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Introduction—Food, the Immune System, and the Gastrointestinal Tract

Douglas A. Corley and Detlef Schuppan

Every May, *Gastroenterology* publishes a supplementary issue, the “13th issue”, dedicated to a major topic that impacts the practice of gastroenterology/hepatology, is important to public health, and in which there have been substantial advances in research knowledge. The theme in 2013 was pancreatic biology and disease; in 2014 it was the gut microbiome in health and disease. For this 2015 issue, given the explosion of knowledge in the field, the editorial board selected an evaluation of food, the immune system, and the gastrointestinal tract.

Food and its interactions with the immune system are a natural fit for both our specialty and the journal: the digestion and resorption of food is the principal role of the gastrointestinal tract and the last two decades have witnessed an marked expansion of research into how food and nutritional elements influence health and disease. From fermentable oligo-di-monosaccharides and polyols (FODMAPS) to eosinophilic esophagitis, celiac disease, non-celiac gluten sensitivity and the influence of nutrients on carcinogenesis, everyone wants to know what we should eat and how it impacts the body. The interactions between food and the immune system, nutrients and the microbiome, food allergies, nutrition and inflammatory bowel disease, eosinophilic diseases, the fundamental biology of how the brain and the gastrointestinal tract sense and respond to different nutrients, and the regulation of appetite and weight, have each resulted in large new areas of research that have filled the pages of *Gastroenterology* and other journals.

The relationships between food and the gastrointestinal system are of interest to both patients and researchers. A web search on food and cancer alone demonstrates over 528 million results, including full sections of popular websites devoted to the topic, such as on Web M.D. and Health.com. A search for a single dietary element, gluten, provided over 141 million web search results and over 11,000 articles indexed in PubMed, including over 2700 publications in the last five years alone. Food selection is viewed as a potentially sustainable and non-pharmaceutical method of improving symptoms and, for some disorders, it has become the only (or simplest) proven treatment method.

Recognizing the complex interactions between diet and the gastrointestinal tract, we present in this issue a multifaceted evaluation of the immunology, biological mechanisms and

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clinical studies of the major health effects of foods and food-related diseases. Given space limitations, we do not include evaluations of diet and the spectrum of liver diseases; these fascinating topics could occupy an entire additional issue.

The issue starts appropriately with an evaluation by Drs. Wu and colleagues from the University of Pennsylvania on the roles of diet in the pathogenesis and treatment of inflammatory bowel diseases (1). The review evaluates numerous clinical trials, the dietary elements examined in these trials, potential limitations of studies to date; and the biological mechanisms through which food and nutrients may influence inflammation within the gastrointestinal tract, including the role of the microbiome. This review can help guide future research by clarifying evidence gaps, as well as to standardize evidence-based clinical recommendations for patients with inflammatory bowel disease.

A recent field of intense interest has been the composition of intestinal bacteria, the “microbiome”, and how it can directly and indirectly modify the host’s immune function, susceptibility to infection, gastrointestinal symptoms, metabolism and energy balance. A particularly intriguing aspect is how the microbiome might be modified to influence health and disease. The second article tackles this complex topic with a lucid evaluation of the relationships between food, immunity, and the microbiome by experts in the field: Drs. Tilg and Moschen (2). They review the evidence through which dietary components influence intestinal bacteria starting with birth and early childhood nutrition, how the bacterial metabolic machinery responds to nutrients through the generation of secondary messengers that alter host responses, the influence of different dietary components on bacterial composition in both animal models and humans, and how we might develop food-based approaches to the prevention and treatment of certain diseases.

Two reviews in this issue are devoted to food allergies. In parallel with inhalational and cutaneous allergies, food ingestion related allergies appear to have increased up to twofold in the last two decades, especially in Western and developing countries (3), where their prevalence ranges between 3 and 7% in children and 1–3% in adults, with a shift in allergen responses (e.g., from milk, egg or soy to fish, shellfish or wheat). The correct diagnosis and an appropriate treatment beyond rigorous allergen exclusion remain a great challenge in gastroenterology. In their article on this topic, Valenta and colleagues highlight the pathogenesis and novel diagnostic and therapeutic developments in this field, particularly those of IgE-associated food allergies(4). However, there are also more difficult to diagnose forms of non-IgE and T cell mediated food allergies. Notably, they can manifest with both gastrointestinal and extra-intestinal symptoms that range from skin reactions to anaphylactic shock. Most primary food allergens have been characterized, allowing specific and sensitive serological testing and allergen-specific immune hyposensitization therapy. The authors nicely illustrate how the recombinant and synthetic engineering of identified allergens will provide novel treatment option for patients. The article by Burks and colleagues (5) focuses on the clinically variant picture of food allergies, epidemiological aspects, correct diagnosis in children versus adults, and established as well as evolving therapies that employ mucosal immunotherapies aimed at inducing allergen tolerance. These methods included desensitization by oral and sublingual application of increasing amounts of food

allergen, which have shown success in many patients with allergies to peanuts, eggs, and milk.

