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Clinical Nutrition

ENTERAL and TUBE FEEDING

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DEDICATION

This book is dedicated to my wife Mercedes and my children Patrick, Florencia, and Victoria for their continued love and support.

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Foreword

Extensive changes have occurred in the delivery of enteral nutritional care since publication of the last edition of this book in 1997. Perhaps the greatest of these changes is the need to continue to provide the highest quality care with fewer resources, and to render this care more efficiently and expeditiously. A continuing trend in enteral feeding is its increased provision at home rather than in the hospital. This shift in venue has created new challenges for both patient and health care practitioner. The relevance of these changes and their appropriate resolutions are well expressed within the contents of this edition.

The indications for enteral feeding continue to be refined. In some conditions there is good "evidence-based" rationale to justify the use of enteral feeding whereas in other instances there is woefully little data to support its clinical utility. Regardless of the availability or quality of evidence-based support, the clinician is still confronted with the dilemma of when and how to feed his or her patient. Moreover, the morally and ethically vexing alternative of permitting continued starvation frequently confounds these decisions.

This edition remains true to the "raison d'etre" of the three previous editions, namely to communicate the highest quality of enteral nutritional science to enable the practitioner to feed patients safely and efficaciously. This information is well described in the sections entitled Physiology of the Gut and Nutrient Metabolism.

Perhaps the fastest growing component of nutritional care delivery is its technology. The section Principles of Enteral Nutrition integrates the technologic advances within the context of feasibility, relevance, and cost effectiveness. This theme is underscored in the chapters on reimbursement and pharmacotherapeutics, which are integral to providing care within the context of today's fiscal realities.

Perhaps the newest content of this edition is contained in the Disease Specific Section. Seventeen chapters are devoted to the intricacies and specifics of enteral feeding for diseases ranging from central nervous system trauma to immunodeficiencies.

Cancer continues to be one of the most important indications for enteral feeding as exemplified in the five chapters devoted to this topic. The sacrosanct principle of improving quality of life and not prolonging suffering of cancer patients is underscored in this content.

Finally, a major strength of this book is reflected in the extensive experience of its Editor and co-contributors. Dr. Rolando Rolandelli is a world renowned expert in enteral feeding and has contributed extensively to past editions of this book. He remains dedicated to providing both high quality science and the best available clinical information. Dr. Rolandelli has included a group of outstanding international contributors from a multitude of disciplines who share his commitment to academic excellence.

In summary, enteral feeding continues to be an integral component of the care of many hospitalized and home patients. The science and application of this important therapy are well expressed in this book in a scholarly and clinically relevant manner.

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The Multidisciplinary Approach to Enteral Nutrition

Peggi Guenter, PhD, RN, CNSN

CHAPTER OUTLINE

INTRODUCTION

Since the introduction of enteral nutrition therapy by John Hunter in 1790, a variety of health care professionals have been involved in this process.[1] Health care has been multidisciplinary as far back as Greek civilization and possibly earlier. The first medical text was a pharmaceutical compendium containing nutritional therapies from Mesopotamia circa 2100 BC. Three Greek gods personified the multidisciplinary concept: Asklepios, god of medicine; Hygieia, goddess of health maintenance (nursing); and Panacea, goddess of medication (pharmacy). Hippocrates was born during this time and contributed greatly to the fields of medicine and nursing.[2] During the mid-1850s Florence Nightingale, founder of modern nursing, was very concerned about nutrition.[3] With the advent of nursing schools in the United States, student nurses were taught about "invalid cookery" and provided therapeutic diets to hospitalized patients. As providing nutrition became a more specialized role, the discipline of dietetics emerged in the early 1900s with the founding of the American Dietetic Association in 1917.[2]

Formal nutrition support teams were not established until the development of parenteral nutrition in the early 1970s, beginning with large medical centers. These teams had a multidisciplinary pattern and were generally made up of a physician, nurse, dietitian, and pharmacist. The number of these teams grew throughout the 1970s and 1980s. In 1985, Dr. John Wesley wrote, "It is apparent that any well-organized multidisciplinary approach to nutrition support can be clinically and economically advantageous, whether or not it embodies a formal nutrition support team."[4] As the prospective payment system and capitated health care plans took hold and began to drive financing of hospitals, these teams began to disband, decentralize, or disperse.

Despite a decrease in the use of formal nutrition support teams and insufficient administrative support in health care systems, the multidisciplinary group of health care professionals specializing in nutritional support and caring for the patient receiving enteral nutrition is vital. In the absence of the multidisciplinary group of specialists, despite well-intentioned policies and procedures, patient care can suffer. In this chapter the history, evolution, and impact of the multidisciplinary approach on the overall delivery of enteral nutrition will be presented.

TRADITIONAL MULTIDISCIPLINARY NUTRITION SUPPORT TEAMS

With the development of nutrition support services (NSS) in the early 1970s, which were formed initially to care for patients receiving parenteral nutrition, came the reawakening of interest in the patient's nutritional status and the use of enteral nutrition. Advances in the composition of liquid diets resulted from the aerospace program, because of the need to nourish astronauts on the much-anticipated trip to and from the moon. Research into the development of more comfortable feeding tubes and enteral feeding pumps led to the expansion of NSS into care for tube-fed patients as well.[2]

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) was founded in 1976 to serve as a forum for nutrition support clinicians and researchers from all disciplines to exchange information about the care of patients with nutritional needs. The first purpose of A.S.P.E.N. is to promote professional communication among disciplines in the broad field of clinical nutrition including parenteral and enteral nutrition. The second purpose is to promote the application of clinical and research experience in the practice of nutritionally sound medicine (see www.nutritioncare.org/bylaws.html).

The rapid growth in the numbers of nutrition support teams during the 1970s and early 1980s has been well documented.[5,6] In a 1991 survey conducted by A.S.P.E.N., 29% of hospitals with greater than 150 beds had a nutrition support team, suggesting that the growth of new teams had tapered off and many institutions did not perceive a need for a nutrition support team.[7] However, The A.S.P.E.N. Standards for Adult Hospitalized Patients have recently stated that if an institution does not have a defined nutrition support service or team, an interdisciplinary group of clinicians should provide specialized nutritional support.[8]

The purpose of the nutrition support team is to provide quality nutritional care. This is accomplished through identification of patients who are at risk nutritionally, performance of a comprehensive nutritional assessment that guides nutritional therapy, and provision of safe and effective nutritional support.[9] To accomplish these goals, nutrition support teams have developed services that include inpatient consultations, staff educational programs, quality assurance protocols, research programs, and home nutrition support services. The overall goals of the nutrition support team include recognition and treatment of malnutrition and reduction of complications, morbidity, and mortality in a cost-effective manner.[4] The quantitative impact of these teams on the delivery of enteral nutrition will be presented later in this chapter.

TRADITIONAL ROLES OF TEAM MEMBERS

An organized nutrition support service or team should include a physician, nurse, dietitian, and pharmacist.[8] Although the structure and function of NSS vary from one health care setting to the next based on needs and available personnel, some traditional roles are reviewed here.

