



Digitally enhanced x-ray of a human colon outlined using barium contrast material. Several diverticula, or bulges protruding from the colon wall, are visible in the distal colon.

Image Courtesy of Scott Camazine/ Photo Researchers, Inc.

Diseases of the Colon and Rectum

SUMMARY OF RESEARCH GOALS

The colon and rectum are susceptible to a variety of diseases and conditions that can impair their primary functions of maintaining water balance and eliminating wastes. The Commission's proposed research goals are aimed at understanding mechanisms of colonic injury, repair, and function so that prevention and treatment strategies for these disorders can be optimized. Key topics for research on colonic diseases are elucidating the role and composition of the gut microflora and manipulating this microbial community to restore health. Studies are also needed to establish the basis for structural defects like diverticular disease and vascular disorders, such as colonic ischemia (CI) and angioectasias. Better means of detection and treatment would improve the health and quality of life of elderly individuals, who are most affected by these conditions. Research is urgently needed on anorectal disorders, including anal fistulas, hemorrhoids, and fecal incontinence, which lack a firm evidence base concerning the causes and effective management strategies for these common, but poorly studied, conditions. Research on ways to prevent and treat radiation injury of the colon would alleviate this treatment-induced complication of pelvic cancer therapy. Finally, appendicitis can be fatal if undiagnosed and untreated. Research on the risk factors for onset and progression of appendicitis would further reduce the burden of this condition, especially in children.

INTRODUCTION AND BACKGROUND

The human colon—or large intestine—is primarily responsible for absorbing remaining water from indigestible food matter that has passed through the small intestine, maintaining the water balance in the body, and absorbing some vitamins. The final section of the luminal digestive tract—the rectum and anus—eliminates wastes from the body. Diseases involving the colon and rectum are diverse and include anatomic conditions (e.g., diverticular disease, fistulas, fecal incontinence), blood flow or vascular disorders (e.g., CI, angioectasias, hemorrhoids), conditions related to the gut microflora or immune dysfunction (e.g., inflammatory bowel disease [IBD], appendicitis), treatment-related disorders (e.g., radiation colitis), and colorectal cancer, gastrointestinal stromal tumors (GIST), carcinoids, and other cancers affecting the colon and rectum (see also the chapter on *Cancers of the Digestive System*).

Colonic mucosal injury and repair: The colon and rectum are lined with epithelial cells that absorb water and nutrients from undigested material and secrete a thick mucus layer that protects the lining from invasion by the gut microflora. Colonic epithelial cell injury requires both restitution and regeneration (proliferation). Rapid restitution of the mucosal epithelium is crucial to quickly restore the epithelial barrier, thereby limiting fluid and electrolyte losses, as well as preventing the introduction of harmful bacteria and foreign antigens. In response to colonic injury, goblet cells of the mucosa secrete a small protease-resistant peptide, termed trefoil factor 3 (TFF3) peptide.

Colonic mucosal absorption and colon vasculature: A primary function of the colonic mucosa is to absorb water and electrolytes from undigested materials before elimination. An imbalance in mucosal

absorption as a result of colonic injury or disease can result in constipation or diarrhea if too much or too little water is absorbed. Chronic diarrhea can result in dehydration and malnutrition; constipation (see also the chapter on *Functional Gastrointestinal Disorders and Motility Disorders*) may lead to the development of hemorrhoids, anal fissure, or rectal prolapse.

Gut microflora: The human intestinal tract is colonized by a complex and diverse community of microbes that are essential to the normal digestive functions of these organs. Little is known about the interaction of the majority of these microbes and their role—individually and collectively—in health and disease due to technical limitations in isolating and culturing individual species in the laboratory. Advances in genomic and proteomic technologies coupled with the prior knowledge of these organisms are set to revolutionize the characterization of the gut microflora. Bacteria in the colon produce small amounts of some vitamins, including vitamins K and B, which are absorbed through the walls of the colon. Alterations in the balance of species in the gut are linked to such diverse conditions as obesity, IBD, colitis (inflammation of the colon), and sepsis. Approximately 20 percent of hospitalized patients who receive an antibiotic will become colonized by the pathogenic bacterial species, *Clostridium difficile*, and many will develop severe colitis. *C. difficile* is kept from colonizing the colon by the normal microflora, and restoration of the microflora following infection is thought to result in eradication of the pathogen, which, if proven, would indicate a vital role of the microflora in maintaining the health of the colon.