Eosinophilic esophagitis (EoE), an increasingly diagnosed condition, overlaps with allergies and is characterized by often massive histological eosinophilia. As described in the review by Rothenberg (6), two variants can be distinguished: a subtype responsive to administration of proton pump inhibitors and another unresponsive subtype. Eosinophils play a prominent pathogenetic role and EoE is triggered or promoted by barrier defects and often unidentified food antigens, since exclusion or elementary diets can lead to significant improvement. EoE has a strong hereditary component, including susceptibility loci on chromosomes 2p23 and 5q22 and an inherited propensity to enhanced release of eosinophil and mast cell mediators and a pro-allergic Th2 T cell response. Therapy is usually straightforward using anti-inflammatory, anti-Th2 cytokine, and/or dietary elimination therapies.

Food is also an important modulator of the irritable bowel syndrome (IBS), as evidenced by the beneficial effect of elemental or restrictive diets in some patients. While the underlying mechanisms are incompletely defined, dietary intervention has become an important component of patient management. Peter Gibson and colleagues describe those foods and diets with a proven and mechanistically defined effect on IBS (7). Apart from the role of (non-IgE-mediated) food allergies (8) or non-allergy/non-celiac gluten (wheat) sensitivity (this issue), foods with an increased content of fermentable oligo-, di- and mono-saccharides and polyols (FODMAPs) can induce dose dependent bloating and/or diarrhea in patients with IBS. Although FODMAPs do not cause intestinal inflammation, their targeted reduction may result in symptom improvement equal to or superior to empirical exclusion diets. However, more studies are required to determine the mechanism of action and efficacy of the different dietary approaches in IBS.

During the last 15–20 years celiac disease (CD) has taken center stage among the inflammatory intestinal diseases; its prevalence in most countries ranges between 0.5%–1%. CD has become the best defined food sensitivity, and its pathophysiology serves as a paradigm for autoimmunity that is triggered and maintained by a food antigen. Gluten is the nutritional trigger, the autoantigen tissue transglutaminase (tTG) is pathogenetically involved by potentiating gluten antigenicity, and the presence of human lymphocyte antigen (HLA) -DQ2 or -DQ8 is the necessary (but not sufficient) precondition for the development of CD(9). The two reviews by Kelly et al (10) and Koning et al (11) cover the breathtaking progress in the diagnosis and clinical management of this disorder, and in the understanding of the immunology and genetics of CD, respectively. They address state-of-the-art and novel diagnostic tools, the myriad of associated diseases and symptoms that often predominate over the classical features characterized by malabsorption, and mechanisms of innate and adaptive immunity that lead to intestinal and extra-intestinal pathology, and that may develop into the premalignant and malignant immune cell proliferation of refractory CD type 2 or enteropathy-associated T-cell lymphoma. These insights not only translate into novel, non-dietary therapies, but also fertilize research and clinical practice in other intestinal and extraintestinal diseases.

The third gluten-related food sensitivity that is covered herein, after wheat allergy and celiac disease, is non-celiac/non-allergy gluten (wheat) sensitivity (NCGS); the definition and characterization of this disorder is still being intensely debated. As discussed by Fasano and colleagues (12), such definition is urgently needed, since up to 20% of Western populations, including the US, avoid or have drastically reduced the intake of gluten containing foods. While many may be following a scientifically unfounded fad of “gluten-free is healthy”, a substantial number experience objective symptoms of disease in close association with wheat consumption. Notably, many of these symptoms are extraintestinal, including skin eruptions, fatigue, or exacerbation of preexisting immune diseases. Intestinal biopsy in these patients reveals no or minimal inflammation, but emerging evidence suggests that NCGS is caused by innate immune activation in the gut, as opposed to the adaptive immunity found in patients with celiac disease and wheat allergy. Moreover, a nongluten protein component of wheat and other gluten-containing cereals, the alpha-amylase-trypsin inhibitors (ATI), have been identified as activators of the innate toll like receptor 4 (TLR4) on intestinal dendritic cells, and TLR4 activation fuels ongoing T cell mediated inflammation (13). NCGS is currently diagnosed only by exclusion and a positive nutritional challenge, but is becoming better defined as a result of expert consensus meetings (14) and prospective clinical studies in select patient cohorts. Moreover, we can expect the emergence of histological and serological biomarkers, based on innate immune activation, to aid in its diagnostic workup.