Physician's Role

The nutrition support physician needs to be familiar with all aspects of enteral nutrition care including patient screening and assessment, development and implementation of an enteral care plan, and termination of therapy. A distinctive role of the nutrition support physician is to select the appropriate feeding access, and, depending on his or her medical specialty, the actual placement of the feeding access. The physician must be capable of managing the policy, procedure, personnel, education, finance, and quality improvement issues pertaining to nutritional support.[10]

Nurse's Role

The nurse's contribution comes from direct observation of enteral feeding delivery and patient response in all settings. The nurse on the nutrition service team communicates directly with the primary care nurses and other health care providers and serves as the liaison with other team members.[9] The nurse's scope of practice includes direct patient care; consultation with other nurses and health care professionals; education of patients, caregivers, students, colleagues, and the public; and participation in research activities and administrative functions.[11]

Dietitian's Role

The dietitian provides nutrition screening and assessment, develops and implements a specialized nutrition support care plan, monitors the nutritional effectiveness of therapy, and develops the transitional feeding care plan.[12] The dietitian's role also includes education and training of patients, caregivers, and health care professionals[13]; management of patients receiving home enteral and parenteral nutrition, and research.

Pharmacist's Role

The role of the pharmacist in the care of the patient receiving enteral nutrition is derived from knowledge of pharmacokinetics, drug metabolism, and drug-drug and drug-nutrient interactions.[9] The pharmacist's scope of practice in the nutrition support team includes direct patient care; administrative management of the specialized nutrition support program; quality improvement; education of health care professionals, patients, and caregivers; and research.[14] A recent study of this role confirmed that pharmacists continue to intervene with patients receiving enteral nutrition in the clinical setting to ensure positive effects on patient care.[15]

Contemporary Definition

A more contemporary definition of the nutrition support team includes some of the discipline-specific role delineation described in the preceding paragraphs and elsewhere but also includes the recognition that clinicians, who are board-certified in nutritional support are capable of addressing all of the nutrition support needs of patients in acute care, extended care, or home care settings. In addition, a board-certified nutrition support team member, regardless of discipline, is responsible for a patients' nutritional assessment, plan of care, monitoring, discharge planning, and follow-up. Much of the nutritional care is based on shared knowledge, with team members

accessing each other as consultants for questions or problems outside their knowledge base. This allows a team member to develop an in-depth relationship with the patient and thus the patient has to call only one nutrition support professional.

EVOLUTION OF THE NUTRITION SUPPORT SERVICE

With the changes in health care financing in the 1990s came the need for hospitals to downsize, merge, and shift care to alternate sites.[16] Consequently, nutrition support team members were forced to justify their salaries and redistribute responsibilities when one or more team positions were eliminated. This health care movement led to an evolution from traditional nutrition support services and team roles. Thus, more quality improvement programs, cost analysis research projects, and innovative use of personnel came into the forefront. In this section some of those shifts and programs designed to better deliver enteral nutrition within cost constraints will be described.

At the same time as many of these health care changes were occurring, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 1995 mandated compliance with specific nutrition care standards. Increased JCAHO requirements, at the same time that nutrition support teams were vanishing, necessitated greater vigilance in patient care, including quality improvement programs.[17] In one such program, practice changes were made to improve the percentage of enterally fed patients in the intensive care unit whose protein and energy goals were being met. A 70% reduction in the percentage of patients whose nutritional needs were not met was achieved.[18]

Another change in the health care arena was to shift much of the delivery of enteral nutrition from the hospital to the home. With this change, efforts were needed to establish a long-term enteral access site early in the patient's hospitalization, to develop more effective patient and caregiver education, to provide coordinated discharge planning, and to expand the roles of traditional inpatient personnel to home care companies. All nutrition support clinicians (dietitians, nurses, pharmacists, and physicians) may play a role in the management and monitoring of safe nutrition support therapy in patients receiving home enteral or parenteral nutrition. Coordination of care is essential between hospital-based and infusion provider nutrition support specialists. Another nutrition support–related position that has emerged is the reimbursement specialist. This team member may be available to educate others about third-party reimbursement, verify insurance coverage, and assist the team in providing cost-effective products and services. In a survey published in 1990, only a small number of dietitians were assuming responsibility for complete home enteral nutrition education.[19] However, by the mid-1990s, reports of dietitians being employed by home infusion organizations[20] and carrying out most of the initial education of patients for home enteral therapy[21] were being published. Pharmacists continue to be involved in outpatient care of patients requiring nutritional support.[15,22,23] Additionally, consultant pharmacists employed by home care or long-term care agencies are often involved with patients receiving enteral nutrition as well.[24]

Other health care professionals who are not traditional nutrition support team members are now more involved in discharge planning and home enteral therapy. In the hospital, speech and language pathologists work with dysphagic patients who need enteral therapy to help smooth the transition to home or rehabilitative care.[25] The hospital case manager and home visiting nurse agency are often involved early in the discharge planning and education process.[26] The primary care physician, who may not have been directly involved in the patient's hospital care, must also be kept informed and involved in discharge decision making. Two surveys of nursing practice demonstrated that primary care nurses needed additional information on how to properly prepare and administer medication through feeding tubes.[27,28] In the first study, when pharmacists gave assistance to the nurses, significantly fewer episodes of tube clogging due to medications were seen.

As a result of the changes in the health care system, traditional nutrition support team members have had to expand their roles by increased sharing of their knowledge, skills, and contributions with other team members. This process has become a greater challenge as the care of patients requiring nutritional support has become more complex, and external expectations have expanded into new areas (e.g., dietary supplements and other alternative therapies). Increasingly, nutrition support team members are educating other health care professionals about enteral nutrition.

IMPACT OF NUTRITION SUPPORT TEAMS ON PATIENT OUTCOME

To justify the resources needed to fund NSS, evidence must be available to demonstrate the team's impact on positive patient outcomes, including cost reduction, decreased incidence of complications, and decreased length of hospital stay and mortality. Although studies in the literature on this topic are fewer than those examining the effects of NSS on total parenteral nutrition (TPN) use, some research with enteral nutrition patients is available.

An important function of most NSS is to recommend a route of feeding for the patient after a nutritional assessment. Using guidelines developed by A.S.P.E.N. and/or their institutions, three support services groups demonstrated cost savings by recommending enteral nutrition rather than parenteral nutrition when appropriate. In 1986, O'Brien and colleagues[29] reviewed 14 cases of patients who did not receive the recommended enteral nutrition but instead received parenteral nutrition. For the 280 days of nutritional support that were considered outside the recommendations, the potential savings were estimated to be more than $70,000. In another study of children

with cancer who needed nutritional support, Bowman and colleagues[30] developed an algorithm for therapy. The use of this algorithm led to increased use of enteral nutrition from 9% of total patient-days in 1989 to 56% in 1996. In 2000, Ochoa and his team[31] reviewed their recommendations over a 9-year period and found a significant decrease in TPN use (616 patients receiving TPN in 1991 vs. 124 patients receiving TPN in 1999) despite the fact that their assessment service grew to more than 1400 patients in 1999. The use of enteral nutrition use grew 387% in the intensive care unit, and these recommendations translated into a more than $2.5 million reduction in cost over this time period.[32]