Diverticular disease: In Western society, many older people develop pockets, or “diverticula,” that bulge outward from the colon wall, a condition known as diverticulosis. While some people have no symptoms of

diverticulosis, others may experience mild discomfort, bloating, or constipation. Infection or inflammation of the diverticula results in diverticulitis, a more serious condition associated with abdominal pain, bleeding, infections, perforations, or blockages. In extreme cases, abscesses may form in the colon wall, leading to peritonitis or fistulas. Diverticular disease is thought to develop as a result of a low-fiber diet and is treated by a high-fiber diet, mild pain medications, or surgery.

Ischemic colitis and angioectasias:

Inadequate blood supply to the colon can lead to inflammation and injury, a condition known as ischemic colitis. The majority of cases occur in elderly patients over 60 years of age. Blood clots or low blood pressure account for some cases of ischemic colitis, although in many patients the cause is unknown. Mild cases of ischemic colitis may resolve without medical intervention. More severe cases can lead to sepsis, intestinal gangrene, or bowel perforation and require surgical care. CI is the most frequent ischemic disorder of the GI tract. Epidemiologic studies have been designed to answer the question of whether CI has a positive association with irritable bowel syndrome (IBS) or whether such an association results from medications used to treat IBS. These studies have shown that CI has an estimated crude incidence rate of 7.2 per 100,000 in the general population. Part of the difficulty in determining the incidence of CI, however, is the difficulty in diagnosing it.

Anorectal disorders: Disorders of the anus and rectum are usually not life-threatening, but can have significant impact on a person's quality of life. Anal fissures—cracks or tears in the skin of the anus—are usually superficial and easily treated. However, chronic fissures that expose the underlying muscle may require surgical intervention. An anal fistula is a pathway that develops between an anal

abscess and the surface of the skin. A surgical procedure known as a fistulotomy can remove both the fistula and the original abscess. Hemorrhoids are inflamed veins in the lower rectum that may cause pain or rectal bleeding. Treatments options include over-the-counter creams, oral pain medications, or surgery to remove the tissue or cut off blood flow to the hemorrhoid. Fecal incontinence, or the inability to control the bowels, affects up to 5.5 million people of all ages in the U.S. and can be treated by dietary changes, medications, bowel training, or surgery.

Radiation colitis: Radiation therapy for cancers of the abdomen can damage the epithelial lining and blood vessels of the colon, resulting in radiation colitis. This inflammatory condition, which can develop within weeks or years after exposure to x-rays or ionizing radiation, causes symptoms that may include abdominal cramping, diarrhea, nausea, vomiting, rectal bleeding, and others. In severe cases, patients may experience complications, such as intestinal blockage, infection or abscess, nutritional deficiencies, or bowel rupture. Treatment for radiation colitis may involve changes to the diet or medications or, in very rare cases, surgery to bypass or remove the colon.

Appendicitis: Appendicitis is an inflammation of the appendix, a small, closed-end tube attached to the first segment of the colon on the lower right side of the abdomen. When the opening of the appendix is blocked, bacteria normally found in the appendix may begin to infect the walls of the organ and trigger an immune response. This blockage can occur with fecal matter, lymphoid aggregates, torsion, or a tumor with subsequent bacterial overgrowth. This leads to bacterial invasion of the appendiceal wall, inflammation, ischemia, gangrene, and perforation. Organisms typically identified include *E. coli*, *Peptostreptococcus* species, *B. fragilis*, and *Pseudomonas* species.

If left untreated, the appendix can rupture, allowing the infection to spread throughout the abdominal cavity. Appendicitis can be treated with surgical removal of the appendix and antibiotic therapy to control the infection. Approximately 325,000 cases of appendicitis occur each year in the U.S., primarily in the second decade of life.

RECENT RESEARCH ADVANCES

Effect of intestinal microflora on repair of the colonic epithelium

A greater understanding of the basic biology of TFF3 and other intestinal growth factors will advance our knowledge of how the gut responds to injury to begin the rapid repair process. In addition to restitution, the gut epithelium must also begin the process of regeneration, which involves repopulation (via proliferation) of the mucosa with new epithelial cells. The discovery that enteric bacteria promote proliferation of epithelial cell progenitors at sites of colonic mucosal injury, via their Toll-like receptor (TLR)-specific interactions with newly recruited macrophages, has proven to be a major advance in understanding the relationship among enteric microflora, the innate immune system, and epithelial repair.

