Gastroenterology 2015;148:1083–1086

INTRODUCTION

Food, the Immune System, and the Gastrointestinal Tract

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Special Issue and Associate Editors

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 Board of Editors 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 2 decades have witnessed a 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 demonstrate 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 5 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 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 Dale Lee, Lindsey Albenberg, Charlene Compher, Robert Baldassano, David Piccoli, James D. Lewis, and Gary D. Wu (pages 1087–1106) 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 by standardizing 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 Herbert Tilg and Alexander R. Moschen (pages 1107–1119).[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,

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.03.043

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 2 decades, especially in Western and developing countries[3], where their prevalence ranges between 3%–7% in children and 1%–3% in adults, with a shift in allergen responses (eg, 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, Drs Rudolf Valenta, Heidrun Hochwallner, Birgit Linhart, and Sandra Pahr (pages 1120–1131) 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 options for patients. The article by Mike Kulis, Benjamin L. Wright, Stacie M. Jones, and A. Wesley Burks (pages 1132–1142) 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.[5] These methods included sensitization 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 Marc E. Rothenberg (pages 1143–1157), 2 variants can be distinguished: a subtype responsive to administration of proton pump inhibitors and another unresponsive subtype.[6] 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 proallergic Th2 T-cell response. Therapy is usually straightforward using anti-inflammatory, anti-Th2 cytokine, and/or dietaryelimination 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 R. Gibson, Jane Varney, Sreepurna Malakar, and Jane G. Muir (pages 1158–1174) 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, 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 2 reviews by Ciarán P. Kelly, Julio C. Bai, Edwin Liu, and Daniel A. Leffler[10] (pages 1175–1186); and Jeroen van Bergen, Chris J. Mulder, M. Luisa Mearin, and Frits Koning[11] (pages 1187–1194) 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 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 Alessio Fasano, Anna Sapone, Victor Zevallos, and Detlef Schuppan (pages 1195–1204), 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.[12] 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 extra-intestinal, 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