Another important function of the nutrition support team is to develop protocols and standards of care to promote positive patient outcome and reduce the incidence of associated complications. In 1997, Pattison and Young[32] studied two groups of patients in whom percutaneous endoscopic gastrostomy (PEG) tubes were placed for enteral nutrition. They used 24 patients as a historical control group, and implemented a five-step standardized protocol for another group. The steps were multidisciplinary, preoperative evaluation; standardized PEG tube placement; administration of preoperative prophylactic antibiotics; surgical outpatient follow-up; and development of patient information booklets. The outcome was measured by the incidence of tube failure, stoma site infection, and gastrointestinal complications. Complications occurred in 92% of patients in the historical control group and in only 50% of the group who were treated using the standardized protocol ($P < .05$). The standards developed by their multidisciplinary team have since been incorporated into general practice. Another team developed an infusion protocol for intensive care unit patients receiving enteral nutrition. Spain and colleagues[33] found in a previous study that critically ill patients were receiving only 52% of their goal calories primarily owing to physician underordering, frequent cessation, and slow advancement of feedings. They developed an enteral tube feeding protocol that incorporated standardized physician ordering, nursing procedures, rapid advancement, and limited feeding interruption. With the use of this protocol, physician ordering improved to 82% versus a control value of 66% ($P < .05$) and delivery of calories improved to 56% of goal by 72 hours versus a control value of 14% ($P < .05$).[33] Although some policies and procedures are intended to give health care providers who are not certified in nutritional support guidelines to manage patients requiring nutritional support, these may not succeed in the absence of specialists.

To optimally test the value of having NSS, studies of use of teams versus no teams need to demonstrate the impact on patient outcome. Four such studies that specifically look at enteral nutrition delivery are available in the literature. In 1985, Weinsier and co-workers[34] retrospectively examined standard hospital nutritional care compared with nutritional support provided by an organized nutrition support service for 70 patients with burns. The group receiving enteral and parenteral nutrition support under the care of the nutrition support service experienced significantly less weight loss and shorter hospital stays. This translated into significant cost savings. Powers and associates[35] conducted a study examining team versus no team management of patients receiving enteral nutrition at a Veterans Administration medical center. This prospective trial studied patient demographics; nutrition assessment; type, modifications, and amount of enteral formula delivered; and complications. The researchers found that significantly more team-managed patients attained 1.2 × basal energy expenditure in calories for a longer period of time; had a positive nitrogen balance; and had fewer metabolic, pulmonary, mechanical, or gastrointestinal abnormalities than did the non-team–managed patients. The results of this study indicated that team-managed enteral nutritional support reduced abnormalities and was nutritionally more efficient compared with the non-team approach. This study was duplicated in a university teaching hospital and the findings were similar.[36] In a more recent report published in 1994, Hassell and colleagues[37] studied team management of enteral nutrition in a community hospital. They found that the nutrition support team management of enterally fed patients was associated with reductions in mortality rate, length of stay in the hospital, and readmission rate. A cost-benefit analysis revealed that for every $1 invested in the nutrition support team management, a benefit of $4.20 was realized.

CONCLUSION

The direct team versus non-team enteral feeding management studies, although limited in numbers, provide evidence for the effects of an organized multidisciplinary approach with protocols and recommendations based on published guidelines. Patients receiving enteral nutrition benefit from this approach, and despite changes in the health care arena, this approach should be used whether a formal team is in place or not. More studies are needed to justify the cost of teams now in the 21st century; however until these studies prove otherwise, this multidisciplinary management of enteral nutrition therapy is vital.

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EDITORS' NOTE

The practice of nutrition support has expanded both in knowledge base required and in the level of clinical expertise over the last several decades. During this time, clinicians on the front line discovered new dimensions in nutrition science through their direct care for patients.[1,2] As noted by Rhoads,[1] an unforeseen result of these advances has been the further development and subspecialization of the various disciplines involved in nutrition support—namely, medicine, nursing, dietetics, and pharmacy—which further improved patient care. The administration of nutritional support has become safe and effective through the multidisciplinary team of these health care providers.[3] Nutritional support has allowed the recovery of patients from catastrophic illnesses that previously were lethal. Two good examples are enterocutaneous fistula and short bowel syndrome. In addition, new forms of therapy that could not be undertaken without effective nutritional support have been developed. These include transplantation and multimodality oncotherapy. The success of the implementation of all of these forms of therapy for critically ill patients has depended on the multidisciplinary approach of medical providers. In an expeditious manner, medical providers from different disciplines contribute expertise and vantage points to help resolve clinical problems that had previously vexed individual medical practitioners.

This team concept has long been recognized as desirable at the level of each discipline represented.[4–8] The added bonus of discipline-specific knowledge has created an appreciation for the complexity of patient care that further fostered interdisciplinary nutrition support practice, as well as many other practices. The model of providing multidisciplinary care to patients requiring nutritional support continues, owing a lot to the pioneers in each discipline for bringing us to the point we are at today. Although each individual discipline was once the focus of an aspect of nutrition support practice, today's nutrition support specialist may come from any discipline. Clinicians have sustained collective efforts, incorporating unique attributes of their own disciplines to the shared common goals of patient care, education, and research in nutritional support. Nutrition support is a specialty now practiced in a variety of settings, regardless of discipline, by those with adequate training (education, experience, and interest) and as recognized by board certification. The day of defining discipline-specific roles based on the route of administration or on a set of monitoring parameters or on a function in obtaining a

product has thankfully passed. The role of the board-certified nutrition support specialist is to manage the patient's care.

The purpose of a team, whether as a formalized service or as a group of committed individuals, is to identify patients requiring nutritional support and assure that they receive safe and effective care. In so doing they educate themselves and other health care providers. Although cost containment has limited the existence of formal organized teams or services in all but a few institutions, the concept of multidisciplinary care continues to be important. A committed team of specialists is ideal; however, the model has changed to one in which perhaps only one specialist serves as a consultant to nonspecialist, patient care providers of all disciplines. For example, the nurse or pharmacist with little training in nutrition support who is called upon to care for such patients will benefit greatly from the help of a specialist, even one from another discipline. The integration into the nutrition support specialty of speech therapists, occupational and physical therapists, respiratory therapists, and others, who may not be otherwise considered by the primary team, may further improve the care of patients.

Each one of our four disciplines has contributed to the birth and growth of nutrition support. At this point, nutrition support can survive independent of each of us as a discipline, but still needs knowledgeable specialists to optimize patient care.

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2

Role of Controlled Gastrointestinal Transit in Nutrition and Tube Feeding

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CHAPTER OUTLINE

INTRODUCTION

There are many excellent reviews[1–4] and textbook chapters that describe the digestion and absorption of specific nutrients.[5,6] Because these topics have been well covered, we will not discuss in detail the enzymatic or transport processes ultimately responsible for nutrient uptake from the gastrointestinal (GI) tract. However, the role of GI motility in digestion and absorption is a neglected topic. In this chapter, we will focus on this area to provide information that is important to the clinician managing enteral feeding.

To understand and manage the problems encountered during enteral feeding, we must begin by reviewing the normal controls that operate to govern the transit of a meal through the GI tract. To begin, we will follow the course of a bolus of food from mouth to colon and present the physiology of the motility response of the GI tract to nutrients as it occurs in the context of tightly controlled transit of a meal. On occasion, we will make references to illustrative pathophysiologic states, highlighting the nutritional consequences when the control of transit is impaired or lost. In this chapter, we will not cover in detail the neural and hormonal pathways controlling motility, because information on these is readily available to the reader.[7–9]

Digestion and absorption are time-demanding events. If food traverses too rapidly through the GI tract, nutrients are lost in the toilet. The transit of a meal is therefore meticulously controlled by a nutrient-triggered feedback system that works to optimize nutrition by ensuring that there is adequate time for digestion and absorption. To achieve this goal, the GI tract consists of nutrient sensors distributed along the entire length of the small intestine that are recruited by their contact with nutrients to generate neuropeptidergic feedback signals that slow or speed transit. Because digestion requires both contact with the digestive enzyme and time for hydrolysis, rapid movement of a meal through the GI tract results in maldigestion. Absorption of nutrients similarly requires contact with the mucosal cell surface transport mechanisms; rapid transit of even a well-digested meal results in malabsorption.[10] With the importance of adequate time for assimilation in mind, we begin with ingestion, mastication, and swallowing of a bolus.