Alterations in colonic sodium absorption underlie diarrheal responses in colitis

It has become clear that diarrheal manifestations of colitis are due to selective inhibition of sodium-absorptive ion transport pathways rather than activation of chloride-secretory pathways, as had been assumed in the past. Moreover, manipulation of sodium and chloride transport pathways appears to impact restoration of mucosal barrier function following injury. These findings suggest that understanding the segmental heterogeneity of ion transport pathways and their alterations during inflammation may lead to the

development of new, non-immunomodulatory approaches to symptom relief and mucosal healing.

Diversity of sodium absorptive pathways and complexity of their molecular regulation

Research advances include the development of transgenic mice lacking expression of selected sodium-hydrogen exchange isoforms, coupled with new data regarding their molecular assembly as multi-protein complexes that regulate via rapid alterations in surface expression. These advances have highlighted the need for more comprehensive understanding of the factors responsible for the coordinated fine-tuning of polarized ion transporters to affect the balance of secretion and absorption in the colon during health and disease.

The influence of luminal factors on colonic mucosal absorption

Major luminal anions (e.g., short chain fatty acids [SCFAs]) and cations (e.g., ammonia) are bacterial fermentation products of dietary fiber and protein that have been shown to affect not only colonic absorptive transporter expression and function, but also mucosal growth and differentiation through genetic and epigenetic mechanisms. The recent identification of novel transporters, including MCT transporters and Rh glycoprotein transporters, illustrates the complexity of colonic handling of these substances. The presence of multiple transporters for SCFAs and ammonia suggests an important interrelationship among diet, luminal microflora, and mucosal fluid homeostasis.

Extreme diversity of the human gut microflora

Most textbooks suggest that the human colon harbors approximately 20-30 genera and 400-500 species, with a total population at least

10-fold that of somatic cells. These numbers were generated by traditional bacteriologic techniques that relied on specialized culture media to isolate, characterize, and identify individual species. Recent studies using modern genetic techniques provide a much more complex picture of the intestinal microflora. The feces of healthy subjects contain thousands of bacterial species, mostly novel, uncultivated organisms. Considerable diversity in the gut microflora exists between individual humans, suggesting the possibility that each person may harbor a distinctive repertoire of bacterial species in addition to common shared species. Adherent bacteria form a thin biofilm attached to the epithelial surface. This mucosal population differs greatly from the fecal population inhabiting the lumen and is quite diverse in different parts of the colon, suggesting considerable “patchiness” in composition.

Human and murine microbes associated with obesity

The human and mouse microflora consist of two main phyla: Bacteroidetes and Firmicutes. The former phylum includes 20 distinct genera, of which *Bacteroides* species are the most abundant. Firmicutes include such well-known genera as *Lactobacillus*, *Bacillus*, and *Clostridium* species. Recently, important differences were shown between the relative abundance of these two phyla in lean compared to obese humans. Obese humans had more Firmicutes and fewer Bacteroidetes than lean people. During weight loss on either a low-carbohydrate or low-fat diet, the relative composition of these two components shifted to fewer Firmicutes and more Bacteroidetes. Similar studies in obese mice showed that the microflora of obese mice were more effective at extracting calories from food, allowing increased energy recovery for the host. These important studies suggest that differences in the intestinal microflora can potentially regulate energy availability and recovery from non-digestible nutrients in the gut lumen. This revolutionary

concept could be exploited to manipulate the microflora to influence body weight.

Extracellular matrix remodeling in patients with diverticulosis

Factors involved in the pathogenesis of diverticulosis include relatively low dietary fiber intake and decreased tensile strength of collagen and muscle fibers in the colonic wall as a result of aging. Research suggests that decreased tissue levels of matrix metalloproteinases, which are involved in extracellular matrix degradation and remodeling, and tissue inhibitors of metalloproteinases may contribute to the structural changes in the colonic wall seen in patients with diverticular disease.

