as for those with catabolic illness that require PN.
- Assess the safety and potential efficacy of prebiotics, probiotics, and symbiotics in the prevention of NEC and catheter-related sepsis.
- Design and test diet formulations to prevent neonatal feeding intolerance and NEC.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

National research resources: Translational and clinical research on intestinal failure and regeneration and related issues are hampered by the small numbers of patients at any single institution. In addition, many investigators have difficulty accessing human intestinal tissue at the time of resection or at regular intervals after adaptation. The establishment of multicenter clinical and basic research networks would promote progress in the field by fostering collaboration and sharing of resources. A national registry for SBS-intestinal failure 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 GI disorders or those who are undergoing bariatric surgery and follow-up would enable researchers to readily access human tissues for research, regardless of the location where the patients received care.

Standardized clinical definitions: Development of a standardized system to characterize SBS 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 both clinical research and 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 SBS and intestinal failure, as well as recipients of intestinal transplants.