MOUTH AND ESOPHAGUS

Chewing stimulates salivation, including release of salivary enzymes. However, the degree of digestion in

the mouth attributable to these salivary enzymes is quite low because a bolus is rarely held in the mouth long enough for significant hydrolysis to occur before swallowing. Deglutition initiates GI transit of the bolus by triggering primary esophageal peristalsis that works to propel the movement of the meal from the pharynx to the stomach. No digestion or absorption occurs in the esophagus as the bolus moves aborally into the stomach over a span of time as short as 2 seconds.

STOMACH

Digestion

Gastric digestion is critically important for two reasons. The first is to prepare chyme for efficient digestion and absorption in the small intestine and the second is to make available the end products of digestion required for the activation of the control of transit. Thus, in addition to providing improved substrates for enzymatic digestion in the small intestine, gastric digestion liberates sugars and oligosaccharides, oligopeptides and peptones, and fatty acids. Each of these components is important in nutrient-triggered inhibitory feedback that works to slow GI transit, allowing more time for digestion and absorption.

Physical Fragmentation, Gastric Sieving, and Peristalsis

Digestion begins in the stomach. Gastric motility converts from the fasted to fed state in response to the same stimuli responsible for the cephalic and gastric phases of gastric secretion. When stimulated by cholinergic pathways and by peptides such as gastrin,[7] the stomach contracts at its maximal frequency of three times per minute to generate a ring-like peristaltic wave that moves the content of the stomach in the antegrade direction toward the pyloric opening. Digestible solids break up into smaller fragments as food is caught between the strong, lumen-obliterating actions of the terminal antral contractions.[11] This process pulverizes food into tiny particles that have the ideal large surface area-to-mass ratio suitable for efficient hydrolysis by digestive enzymes in the small intestine.

As the content of the stomach is squeezed by the moving ring-like peristaltic wave, gastric fluid and all the solids suspended in the fluid pick up aboral velocity to behave as a laminar flow. In that setting, only the smallest particles travel in the center of the flow and move at the highest velocity. Because the pylorus is positioned to receive the center of the flow, size selectivity takes place as the smallest particles are ejected through the pylorus whereas the larger chunks fall to the side for further fragmentation (trituration). This function, called gastric sieving, is a highly efficient property of the fed motility state that works to prevent solid particles larger than 0.1 mm from exiting the stomach[12,13] and is responsible for the lag phase of the gastric emptying time course for digestible solids. Solids that are larger in size (e.g., a nasojejunal feeding tube) are only expelled from the stomach when motility reverts back to the fasted state and cycles to the phase III of interdigestive motility (intestinal housekeeper wave). A feeding tube is then moved into the postpyloric small intestine during an intestinal housekeeper wave.

Chemical Hydrolysis

Aside from physical fragmentation as a form of digestion, chemical hydrolysis also begins in the stomach. The gastric zymogens—pepsinogen I and II, progastricsin (pepsin C precursor), and prochymosin (in neonates)—are secreted in response to initiation of feeding and activated by autocatalysis and structural rearrangement below pH 5.0,[14] the typical range for gastric contents. The predominant peptic enzymes, pepsin 1, 3, and 5, operate mostly below pH less than 3.0.[15] Gastric proteases are responsible for 10% to 20% of total protein digestion and are inactivated in the relatively high pH of the duodenum. This gastric protein digestion may be critically important for protein assimilation because intestinal absorption of protein in the setting of pancreatic insufficiency is significantly improved by incubation of the protein with stomach acid or pepsin.[16]

The contribution of gastric proteolysis is reduced by the use of antisecretory agents. Correspondingly, many patients treated with these agents are found to have a prolonged lag phase of solid emptying. An important outcome of this impairment of trituration is that patients may be mistakenly thought to have gastroparesis. Gastric proteolysis may also be important to fat digestion. In the setting of impaired biliary function, gastric proteolysis that liberates amphipathic peptides capable of stabilizing lipid emulsions functions to enhance gastric lipolysis.[17] The digestion of carbohydrates that began in the mouth with saliva continues in the stomach. Salivary amylase survives pepsin hydrolysis and continues to work in the stomach as long as the gastric content is retained for at least 1 hour and the pH is greater than about 3.[18,19] Salivary amylase activity can account for 55% to 60% of starch hydrolysis by the time the bolus enters the duodenum.[19,20]

Although only trace amounts of lingual lipase are secreted and contribute little if anything to lipid hydrolysis during a meal in the adult,[21] the stomach is very important to fat digestion. Gastric lipase and acid are cosecreted in the fundus by vagal cholinergic stimulation in response to feeding. Gastric lipase is responsible for 10% to 30% of total triglyceride hydrolysis[22,23] and is aided in this process by emulsification of lipids secondary to duodenogastric reflux of bile.[24] The retrograde entry of bile salts into the stomach is then not only normal but also quite important to optimal fat digestion. Gastric lipase is most active at pH values between 2 and 7[25] and contributes to further hydrolysis in the duodenum[22,26] and jejunum.[26] Gastric lipase is equally efficient at hydrolysis of liquid and solid fat, whereas pancreatic lipase is more efficient at hydrolysis of fat in the liquid than solid state.[27] Gastric lipolysis enhances emulsification of the meal,[28] which is important for providing readily hydrolyzable substrate for pancreatic lipase.[29–31]

Most importantly, the process of fat digestion begins in the stomach so that gastric emptying can be tightly

controlled. Because the inhibitory feedback that slows gastric emptying is triggered by the end products of fat digestion such as fatty acids, the availability of some end products of lipid digestion early in the course of gastric emptying allows for the control of gastric emptying to be activated in time to govern the movement of most of the meal.

Gastric Emptying

Gastric emptying of solids can be separated into two phases: lag, during which large food particles are triturated into smaller particles suitable for digestion, and linear, during which the gastric content exits via the pylorus into the lumen of the proximal small intestine. Gastric emptying of liquids begins rapidly and slows to approximate an exponential decay.[32] For liquids, the rate of gastric emptying depends on the volume of the gastric content (first-order kinetics). For solids, the rate of gastric emptying is rate-limited by the process of trituration so that the amount emptied per unit time remains fixed and independent of the volume of the gastric content (zero-order kinetics). Because the assimilation of solids takes more time, by limiting the amount that is delivered into the small intestine, the GI tract is able to optimize digestion and absorption by ensuring that the capacity of the proximal small intestine to assimilate food is not overwhelmed.