Alteration of nervous system and smooth muscle activity in diverticulosis

Patients with diverticulosis have reduced numbers of colonic interstitial cells of Cajal and enteric glial cells, but normal numbers of enteric neurons, compared with healthy controls. These changes may decrease colonic electrical slow-wave activity, thereby resulting in delayed transit and possibly contributing to increased intraluminal pressure. In addition, these patients exhibit loss of colonic smooth muscle choline acetyltransferase activity, up-regulation of muscarinic M3 receptors, and increased *in vitro* sensitivity of the smooth muscle to exogenous acetylcholine (cholinergic denervation hypersensitivity). This finding may explain increased colonic contractility in patients with diverticulosis.

Visceral hypersensitivity in diverticular disease

Heightened visceral perception to rectosigmoid distention has been found in patients with symptomatic diverticular disease, but not in those with asymptomatic diverticulosis. Evidence suggests that the visceral

hypersensitivity may relate to release of proinflammatory mediators that sensitize enteric afferent nerve terminals and, thereby, heighten the response to noxious stimuli.

Treatment for inflammation in diverticular disease

Based on the possible role of low-grade colonic inflammation in symptomatic uncomplicated diverticular disease, trials have been undertaken of the non-absorbable antibiotic rifaximin, the anti-inflammatory agent mesalamine, and probiotic and prebiotic agents. Preliminary results suggest that these agents, particularly rifaximin and mesalamine, may reduce symptoms and prevent relapses, especially in patients with recurrent diverticulitis, although the benefit may be marginal.

Colonic vasculature injury in Crohn's disease

The cause of CI is rarely apparent, and most cases are believed to result from localized episodes of non-occlusive ischemia. A hyper-reactivity of the colonic arterial microvasculature is suggested by the approximately six-fold increased incidence in patients with IBS. A venous abnormality is suggested by the finding of increased incidence of various forms of coagulopathy in patients with CI. Segments of bowel removed for Crohn's disease show a spectrum of vascular injuries, suggesting that the pathogenesis of Crohn's disease includes multifocal infarction. Additional evidence for this hypothesis is found in the observation that the majority of granulomas in Crohn's disease form within the walls of blood vessels.

Relation of angioectasias and cardiac disease

Vascular lesions of the colon, especially angioectasias, are not an uncommon finding in the healthy elderly colon and are more commonly

seen in elderly patients with major episodes of lower intestinal bleeding. Angioectasias are seen in up to 32 percent of patients with aortic stenosis, suggesting a relationship with cardiac valvular disease, perhaps via abnormal von Willebrand factor multimers, resulting in a predisposition to bleed.

Etiology and treatment of fecal incontinence

Incontinence of stool is more common than previously thought, with a prevalence of 2-15 percent, depending upon the population studied. Continence for stool is a complicated process; recent work focuses on the contribution of obstetrical injury and aging to fecal incontinence, but our understanding is still limited. New treatment modalities, including the artificial bowel sphincter and sacral nerve stimulation, show promise for patients with fecal incontinence.

Treatment of perianal fistulas

The prevalence of perianal fistulas in patients without IBD is not well described. Depending upon the location of intestinal disease, 25-50 percent of patients with Crohn's disease have perianal fistulas. The mechanism of development of perianal abscess and fistula is poorly understood. Anal fistulas may be cured with fistulotomy (unroofing the fistula tract), but the procedure carries a significant risk of fecal incontinence. For patients with Crohn's disease, the use of immunomodulators has significantly changed the treatment of perianal fistulas. For patients with cryptoglandular fistulas, new treatment modalities, including the use of fibrin glue and plugs, have been developed to cure the fistulas without the risk of fecal incontinence.

Advances in treatment of hemorrhoids

In phone surveys, 20 percent of respondents noted bothersome anal symptoms. Poor patient and provider understanding of

anorectal anatomy and pathology lead to frequent misdiagnosis and treatment of anal symptoms. Because of the pain associated with recovery from conventional hemorrhoidectomy, innovations in this treatment area have been sought. Stapled hemorrhoidectomy is a new technique for treatment of prolapsing internal hemorrhoids. Division of the internal sphincter (i.e., lateral internal sphincterotomy) is the standard surgical treatment for anal fissures. Because of the risk of post-operative fecal incontinence, new treatments have been developed, including calcium channel blockers and Botox injections.