Perhaps no issue is of greater impact on public health than the rapid increase in obesity. Central to understanding and managing this challenge is a greater appreciation of the complex interactions between different nutrients, food and appetite. In particular, how our brain responds to eating and how it communicates with the enteric nervous system to modify appetite stimulation and suppression. In an article on how the brain responds to nutrients, Nicole Avena and her colleagues describe the intricate mechanisms through which the brain responds to nutrients, how this system of neural rewards controls feeding, why the responses vary for different types of food, and how they are dysregulated in overeating and obesity (15). The article specifically explores the brain's responses to diets high in fat, sugar, protein and other carbohydrates, and to clinical intervention studies that modify diet composition. The discussion complements recent publications in *Gastroenterology*, such as the influence of carbonated beverages on perceptions of sweetness (16). Cumulatively, the authors help us understand why certain types of weight-loss diets may fail, and the biological pathways through which future research may help prevent unhealthy weight gain.

The evaluation of how the brain influences food intake is complemented by Michael Camilleri's comprehensive evaluation of how the gastrointestinal tract and its neural mechanisms influence appetite regulation (17). He provides insights into how the central nervous system works with the peripheral nervous system to modify energy intake during meals and stimulate hunger during fasting. The review explores the mechanisms that modulate appetite and satiety through which gastric motility, centrally acting receptors such as for cannabinoids, neuropeptide Y, pro-opiomelanocortin, melanin-concentrating hormone, α -melanocyte stimulating hormone, agouti-related peptide, cocaine- and amphetamine-regulated transcript, cholecystokinin, and glucagon-like peptide 1, leptin,

cholecystokinin, PYY, and oxyntomodulin. It also addresses the roles of taste receptors for elements of sweet, bitter, amino acids and umami, the mechanisms of action of artificial sweeteners, and how energy density, nutrient composition, meal volume, and other properties of food modify appetite and satiation. Finally, the article discusses how these mechanisms may be dysregulated in obesity, and how they might be modified by bariatric surgery.

The issue concludes with two reviews that address nutrients in the context of gastrointestinal malignancies. The first review in this section, by Christian Abnet colleagues at the National Cancer Institute (18), evaluates ten highly touted hypotheses regarding specific nutrients or food compounds and their associations with different gastrointestinal malignancies, including cancers of the esophagus, stomach, and liver. They summarize the extensive literature on dietary patterns, such as diets high in meat, fruits and vegetables or fiber; the roles of common foods such as salt, alcohol, and coffee; and the influence of micronutrients, multivitamins, and vitamin D. They deliver an extensive review of the data, which in turn provides the reader with a stronger evidence-base for dietary recommendations on foods to potentially include and avoid, which ones still need more data to make a recommendation, and which areas are ripe for further investigation including randomized trials.

The final article, by Andrew Chan and colleagues summarizes the extensive literature between nutrients, foods, and colorectal cancer (19). They evaluate the data from both epidemiological studies and randomized trials on the associations between dietary components and cancer risk, including milk, fiber, grains, calcium, vitamin D, fruits and vegetables, and folate. They describe potential biological mechanisms through which some foods might modify the process of carcinogenesis, summarize the evidence for each nutrient or food component, and describe the questions that remain to be addressed, including the dose formulation and time windows during our lifetimes when exposures to specific nutrients might influence carcinogenesis. They also discuss the potential interactions between dietary components, the microbiota and cancer risk.

In conclusion, this 13th issue provides a tour de force of biological and clinical data regarding how food impacts health and disease. We hope this will inform future research by identifying gaps in knowledge, while providing patients and clinicians with evidence-based summaries to guide clinical recommendations. We wish to extend our special thanks and gratitude to our authors for their expertise, dedicated pursuit of the literature, outstanding efforts at summarizing challenging topics, and working within a short timeline; our reviewers for their insightful reviews and dedication to improving each article; and to the tireless work of our editorial associates (Brook A. Simpson, Special Issue Managing Editor; Sarah Williamson, Senior Medical Illustrator) in helping produce this issue. We hope you'll enjoy their collective efforts and find the reviews both informative and useful.

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