Nutrient-Regulated Gastric Emptying

Gastric emptying is controlled by nutrients hydrolyzed from the meal[33–35] by titratable acidity and pH[35,36] and by osmolarity.[37] Incomplete digestion and absorption of a meal increases the osmolarity within the lumen.[38] Gastric emptying is slowed by increased osmolarity because of increased outflow resistance owing to stimulated duodenal nonpropagated motility.[37] This is an example of an inhibitory feedback on gastric emptying that does not involve a change in the motility of the stomach itself. In the setting of maldigestion, undigested and unabsorbed nutrient substrates escape complete assimilation within the length of the small intestine to present to the bacterial flora of the large intestine. An important consequence of such abnormal presentation is the conversion of the maldigested food to osmotically active substances via bacterial fermentation, further increasing the osmotic load and promoting secretory diarrhea. Osmotic inhibition of gastric emptying thus reduces the osmotic load presented to the small intestine and extend the available time for digestion and absorption of a meal.

Inhibition of gastric emptying is also nutrient-specific. Whereas it takes 1000 mM glucose to generate maximal inhibition of gastric emptying,[34] it takes only 27 mM oleate to do the same.[36] The greater potency of fat can be explained on the basis of the slower rate of assimilation of fat compared with that of glucose and the length-dependent mechanism for determining the slowing of gastric emptying. For the same amount of nutrient, fat would linger in the intestinal lumen longer than glucose to access a longer length of the small intestine. As a result, more nutrient sensors would be stimulated and recruited to generate greater inhibitory feedback after fat than glucose. Despite the importance of nutrient-specific potency and the great variability of fat content in the formulas that are used in clinical practice, the nutrient-specific inhibition of gastric emptying of one formula versus another is rarely taken into account in enteral feeding.

Load-Dependent Inhibition

Gastric emptying decreases proportionally to increasing load of nutrients.[39,40] The nutrient load of a meal is linked to other digestive responses of the GI tract. For example, pancreatic secretion is proportional to the nutrient load because it depends on the saturation of the proximal mucosal absorptive surface, the spillover of nutrients to more distal parts of the intestinal mucosa, and the exposure of the mucosa of the distal small intestine to the still unabsorbed nutrient load.[41,42] Load-dependent inhibition of gastric emptying extends the available time for digestion and absorption.

Load-dependent inhibition of gastric emptying is possible through a length-dependent inhibitory feedback mechanism. After 500 mL of glucose solution was delivered into the stomach (0 M saline control; glucose concentrations of 0.25 M, 0.5 M, or 1.0 M), the meal with the largest glucose load emptied from the stomach at the slowest rate and the meal with the smallest load emptied at the fastest rate.[34] This load-dependent slowing of gastric emptying is generated as follows: early in the meal, there is no intestinogastric inhibitory feedback from the small intestine because the small bowel is devoid of nutrients. During that brief period without feedback, the rate of gastric emptying of a liquid meal follows first-order kinetics whereby the rate is greater with a larger volume of liquid in the stomach. After a large meal, more nutrients squirt out of the stomach with the initial gastric output, whereas after a smaller meal, fewer nutrients are released per unit time. This load-dependent initial surge is critical in setting the feedback response because the intensity of the inhibitory feedback depends on the length of the small intestine exposed to nutrients.[34,36] Length-dependent inhibitory feedback is generated by the recruitment of stimulated nutrient sensors along the length of the small intestine so that after a large meal, nutrients spread along a longer length of the small intestine to trigger a great number of nutrient sensors. The extent of the spread of a nutrient-containing meal down the length of the small intestine depends on how quickly the exposed intestine can absorb the nutrients as well as how quickly the meal moves down the intestine. As absorptive capacity is exceeded the meal will travel further down the intestine to recruit more absorptive surface and hence trigger additional inhibitory feedback. When the ileum is exposed to glucose, inhibition of gastric emptying of a solid meal is threefold greater than when the jejunum is exposed to glucose.[43]

Thus, larger and more nutrient-dense liquid meals are likely to initially travel further down the intestine and recruit more nutrient sensors. This will result in more potent inhibitory feedback as the nutrient density of the

meal increases. Gastric emptying is therefore slower after a can of enteral formula containing a 1.5 kcal/mL nutrient load than a formula containing a 1.0 kcal/mL nutrient load. Feeding large volumes of a high-calorie formula could lead to physiologic accumulation of the formula in the stomach so that the delivery of nutrients to the small intestine does not overwhelm the assimilation capacity of the gut.

Delayed Gastric Emptying

This gastric residual volume (GRV) is the amount of an enteral feeding product that remains in the stomach after some length of time. When this volume reaches an arbitrarily determined threshold,[44] the patient is often but erroneously considered to have impaired gastric emptying. Feeding is typically halted in this situation because excessive GRV has been reportedly associated with increased risk of pulmonary aspiration of formula in some situations.[45]

GRV is a balance between input to the stomach from endogenous secretions and ingestion and output from the stomach as controlled by nutrient-triggered inhibitory feedback based on the nutrient load of the stomach output. On the input side of the equation, saliva plus gastric secretions accounts for approximately 188 mL/hr in a normally fed adult human,[6] and enteral formula is delivered at rates ranging from 25 to 125 mL/hr.[46] On the output side of the equation, gastric emptying rates commonly range from less than 20% to more than 50% of the stomach contents per hour when a patient is fed with a typical iso-osmolar formula[34,36] and depend on the total load and nutrient composition (fat, carbohydrate, and protein) of the stomach contents.

When input into the stomach equals output from the stomach, equilibrium is reached and GRV plateaus. However, if input exceeds output, then GRV will theoretically increase unbounded. Although an unlimited increase in GRV should be considered pathologic impairment of gastric emptying (assuming the enteral delivery rate is reasonable), reaching an equilibrium state should be considered normal and should not require intervention unless the total GRV is poorly tolerated and generates symptoms (pain from distension, nausea, and vomiting).

When we subjected this equilibrium model to mathematical analysis,[47] we found that even with a fairly high rate of formula delivery of 100 mL/min, the GRV exceed 2000 mL only when the rate of gastric emptying dropped below 10%/hr. The capacity of a normal adult stomach is 4000 to 6000 mL,[48] so most rates of formula delivery and gastric emptying should not result in GRV greater than that of the normal postprandial stomach, which may exceed 3000 mL.[6] The most important reason for a reduced rate of gastric emptying is nutrient-triggered inhibitory feedback. The magnitude of this physiologic slowing of gastric emptying depends on the nutrient load of the delivered formula. Although increased delivery of formula may accelerate intestinal transit via a volume-dependent mechanism,[49–52] the greater formula delivery concurrently increases load-dependent nutrient-triggered inhibitory feedback. The net effect on transit then depends on the balance between these two forces. Because the nutrient load in even the most calorically dense formulas does not slow gastric emptying below 20%/hr, GRV should remain within the normal postprandial range. Therefore, an absolute value of GRV is not a sign of a pathologic impairment or an indication for stopping enteral feeding. Rather, it is more important to determine the temporal trend in GRV (increasing vs. plateau) after at least 6 hours to decide whether to discontinue feeding. Withholding enteral feedings for an arbitrarily determined low threshold of GRV is not a physiologically sound practice and may unnecessarily place the patient at increased risk of malnutrition.