Innovations in radiation therapy to reduce radiation proctitis

Newer techniques of radiation therapy using computer-based treatment optimization, intensity-modulated radiation therapy allow for variation in the dose in a specific field, facilitating the sparing of normal tissue (i.e., rectum) with a resultant decrease in acute radiation proctitis. Higher doses with increased efficacy have been associated with a decrease in complications. Moreover, cytoprotective agents have been found to reduce toxicity without compromising radiation efficacy. Amifostine, an agent that protects tissues from the cytotoxic actions of radiation and chemotherapy that was developed by the military for use as a radioprotectant in the event of nuclear warfare, has selective cytoprotective effects for normal tissues. Parenteral and intrarectal amifostine is effective in preventing radiation proctitis without reducing efficacy. Local agents include balsalazide, a non-absorbable salicylate that has demonstrated clinical efficacy in management of radiation injury. Sulfasalazine has not been consistently effective in clinical trials, though it is recommended by some clinicians.

Treatment for chronic radiation proctitis

Chronic radiation colitis/proctitis is most commonly characterized by rectal bleeding with mucosal pallor, multiple large telangiectasias, and strictures. Chronic injury is secondary to epithelial atrophy and fibrosis associated with endarteritis and resultant ischemia. Argon plasma coagulation has been demonstrated to decrease rectal bleeding and improve anemia within a few sessions with minimal complications. Formaldehyde has been used for several years for treatment, with recent studies demonstrating efficacy and ease of application with flexible sigmoidoscopy. Good response to single applications has been noted.

Pathophysiology of appendicitis

Fiber intake and resultant constipation have been evaluated in the pathophysiology of appendicitis. Studies of children with appendicitis showed that they have less fiber in the diet. Other studies have revealed that children in Western countries have low fiber content in their diets, which is associated with constipation. Dietary fiber intake in the young is associated with increase and maturation of microbial mass, volatile fatty acids, and lower pH. These changes in animal models correlate with fewer GI disorders. Prebiotics—non-digestible food ingredients that benefit the host by affecting the activity or growth of gut bacteria—may have a similar effect on gut microflora. Agents like inulin and fructooligosaccharides are fermentable and selectively increase the growth of bifidobacteria. These agents are fermented primarily in the proximal colon near the appendix.

A small study of patients with gangrenous and phlegmonous appendicitis showed a different cytokine profile. Researchers observed a

positive correlation of gangrenous appendicitis with Th1-mediated immunity with higher levels of interferon- γ and IL-10 when the patients were studied at least 6 months after

appendectomy. Thus, individual differences in tendency toward Th1-mediated immunity with cytotoxic consequences may determine the outcome of appendicitis.

GOALS FOR RESEARCH ¹⁶

Research Goal 9.1: Establish mechanisms of colonic injury and repair to use as a basis for development of therapeutic interventions. (See also Goal 1.6.)

The interior lining of a healthy colon regenerates continuously to replace old or damaged cells. Understanding the mechanisms that regulate this normal cellular turnover will allow researchers to develop therapies that stimulate the regenerative process to repair colonic tissues damaged by infection, inflammation, radiation, or other adverse events. Molecules such as TLRs, TFFs, and other growth factors appear to play a role in proliferation of the mucosal epithelium and represent prime candidates for drug discovery and development.

Objectives:

- Identify the specific interactions (e.g., via receptors/ligands) between enteric microflora and TLRs that promote macrophage-dependent proliferation of progenitor cells and determine which mediators released by macrophages are required for epithelial cell proliferation.
- Determine the bioavailability, safety, and efficacy of orally administered TFFs and other epithelial cell growth factors in models of mucosal injury and inflammation.
- Develop strategies for mimicking the enteric antigen/TLR interactions to promote gut healing.

- Identify other gut-specific growth factors capable of promoting colonocyte restitution and repair.
- Develop TLR agonists that mimic the protective effect of enteric bacteria.

Research Goal 9.2: Understand colonic mucosal absorption in health and disease. (See also Goals 1.11 and 1.12.)

Absorption of water and electrolytes in the colon is necessary for maintaining proper hydration of the body and recovering vital micronutrients from ingested food. Nearly all individuals throughout the lifespan experience occasional acute bouts of diarrhea or constipation. These conditions are often easily treated with lifestyle or dietary modifications or by the use of readily available over-the-counter medications. However, some people develop chronic disease that can severely affect their nutritional status and quality of life. By investigating the molecular mechanisms that govern mucosal absorption, researchers can better understand how these mechanisms break down in chronic disease and identify targets for therapeutic intervention.

