

Review Article

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The Ambivalent Role of Food in Crohn's Disease: An IDI Perspective

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ABSTRACT

Being astute interpreters of experiments-in-nature (diseases), ancient physicians thought of food as medicine. Food selection formed a significant part of their pharmacopeia. The pathogenesis of Crohn's disease has now put into evidence food's ability to both induce one of the major chronic diseases of industrialized nations and its ability to induce prolonged remission (and potentially permanent remission) of the very same disease that it had created.

The induced addiction to therapy via pharmacopeia has obscured what ancient healers of men understood: food is medicine. With Crohn's disease, food demonstrates its ambivalent potential. It is the first major chronic disease.

For surgeons, the lesson is anatomical: the uncinate process is among the most technically demanding regions of the pancreas, and tumor location not tumor size determines whether enucleation is safe. When a lesion in this region lies in close proximity to the main pancreatic duct and the superior mesenteric vessels, pancreaticoduodenectomy is not an escalation of treatment but the anatomically correct response. Framing this choice accurately prevents both under-treatment and unnecessary patient anxiety about receiving a 'bigger operation' than expected.

Insulinoma is a curable disease. The diagnostic and surgical tools to cure it exist and are accessible. What this case demonstrates is that multidisciplinary awareness spanning emergency medicine, endocrinology, radiology, and surgery is the non-negotiable prerequisite for translating those tools into outcomes.

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Food as Disease Causation - Crohn's Disease

Crohn's disease is the consequence of widespread adulteration of milk and milk-based foods within the diet of industrialized nation. Crohn's disease is an immune-mediated disease induced by a zoonotic mycobacterium, *Mycobacterium avium* subspecies paratuberculosis (MAP) in milk and milk-based products [1]. The inability of pasteurization to neutralize MAP presence in milk allowed its widespread insertion into the human food chain [2,3]. For humans with intact immunity intact, MAP infection is of little to no consequence. At birth, a newborn lacks the acquired immunity component of its immune system. Administration of MAP-adulterated milk or milk-based products to newborn infants initiates mycobacterial infection within the newborn's period of immunological vulnerability. Under these circumstances, the newborn's inherited immune system. Th1 proinflammatory response direct at MAP sustained to preclude extracellular MAP replication. For disease to manifest, the antigen challenges within food must be sustained and concentrated to overwhelm the regenerative capacity of the gastrointestinal mucosa at the point of maximum MAP attachment: the ileocecum.

Currently, Crohn's disease stands to be the first chronic disease of industrialized nations to be the consequence of sustained exposure to adulterated food.

Food as Medicine – Crohn's Disease

Plant-based diets primarily affect Crohn's disease by removing from consumption milk-based foods and meat from herbivores that have been documented as being adulterated by MAP. That strict adherence to such diets has induced permanent cures is an example of food being medicine.

In Crohn's disease, rare instances of permanent remissions have resulted from rigid adherence to vegetarian-like diets. Using the Mediterranean diet, Sigell-Boneh et al. demonstrated that 70% of Crohn's afflicted individuals achieved clinical remissions on a Crohn's disease exclusion diet [4]. Chiba et al. have demonstrated that 94% of Crohn's afflicted individuals who achieved remissions on a semi-vegetarian diet remained in clinical remission so long as dietary guidelines were adhered to, whereas 33% of individuals who returned to a regular diet relapsed [5]. The diet It has been shown to lower the risk of adult-onset Crohn's disease [6] In its application submitted to the Food and Drug Administration (FDA) for licensure, the manufacturer of Humira® identified drug failure that exceeded 60% of treated individuals.

Food becomes medicine via its composition. Its biosynthetic composition selectively promotes accelerated replication of selected bacterial groups and their dominance within the gastrointestinal tract's microbiota. Through the metabolites produced, bacteria modulate the efficacy of acquired immunity. In mediating communication between the commensal microbiota and the immune system, bacterial metabolites affect the balance between pro- and anti-inflammatory mechanisms. Particularly,

polysaccharides produced by the gastrointestinal bacterial microbiota are apparent mediators of the critical balance between health and disease in the host [7].

The prototypic Mediterranean diet exerts anti-inflammatory efficacy by affecting the arachidonic acid cascade as well as expression of proinflammatory genes. The diet partially modulates host acquired immunity efficacy through eliciting the clonal expansion of CD4(+) T-cell populations that exert a beneficial influence on the status of the body's acquired immunity [8]. Polysaccharides (PSA) from the gastrointestinal microorganism *Bacteroides fragilis* are the presumed archetypal molecule of commensal bacteria that mediates development of the host immune system. *Bacteroides fragilis* appears to orchestrate the cellular and physical maturation of the developing immune system [9]. Its polysaccharides act to suppress the production of the proinflammatory cytokine, Interleukin-17 produced by intestinal immune cells rebalance skewed systemic T helper responses and promote T regulatory cells [10]. In contrast, *Prevotella copri* over representation correlates with disease in new-onset untreated rheumatoid arthritis patients. Increases in *Prevotella* abundance within the microbiota is associated with a reduction in *Bacteroides* and a loss of beneficial microbes [11,12].