Accelerated Gastric Emptying

Patients complaining of early satiety and postprandial pain, distention, nausea, and vomiting are often given the clinical label "gastroparesis" with an expectation that these symptoms are always the result of abnormally slow gastric emptying. In the enterally fed patient the assumption is that these symptoms are related to high GRV. However, these symptoms may also be triggered from the small intestine as demonstrated by the onset of nausea when triglycerides are infused into the duodenum of test subjects.[53] A common setting in which similar symptoms are generated from the small intestine is after ulcer surgery. After gastrectomy patients, postmeal bloating, pain, and nausea are often grouped under the term *dumping syndrome*. In this case, the problem is related to accelerated rather than delayed gastric emptying.[54] This accelerated emptying increases delivery of nutrients to the small intestine, triggering exaggerated nutrient-triggered inhibitory feedback that generates the GI symptoms of dumping syndrome.

The same scenario occurs in the context of a rapidly emptying liquid meal. Although gastric emptying of a solid meal is normally held back by the requirement of trituration,[12,13] liquid fats (oils) need not be triturated and therefore empty more rapidly from the stomach.[55] Fat intolerance is a common complaint of many patients. These patients may complain of bloating, pain, and nausea after a meal containing liquid fat (e.g., creamy soup) but have no symptoms after a meal containing solid fat (e.g., well-marbled steak). Even though the symptoms suggest gastroparesis, fat intolerance is associated with abnormally accelerated gastric emptying.[56] Thus, when an enteral formula is administered into the stomach, symptoms may be generated from either the stomach or the small intestine as a result of either abnormally delayed or abnormally accelerated gastric emptying, respectively. The importance of the small bowel as the source of symptoms of gastroparesis symptoms is reinforced by the bloating, pain, and nausea that may be encountered during nasojejunal feeding.

Regardless of the underlying physiologic dysfunction, patients receiving enteral feeding who complain of symptoms normally associated with gastroparesis should be suspected of having exaggerated feedback. Lowering the fat content and reducing the formula delivery rate may improve tolerance in these patients.

SMALL INTESTINE

Digestion

The end products of digestion that are liberated from a meal control the remainder of the processes of digestion and absorption in part by regulating transit of the meal through the small bowel. As the partially digested gastric content empties into the duodenum, bile and pancreatic exocrine secretions are released to mix with the chyme. Gut peptides including cholecystokinin (CCK) and secretin are secreted in response to the end products of gastric fat digestion, stimulating both biliary and pancreatic secretion as well as gall bladder contractions.[57] CCK release is attenuated in the absence of gastric digestion[58] because the end products of digestion are not available but are needed to stimulate release of the peptide. Acid in the duodenal lumen also triggers bicarbonate release because the threshold for stimulation of pancreatic exocrine secretion is less than pH 4.5.[59]

Protein

Protein is digested in the intestine by a set of pancreatic endopeptidases (trypsin, chymotrypsin, and elastase) and exopeptidases (carboxypeptidase I and II). Enterokinase activates the digestion of trypsinogen to trypsin; trypsin in turn activates the other protease zymogens to produce the active proteases.[60] Even in the absence of pancreatic protease secretion, up to 37% of ingested protein still can be digested by intestinal acid proteases.[16,61] The end products of luminal protein digestion are primarily oligopeptides of two to eight amino acids, which are further hydrolyzed and assimilated in the brush border.[60] Similar to load-dependent slowing of gastric emptying, intestinal transit time depends on the total protein load contained in the meal. As meal protein content increased, intestinal transit time decreased and protein uptake increased without significantly altered efficiency of uptake.[62] The magnitude of the inhibitory feedback depends on the contact of the protein with the small intestine. Because a predigested formula is rapidly assimilated, less content would be available in the intestinal lumen to activate inhibitory feedback. Compared with a prehydrolyzed formula, a formula containing intact protein more potently triggered greater inhibitory feedback response.[63] Partially digested protein in the form of oligopeptides may be more completely assimilated by stimulating pancreatic enzyme and bicarbonate secretion to further enhance protein digestion.[41]

Starch

Salivary amylase activity resumes in the relatively neutral environment of the proximal small intestine.[19] In addition, α-amylase secreted by the pancreas begins digestion of $\alpha^{1,4}$ starch bonds[60] to produce oligosaccharides and α-limit dextrins. The degree of starch hydrolysis depends on the source of starch[64–66] and leaves an average of 10% of ingested starch undigested through the small intestine.[66] Undigested carbohydrate in the ileum not only slows gastric emptying but can also stimulate further release of pancreatic enzymes, particularly amylase.[67]

Fatty Acids

Fatty acids, the end product of triglyceride digestion, are critically important in the control of postprandial motility. Maximal lipolysis requires emulsification of the lipid components of the meal. Although meal lipids are substantially emulsified by the mechanical and enzymatic actions in the stomach,[28,68] the formation of mixed micelles requires the phospholipids and bile salts in bile. Mixed micelles are required for optimal lipid absorption.[69] These mixed micelles containing acylglycerols, cholesterols, phospholipids, and their hydrolytic products as well as bile salts facilitate further digestion of dietary fat by promoting hydrolytic interaction with pancreatic lipase/colipase, bile salt–activated lipase, and phospholipase A_2.[31] In the absence of colipase, the high concentrations of bile salts normally found in the duodenum are sufficient to disrupt lipolysis.[70] Although colipase anchors lipase to the lipid interface, minute quantities are sufficient for this function.[71]

Bile Acids and Bile Salts

Completion of fat absorption within the small bowel is important because fatty acids stimulate secretory diarrhea.[72] Depending on the load, fat absorption normally occurs throughout the small intestine.[73] The amount of bile secreted in response to intestinal fat is mediated by bile salt–induced inhibitory feedback on gallbladder emptying.[74] Thus, the presence of unemulsified bile salts in the intestinal lumen slows the release of bile. Because bile salts (similar to fatty acids) also stimulate a secretory diarrhea,[75,76] the existence of bile salt–induced inhibitory feedback on gallbladder emptying ameliorates bile salt–induced diarrhea. Bile salts are actively reabsorbed by the terminal ileum. Recovery of bile salts is necessary because the amount of bile salts moving through the small intestine each day is four times the maximal synthetic capability of the liver.[77] Although resection of less than 100 cm of ileum may lead to loss of bile salts into the colon, causing watery diarrhea that can be corrected by bile acid sequestration,[78] resection of more than 100 cm of the distal small intestine leads to loss of bile acids in excess of the hepatic synthetic rate,[72] causing steatorrhea. With severe depletion of the bile acid pool, the micellar phase of fat digestion and absorption is impaired, reducing fat digestion in the proximal gut and resulting in steatorrhea.[72,78,79] In substitution, peptic protein digests are able to somewhat replace the role of bile salts in lipid emulsification.[41]

Bile acids precipitate in an acidic environment[80] and become unavailable for emulsification and stimulation of lipolysis. Enteral feeding is difficult under these circumstances because the feeding tube may occlude from protein and bile salt precipitates. One strategy that may prevent feeding tube occlusion in an acidic environment is to include 20 mM taurocholate in the formula.[81]

The Ileal Brake

As lipolysis progresses, the end products of fat digestion become available to serve as triggers to slow intestinal transit by activating proximal and distal motility/transit control mechanisms. The distal control mechanism responsible for regulating intestinal transit was first described as the "ileal brake." The concept of the ileal brake arose from human studies by Spiller and associates[82] and Read and colleagues[83] in 1984. These investigators separately but concurrently described the slowing of intestinal transit by fat emulsions perfused into the distal small intestine. Read and colleagues[83] showed that the orocecal transit time of an indigestible carbohydrate was slowed when Intralipid triglyceride emulsion was administered into the distal small intestine 205 cm from the teeth compared with a saline perfusion. Both gastric emptying and intestinal transit of a solid meal were still more delayed compared with the jejunal carbohydrate bolus. Spiller and associates[82] demonstrated similar slowing of intestinal transit when partially hydrolyzed Intralipid containing ≈60 mM free fatty acids was perfused into the ileum 170 cm from the teeth. Jejunal motility was slowed regardless of the nature of the jejunal content (saline vs. nutrient).