Objectives:

- Survey known sodium, chloride, SCFA, and ammonia transporter expression in human colon with comparison to murine models and evaluate segmental alterations in transporter expression on varied, defined fiber, and protein diets.

¹⁶ Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.

GOALS FOR RESEARCH

- Understand the regulation of sodium-absorptive and chloride-secretory pathways during disease and identify targets for potential therapy of diarrheal disorders and non-immunosuppressive approaches to enhance repair.
- Screen pediatric and adult U.S. populations for altered transporter complex expression and/or gene mutations in congenital and acquired constipation and diarrheal disorders, with the goal of developing individualized strategies for patients with chronic constipation or diarrhea.

Research Goal 9.3: Determine the role of gut microflora in health and disease states of the colon. (See also Goals 1.20, 1.21, 3.1, and 5.3.)

Microbes begin to colonize the digestive tract at birth and seem to have important roles in normal physiology, including digestion, nutrition, and immunity. Perturbations in the microflora have also been associated with various disease states. In some cases, overgrowth of a specific pathogenic bacterial species can cause disease, such as inflammation of the colon in response to *C. difficile* infection. Other conditions, like obesity or IBD, are associated with changes in the overall balance of different microbes. Research to characterize the gut microflora will generate new insights for therapeutic manipulation of the microflora to maintain the health of the colon and reverse disease.

Objectives:

- Establish tissue banks of mucosal biopsies to allow large-scale, chip-based comparison of adherent bacteria on the surface epithelium (biofilm) to bacteria in the normal microflora in feces.
- Compare bacterial microflora in obese and lean humans using molecular fingerprint assays and sequence analysis of cloned 16S rDNA.

- Compare colonic microflora before and after antibiotics in patients, with and without colonization by *C. difficile*, and use these data to develop a rational approach to reconstitute the microflora.
- Conduct randomized, double-blind, controlled trials to manipulate the colonic microflora in obesity as a possible adjunct therapy.

Research Goal 9.4: Establish the cause of diverticular disease and its complications, with modulation of disease.

Diverticular disease and its complications can cause significant discomfort and reduced quality of life in many elderly individuals. Understanding the risk factors for diverticulosis and its progression to diverticulitis will enable researchers to develop effective preventive strategies to reduce the burden of illness in this vulnerable population. For those patients who develop complications of diverticular disease, rigorous evaluation of medical and surgical options is needed to determine the most effective approach.

Objectives:

- Identify risk factors for diverticular disease, including genetics and lifestyle, and association with complications (specifically diverticulitis and bleeding).
- Determine whether treatment with non-absorbable antibiotics, mesalamine, prebiotics, probiotics, or other agents reduces the risk of recurrent diverticulitis and is cost-effective.
- Determine indications for surgery and the optimal surgical approach to complicated diverticular disease.
- Determine whether changes in lifestyle, especially diet, reduce the prevalence of diverticulosis and its complications (specifically, avoidance of specific dietary factors, such as seeds and popcorn) and reduce the risk of diverticulitis.

GOALS FOR RESEARCH

Research Goal 9.5: Understand mechanisms and develop tools for early diagnosis of colon ischemia and angioectasia.

CI is the most frequent ischemic disorder of the GI tract, yet it is very difficult to accurately diagnose. No specific tests are available to diagnose CI, except when infarction is present. Most episodes of CI resolve spontaneously and do not recur; however, approximately 25 percent of patients present with or develop irreversible disease requiring surgical intervention, and approximately 5 percent develop a chronic colitis resembling ulcerative colitis or Crohn's disease that may worsen with the standard treatment for IBD. Identifying biomarkers for early stage CI would allow earlier intervention and reduce the rate of complications.

Objectives:

- Devise a means of diagnosing CI early (i.e., before infarction ensues) and of differentiating it from other disorders by developing biomarkers for this disease process.
- Determine the underlying, proximate cause of CI, especially with regard to the behavior of colonic arteriolar and venular microvasculature, as well as the relationship of the bowel vasculature to serotonergic agents.
- Determine why angioectasias develop and understand the potential mechanisms for altered vasculature and blood flow.