A cow with terminal-stage Johne's disease effectively demonstrated food as medicine [13]. Johne's disease is the consequence of massive involvement of the gastrointestinal tract by a mycobacterium, *Mycobacterium avium* subspecies *paratuberculosis* (MAP). The study animal was removed from her milking herd to lessen stress and placed in a research facility where she received enhanced nutritional feed and supplements that specifically targeted acquired immunity enhancement to prolong her life to collect added aliquots of high titered anti-MAP sera. Rather than dying, over a four-month period in which a specialized diet was administered, the animal made a remarkable total recovery over a four-month period, regaining over 200 kilograms of lost weight. At necropsy, histological examination of previously diseased tissues failed to reveal the presence of a single acid-fast bacillus. The destruction of billions of individual acid-fast MAP bacilli illustrated diet's impact on the animal's acquired immunity. The rare cures with strict adherence to plant-based diets and longer and more numerous prolonged clinical remissions induced by Mediterranean-like diets are presumed to be the consequences of progressive destruction of intracellular MAP's intra-cellular templates [14].

Understanding Crohn's Disease

As interpreted through the Hruska Postulate, The Hruska Postulate and its further elucidation with medical literature have effectively explained every known fact embedded in the natural history of Crohn's disease. When large white blood cells from Crohn's disease afflicted individuals are incubated with a specific MAP antigen array, proinflammatory cytokines appear in the supernatant. The message within the message of Crohn's disease is that Crohn's disease is the first major chronic disease of industrialized nation to be the consequence of widespread adulteration of food.

Food as Therapy

Virtually every clinical study to date has demonstrated dietary manipulations to have not only a positive impact on symptomology and once remission is induced, but the ability also to sustain. Sigell-Boneh et al. demonstrated that 70% of Crohn's afflicted individuals achieved clinical remissions on a Crohn's disease exclusion diet. The temporary remission presented by the manufacturers of the principal biologic used in the treatment of Crohn's disease in its application submission to Food and Drug Administration (FDA)

was 40%. Chiba et al. have demonstrated that 94% of Crohn's afflicted individuals who achieved remissions on a semi-vegetarian diet remained in clinical remission so long as dietary guidelines were adhered to, whereas 33% of individuals who returned to a regular diet relapsed.

The next conceptual advance was the observation that pharmaceutical disruption of the immune system's Th1 pro-inflammatory response could often plicated disease symptomology and induce transient remissions. These clinical set into motion the race to develop a patentable product. The victor has ruled the therapeutics of Crohn's disease for well over two decades.

What biologics did was confirm the constancy of the dysfunctional Th1 response. In its "evidenced-based" FDA filing, Humira® achieved clinical efficacy in 40 that declined with time in which was twice that of those trial subjects that received placebo what went under addressed in FDA's licensing was that clinical efficacy had not occurred in 60% of treated individuals with Crohn's disease and that number increased with time.

In primarily Israel and Japan clinical trials of diet began documenting the greater clinical efficacy of vegetarian and plant-based diets in Crohn's disease. The demonstration of efficacy put into focus the role of the gastrointestinal microbiota in the maintenance of health. Advances in microbial diagnostic technology allowed qualitative and sometimes quantitative analysis of the gastrointestinal microbiota. Significant divergence in bacterial group representation then translated to elucidation of the role of substrate and local redox potential have in determining the prevalence of both anti-inflammatory and pro-inflammatory metabolic products derived from bacteria influence an individual's immune status

Diet as Therapy

The Mediterranean diet exerts important anti-inflammatory efficacy by affecting the arachidonic acid cascade, the expression of proinflammatory genes and interaction with the immune system. Dietary manipulations have been put forth as effective adjunct therapy for rheumatoid disease. Its rationale centers on the immunomodulatory molecules produced by the gastrointestinal microbiota. The ability to modulate host acquired immunity efficacy through eliciting the clonal expansion of CD4(+) T-cell population appears to exert a beneficial influence on the status of the body's acquired immunity.

Bacterial metabolites, in mediating communication between the commensal microbiota and the immune system, affect the balance between pro- and anti-inflammatory mechanisms. Polysaccharides produced by the gastrointestinal bacterial microbiota are postulated to be mediators of the critical balance between health and disease in the host. Polysaccharides (PSA) from the gastrointestinal microorganism *Bacteroides fragilis* has been shown to be the archetypal molecule of commensal bacteria that mediates development of the host immune system. PSA stimulates the innate immune system as a ligand for Toll-like receptor 2 and promotes interactions with the acquired immune system that are required for T-cell activation. *Bacteroides fragilis*, a bacterial polysaccharide (PSA), appears to orchestrate the cellular and physical maturation of the developing immune system. PSA rebalances skewed systemic T helper responses and promotes T regulatory cells (Tregs)

Diet can adversely affect host immunity by reregulation of the dominant anti-inflammatory inducing bacteria within the microbiota

and thereby redirect substrate synthesis byproducts. Prevotella copri dominance correlates with disease in new-onset untreated rheumatoid arthritis patients. Increases in Prevotella abundance within the regional microbiota is associated with a reduction in Bacteroides and a loss of reportedly beneficial microbes. PSA is presumed to suppress the production of the proinflammatory cytokine interleukin-17 by intestinal immune cells and protect via a requirement for interleukin-10-producing CD4⁺ T cells. Regulatory T cells (Treg cells), expressing transcription factor Foxp3, have a key role in limiting inflammatory responses in the intestine.

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