A putative duodenal brake was described in the early 1970s.[84,85] This neurohormonally mediated, nutrient-triggered inhibitory feedback in response to duodenal perfusion with acid, glucose, or fat slowed gastric emptying. However, the duodenum was taken out of continuity with the stomach but remained in continuity with the jejunum, suggesting that the observed effects may have been caused by activation of more distal braking mechanisms.

The Jejunal Brake

Clinical observations in the 1970s also suggested that the ileal brake was not the only control mechanism for intestinal transit. Woolf and co-workers[86] reported in patients with short bowel syndrome who had resection of the ileum that the total calories excreted in the stool remained constant even after the fat intake was increased threefold. In these patients lacking an ileal brake, such adjustment for the higher fat load would only be possible if a control mechanism located outside of the distal small intestine were available to slow transit so that there was more time to process the greater workload. Indeed, there is indeed another transit control mechanism located in the proximal small intestine that is known as the *jejunal brake*.[87] This proximally located control mechanism responds to the presence of end products of fat digestion (i.e., fatty acids) in the jejunum.

The existence of transit control mechanisms in both the proximal and distal small intestine allows for graded inhibitory feedback on intestinal transit. As with the control of gastric emptying, after a larger meal, nutrients spill farther down the small intestine to activate both proximal and distal braking mechanisms. This extensive spread of nutrients allows for the activation of the jejunal brake and ileal brake in the setting of a large nutrient load to provide more time for digestion and absorption of the meal and therefore to minimize potential nutrient loss. When the dose responses of the jejunal brake and the ileal brake to fatty acid were compared, the ileal brake was observed to be more potent than the jejunal brake.[88] This difference in potency is useful for a proper response to the work required for assimilation. If nutrients were to escape processing by the proximal small intestine to enter the distal small bowel, intestinal transit should be more potently slowed to avoid the loss of nutrients into the large intestine. Although the jejunal brake is less potent, it may be more important than the ileal brake because this proximal gut control is able to respond rapidly to the meal as it empties from the stomach. The jejunal brake may be the only available control mechanism for regulated intestinal transit in the setting of extensive ileal resection.

Importance of Nutrient-Regulated Intestinal Motility

Many standard antidiarrheal agents act by slowing intestinal transit, which may be accomplished by changing the pattern of intestinal motility from propagative to nonpropagative. As a result of an increase in the contact time between the luminal contents and the absorptive mucosa,[89] the incidence of diarrhea is reduced.[90] However, nutrients may be more effective than these traditional antidiarrheal agents. By exploiting region-specific differences in the slowing of intestinal transit, our knowledge of nutrient-regulated intestinal motility presents a unique opportunity to manipulate the interaction of food and the gut to optimize digestion and absorption. The roles of these controls can be discussed in terms of the following four examples.

Example 1: Distal versus Proximal Gut Resection

The first example is taken from surgical literature. In dogs with the distal 50% of the small intestine taken out of continuity as a Thiry-Vella fistula, intestinal transit was accelerated and fecal fat recovery increased 80% to 90% of the fat intake compared with values of 8% to 10% in dogs without a fistula.[91] In contrast, removing 50% or even 70% of the proximal small intestine was far less harmful, with only 15% to 24% of the fat intake being recovered in the stool.[91] Similarly, Reynell and Spray[92] observed more rapid intestinal transit in rats with distal compared with proximal gut resection. Because fat absorption is known to be less efficient in the distal small intestine and transit was faster and steatorrhea was far worse after the removal of the distal segment, these findings could not be explained by a difference in the kinetics of fat absorption. Instead, these observations can all be explained by the greater potency of the ileal brake. With a loss of the ileal brake, transit becomes so uncontrolled that 90% of the ingested fat ends up in the stool.

Example 2: Soy Protein

The second example of region-specific control of transit and absorption is taken from a comparison of the effects of delivery of an intact soy protein formula into the small intestine versus delivery of a hydrolyzed form of the same protein.[63] We found that when the load of protein was increased from 24 to 48 g, intestinal transit was slowed in a load-dependent fashion by both intact and hydrolyzed soy protein, soy protein inhibited intestinal transit more potently in the intact than the hydrolyzed form, the efficiency of protein absorption was maintained at a high and nearly constant level of 82.6% to 87.4% for intact soy protein compared with 89.0% to 92.3% for hydrolyzed soy protein, and absorption of nutrients increased when intestinal transit was slowed.

Specifically, when the protein load was doubled, intestinal transit slowed significantly for intact but not hydrolyzed protein. Because the mean amount of protein recovered from the midintestinal fistulous output increased from 2.3 to 4.7 g for intact soy protein but only from 1.2 to 1.8 g for hydrolyzed soy protein, the fourfold greater protein load delivered into the distal half of the small intestine was responsible for triggering the greater slowing of intestinal transit in response to intact protein. As intact protein spilled into the distal small intestine, the ileal brake was triggered. Intestinal transit was slowed, and digestion and absorption were more complete because more time was available for assimilation.

Example 3: Fiber

The third example of region-specific control of transit and absorption is taken from the effect of fiber-supplemented formulas in displacing nutrients to the distal small intestine. Diarrhea is a common complication of enteral feeding that affects up to 68% of patients receiving this form of nutritional support.[93,94] Based on the idea that increased flow through the intestinal lumen accelerates transit of a meal, a frequently recommended treatment of tube feeding–related diarrhea is to reduce the rate of formula delivery.[95] Although this does indeed ameliorate the accelerating effect of a high flow rate, it also reduces the amount of nutrients delivered. Because intestinal transit is slowed by nutrient-triggered inhibitory feedback, decreasing the delivery rate may also reduce the slowing effect of nutrients. Alternatively, high-fiber formulas are now widely used to prevent the occurrence of tube feeding–related diarrhea because the incidence of this complication is reduced and bowel function is improved in patients given a high-fiber formula compared with those given a low-fiber formula.[96,97] Because fiber thickens the unstirred water layer at the surface of the absorptive mucosa and decreases the rate of nutrient absorption,[98] the addition of fiber to a formula should displace unabsorbed nutrients more distally along the gut. Indeed, soluble fiber prolongs colonic transit, suggesting a role for nutrient-triggered inhibitory feedback.[99] We hypothesized that a high-fiber formula achieves its beneficial effect on tube feeding–related diarrhea by shifting the balance between the opposing effects of nutrient flow and load in favor of nutrient-triggered inhibition from the distal small intestine. To test this hypothesis, we compared intestinal transit while two different formulas (low vs. high fiber) were perfused into the small intestine at 50 or 100 mL/hr. In addition, we also compared intestinal transit when the formulas were excluded from the distal half of the small intestine to test the idea that the inhibitory effect of high-fiber formula depended on the spread of nutrients into the distal intestine.