Research Goal 9.6: Improve management of anorectal disorders.

Anorectal disorders are common clinical conditions, but limited basic science data exist about these disorders. While not life-threatening, the conditions may have a significant impact on a person's quality of life. The prevalence of these disorders is poorly studied, with the exception of fistulas in Crohn's disease and, recently, fecal incontinence. Limited scientific information is available on the underlying

mechanism(s) of each of the conditions despite commonly accepted theories, and little is known about prevention strategies or the effectiveness of current therapeutic recommendations. Finally, new treatment modalities have been developed in recent years; however, long-term outcomes and cost-effectiveness information are not yet available.

Objectives:

- Understand risk factors and preventive strategies for anal disorders, including anal fistulas and hemorrhoids, with appropriate modification; natural history and impact of obstetrical sphincter injury; medical and neurological conditions; pelvic surgery; and the role of surgical repair of sphincter defects.
- Develop evidence-based algorithms for prevention, diagnosis, and treatment of perianal fistulas (cryptoglandular and Crohn's) and for treatment of hemorrhoids.
- Develop educational tools for providers and the public to raise awareness of anorectal disorders, including perianal abscess and fistula, and hemorrhoids, with particular focus on accurate diagnosis, initial treatment, and prevention.

Research Goal 9.7: Improve the understanding and management of fecal incontinence. (See also Goal 2.2.)

Fecal incontinence is an underreported and underappreciated condition frequently associated with shame, embarrassment, and stigma. Because of these aspects, it has been difficult to identify persons affected, risk factors, biologic causes, and social and environmental factors. Fecal incontinence has a major impact on quality of life of individuals living at home and in nursing homes, impacting people of all ages, especially women and the elderly. New treatment modalities and appropriate utilization and acceptance of prevention and management strategies are needed.

GOALS FOR RESEARCH

Objectives:

- Develop generally accepted definitions of fecal incontinence with longitudinal studies to identify risk factors, including medical and surgical treatments that may cause incontinence, and preventive strategies.
- Understand the existence and causes of differences in the rate and impact of fecal incontinence in different groups.
- Investigate medical and surgical treatment modalities with development of improved measures and algorithms for treatment of fecal incontinence.
- Develop evidence-based strategies for the diagnosis, prevention, and management of fecal incontinence, particularly in the aged and residents of long-term care facilities.
- Understand the direct and indirect economic and societal impact of fecal incontinence and the potential benefits of prevention and treatment interventions.
- Develop educational tools for providers and the public to raise awareness of fecal incontinence.

Research Goal 9.8: Reduce the frequency and severity of radiation injury to the colon.

Radiation colitis—damage to the colon mucosa or vasculature due to radiotherapy for abdominal or pelvic cancer—can manifest within weeks or even years after radiation exposure. Researchers are looking for ways to precisely modulate radiation dosage to maximize therapeutic effectiveness, while simultaneously minimizing or eliminating radiation-related injury to healthy colon tissue. Algorithms to accomplish this goal must allow for variation among different types and stages of cancers, as well as other patient-specific characteristics.

Objectives:

- Determine prognostic factors (e.g., genetic factors, co-morbidities) that are important in the development of chronic radiation injury.

- Determine efficacy of pharmacologic agents in prevention of radiation injury via multicenter trials with collaboration among experts in gastroenterology, oncology, and radiation oncology. Agents may have additional applications for biodefense.
- Develop evidence-based algorithms for prevention and treatment of radiation proctitis.

Research Goal 9.9: Determine causes of appendicitis and modulate the course of the disease.

The onset of appendicitis is nearly always a medical emergency. Delays in diagnosis and treatment increase the likelihood that the organ will rupture and disperse bacteria into the peritoneal cavity. The resulting peritonitis may contribute to complications, such as abscess formation, wound infection, urinary tract disorders, small bowel obstruction, or even death in a small minority of patients. Understanding the causes of appendicitis and ways to delay progression will help reduce the morbidity and mortality associated with this serious disease.

Objectives:

- Determine the effect of dietary factors, such as fiber content, prebiotics, probiotics, and bowel function (constipation), on the incidence of appendicitis, especially in children.
- Determine the role of the immune-mediated response in the histopathology and clinical course of appendicitis.
- Identify high-risk patients from an immune standpoint and develop modifications of the clinical approach to treatment of patients with different immune profiles.
- Determine the role of antibiotic therapy and other non-surgical approaches for the management of appendicitis.
- Develop improved methods for early detection of appendicitis.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Collaboration with industry: Collaboration with protein chemists and the biotechnology and pharmaceutical industries to provide sufficient quantities of TFFs and other growth factors would accelerate the testing of these factors in chronic preclinical studies and clinical intervention trials in human patients.

Research resources: Progress in the field would be aided by the establishment of centralized resources that would encourage sharing of biologic samples and patient data, as well as provide opportunities for collaborative research. A comprehensive tissue bank could be created to collect, store, and disseminate normal and diseased human colonic specimens that are defined with respect to anatomic segment and clinical data. The development of database capabilities and clinical consortia for randomized clinical trials with standardized endpoints would enable direct comparisons among clinical research outcomes. The development of a systems-based approach to the study of colonic transport using a limited number of defined cultured cell and transgenic mouse models and comprehensive expertise in cell biology, structural biology, transepithelial transport, nutrition, imaging, and computational modeling would generate a new perspective on the causes and treatments of colorectal diseases.

Research tools for the microflora: The vast and complex gut microflora present several challenges to research on the physiology of the colon and rectum in health and disease. For example, the microflora adherent to the colonic mucosa—the “biofilm”—may be more relevant than the microflora in feces. Thus, research on the microflora would benefit from the use of mucosal biopsies from colonoscopy rather than the traditional reliance on stool specimens.

In addition, sensitive molecular techniques, such as PCR or microarrays, do not reliably distinguish between dead or non-viable organisms and organisms that are ingested and simply passing through the gut compared to microbes that are viable and capable of growth in the gut. The total metabolic activity (metabolome) of the microflora represents the sum of thousands of species and, in theory, could provide a less complex, quantitative approach to studying the microflora. New technology development would facilitate measurement of the metabolome of the colonic microflora. Metabolomic techniques could be developed to study the human or animal microflora *in vivo* using noninvasive methods, such as breath analysis. The use of radioactive precursors of bacterial end-products, like ammonia or hydrogen, would allow for assays of microbial metabolism.

Given the expected complexity and diversity of the microflora, the development of robust databases and software tools to analyze large amounts of data from multiple laboratories would accelerate research across the field. The Human Microbiome Project, which is being implemented through the NIH Roadmap for Medical Research, represents an important step toward meeting these challenges by providing a basic catalogue of the constituents of the stable microflora in all humans and a description of variations in the microflora that occur among individuals. The Human Microbiome Project will also facilitate the development of essential research tools and resources.

Clinical research: Diverticulosis is common in Western countries, but infrequent in underdeveloped countries. Conducting clinical research studies to compare different populations would help to define the risk factors. Clearly defining symptomatic diverticular disease and distinguishing symptomatic diverticular disease from IBS is a

difficult, but important, challenge. Prevention trials for diverticular disease will involve follow-up for several years to detect significant differences in outcomes. Similarly, intervention trials will also require long time periods, during which a method to control differences in diet among participants will be an important consideration. Central resources are especially important for diseases that are difficult to study in a single center with limited access to patients, such as radiation colitis, which generally affects an elderly population with multiple medical issues.

The frequency of anorectal disorders and interface of patients with multiple providers makes it difficult to develop an effective system of data collection for these conditions. Moreover, anal disorders often occur concomitantly, which complicates the evaluation of treatment outcomes. The field would benefit from broader understanding of the variety of anorectal disorders, the typical symptoms, and the criteria for diagnosis.

Particularly for fecal incontinence, methods to overcome the reluctance of patients to discuss their symptoms and the reluctance of providers to inquire about these symptoms would improve opportunities for research and treatment. Prevention trials would require long time periods and be complex to manage.

Research on appendicitis is limited by difficulties in developing a network to study this condition in a pediatric population with an acute, self-limited disorder. Innovative approaches to research collaboration would promote progress on appendicitis. In addition, new methods are needed to obtain accurate dietary histories in patients, including children.

Animal models: Research progress could be stimulated by encouraging the development of novel animal models that faithfully mimic colonic and rectal disorders in human patients, such as diverticular disease and radiation colitis.