We found that the effect of increasing the rate of formula delivery on intestinal transit was different between the formulas. Although intestinal transit of the low-fiber formula was accelerated by a higher flow rate, this flow-dependent accelerating effect was absent with the high-fiber formula. Addition of fiber to an enteral formula delays the absorption of nutrients from the small intestinal lumen by increasing the thickness of the unstirred water layer. This effect may then increase the inhibitory feedback triggered by nutrients because the length of the small intestine that ultimately comes into contact with nutrients is increased. Fiber may also achieve its slowing effect by increasing the amount (load) of nutrients that spreads into the distal small intestine.

The idea that the potent inhibitory effect of fiber depended on this spread of nutrients to the distal gut was strongly supported by the intestinal transit results when the formulas were diverted completely and excluded from the distal half of the small intestine. We found that there was no longer a difference in intestinal transit between the formulas. This change was primarily the result of a 400% difference in the speed of transit for the undiverted high-fiber formula compared with mid-gut diversion of the same formula. Diverting the low-fiber formula had no significant effect on intestinal transit. Therefore, decreasing the rate of delivery of a low-fiber enteral formula may slow intestinal transit but is unlikely to affect the transit of a high-fiber formula.

Example 4: Oleic Acid

The fourth example of region-specific control of transit and absorption is taken from our clinical observations using a premeal containing a fatty acid (oleic acid) to slow intestinal transit before a meal.[100] We administered an emulsion consisting of a liquid enteral formula with 0, 1.6, and 3.2 mL of oleic acid to 45 patients with chronic diarrhea and compared their intestinal transit times to those of 7 healthy control subjects. The oleic acid premeal was swallowed 30 minutes before the test meal to trigger inhibitory feedback on GI transit. The clinical condition of patients tested with this novel, nutrient-based treatment included acquired immunodeficiency syndrome (AIDS), diabetes, idiopathic diarrhea, postgastrectomy dumping syndrome, and short bowel syndrome. The mean basal transit time (0 mL of oleic acid) for healthy subjects was 102 minutes compared with 29 minutes for the patient group. We observed dose-dependent slowing of intestinal transit by oleic acid: transit time increased to 57 minutes at 1.6 mL of oleic acid and 83 minutes at 3.2 mL of oleic acid. In most patients transit time was more than doubled with at least one of the doses.

Both frequency and volume of stool also decreased with continued oleic acid treatment.

COLON

The Ileocecal Junction

The ileocecal junction may play a significant role in orocecal transit time as evidenced by accelerated transit after resection[101,102] and delayed transit after ileocecal valve reconstruction.[103] Reduced transit time after ileocecal resection may depend on altered nutrient-triggered inhibitory feedback[101]; i.e., the ileocecal junction is a traffic controller that does not rely on nutrient sensing per se. Specifically, the accelerating effect of ileocecal resection is even greater when a significant length of the ileum is lost along with the ileocecal junction. Because the density of nutrient sensors is greatest in the terminal ileum, ileocecal resection may result in substantial loss of cells capable of responding to nutrient triggers of inhibitory feedback.

The Colonic Brake

Nutrient-triggered inhibitory feedback has recently been described in the colon[104,105] as the *colonic brake.* The presence of undigested or unabsorbed nutrients in the colonic lumen is associated with delayed gastric emptying and slowed intestinal transit.[104,106] The intestinally derived hormones PYY[105–107] and to a lesser extent GLP-1[105] participate in this feedback control. The colonic brake is inactive when the colon is not in continuity with the small intestine (e.g., ileostrom patients). In that setting, nutrient triggers are not elicited and consequently no nutrient-triggered inhibitory feedback to the stomach or small intestine is possible. This may explain the difficulty in maintaining nutritional homeostasis in patients lacking both ileum and colon.

Colonic Fermentation

The presence of undigested nutrients in the colonic lumen also results in bacterial fermentation of these substrates. Up to 20% of daily starch intake may remain undigested by the time it enters the colon.[108] Enteric bacteria avidly ferment undigested starches and dietary fibers, producing hydrogen, carbon dioxide, methane and other gases as well as short-chain fatty acids (SCFAs), mainly propionate and butyrate.[109–111] On average, 80% to 90% of soluble fiber is utilized by the colonic bacteria, with some being virtually 100% degraded to produce gases and SCFAs.[110,111] In patients consuming low-fiber diets, energy salvage from SCFAs constitutes 2% to 7% of the daily caloric intake.[111] This figure may be considerably higher for patients with maldigestion and malabsorption in whom a larger volume of fermentable substrates is presented to the colonic microflora.

Unabsorbed carbohydrate in the colonic lumen triggers inhibitory feedback on upper digestive tract secretion, including gastric, pancreatic, and biliary secretions.[112–114] In addition to altering digestive secretions, GI motility may be affected. Gastric tonicity is decreased by both undigested carbohydrate and SCFAs present in the proximal colonic lumen,[115] suggesting that delayed gastric emptying observed under similar circumstances[116] may directly result from fermentation of nondigestible carbohydrate in the colon. Similarly, the presence of undigested carbohydrate or SCFAs in the proximal colon has been associated with impaired lower esophageal sphincter function.[117] A specific role for colonic fermentation in intestinal transit or motility remains to be clearly demonstrated.

The SCFAs generated by bacterial fermentation are specifically trophic to colonic mucosa and may have other widespread metabolic effects including altered glucose and fatty acid metabolism and ketogenesis.[111,118] Pectin has been shown to induce hypertrophy and hyperplasia of the gut mucosa after extensive small bowel resection,[111] an effect possibly mediated by SCFA production.[109,111] SCFAs can also be a significant source of energy for the host, particularly when digestion or absorption of nutrients is impaired (e.g., in the short bowel syndrome as long as the colon remains in continuity with the small intestine). Such massive colonic fermentation results in the generation of a high volume of flatus and SCFAs. The resultant volume distention is associated with pain and cramping, whereas the SCFAs increase osmolarity of the colonic content, exacerbating osmotic diarrhea.

Bacterial Overgrowth

Loss of the ileocecal junction or gross disruption of transit in the setting of active disease or intestinal resection may permit colonic bacteria to populate the small intestine, which is normally nearly devoid of bacteria.[101] This small intestinal bacterial overgrowth (SIBO) has a number of detrimental effects on GI motility and nutrient digestion and absorption. Phase III of the migrating motor complex (MMC) is the strong propulsive interdigestive "housekeeping" wave that empties the stomach and propels the intestinal content aborally, normally lasting about 5 minutes.[7] Although inhibition of the MMC is associated with subsequent SIBO,[119] it is not clear whether motility abnormalities are permissive for SIBO or whether SIBO results in altered motility. The frequency and duration of the intestinal housekeeper wave are reduced[120,121] or absent[122] in patients with SIBO. In these patients, antral motility is severely reduced whereas duodenojejunal motility is increased.[123] Complete eradication of the bacterial overgrowth restores normal responsiveness to nutrient triggers of inhibitory feedback.

SIBO is associated with weight loss and diminished nutritional status,[124] probably caused by monosaccharide,[119] protein,[125] and fat[126] malabsorption and vitamin deficiencies[126] possibly coupled with anorexia or nausea.[127] Bile acid metabolism is disturbed in SIBO, resulting in increased amounts of total and unconjugated bile acids[119] and probably exacerbating fat malabsorption. SCFAs and byproducts of bacterial substrate