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The WHY? of Crohn's Disease

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Abstract

Using the four-letter Why? the major epidemiologic factors embedded in the natural history of Crohn's disease are reviewed within the context of the Hruska Postulate

Keywords: Crohn's disease; Chronic inflammatory; Gastrointestinal disease; Epidemic

Introduction

Crohn's disease is a chronic inflammatory gastrointestinal disease that is characterized by diarrhea, abdominal pain, and a progressive course in the absence of therapy. In the 1930s, Crohn's disease was a medical rarity. Today, Crohn's disease has attained epidemic proportions, affecting between 1,000, 0000 – 1,200,000 individuals in the United States. Why has Crohn's disease attained epidemic proportions within industrialized nations? A Why unanswered becomes four letter words.

Temporary remission of signs and symptomology of Crohn's disease can be attained by a number of compounds that disrupt key elements of the inflammatory response. Why? Target-specific compounds termed biologics disrupt key components within the inflammatory response. By so doing, they produce closure of the diseased gastrointestinal mucosa. The remissions induced are contingent upon continued administration [1-3].

Crohn's disease occurs in a specific area of the small bowel, the ileocecal area. This fact alone had put causation due to autoimmunity to rest. If the mucosa of the gastrointestinal tract were the target organ, location of disease would be markedly less restricted and not the entire small bowel. The question arises as to why, in the absence of prior surgery to remove diseased bowel, is this selective the selected site of disease?

The ability to prevent Crohn's disease has long been known [1,4]. Retrospective analysis of risk factors for Crohn's disease and prospective assessment of the progression of Crohn's disease within nations and subpopulations have demonstrated that breast feeding markedly reduces the risk of the future development of Crohn's disease:

Corrao G et al. [5] International Journal of Food Epidemiology 1998. Lack of breastfeeding was associated with an increased risk of UC and CD" (Crohn's disease).

Klement E et al. [6] American Journal of Clinical Nutrition. American Journal of Clinical Nutrition. 2004." ... meta-analysis supports the hypothesis that breastfeeding is associated with lower risks of Crohn's disease and ulcerative colitis.

Thompson NP et al. [7] European Journal of Gastroenterology & Hepatology. 2000. "...those with Crohn's disease were more likely not to have breast-fed.

Shamir R [8] Journal of Pediatric Gastroenterology and Nutrition 2009 "Finally, nutrition may play a role in IBD via the protective effect of breastfeeding against UC and CD. .... The current evidence (meta-analysis) demonstrates a possible protective effect for breast milk in the early development of IBD.

This observation was buttressed by the rarity of Crohn's disease in economically challenged populations [9,10]. The question is Why? The appearance of Crohn's disease within relatively insulated populations not only substantiated the protective effect of breast feeding, but also provided a linkage to Mycobacterium avium subspecies paratuberculosis (MAP). Once Crohn's disease began to appear within the general populations, subpopulations within Israel and the Czech Republic that retained breast feeding as the prime source of infant nutrition failed to exhibit a comparable incidence of Crohn's disease [11,12]. In Iceland and The Czech Republic, MAP had to become widespread among the milk-producing herds before Crohn's disease appeared in the general population.

In the 1990s, Chiodini [13] noted the similarities between Crohn's disease and a chronic inflammatory gastrointestinal disease in cattle (John's disease). He subsequently identified MAP as being almost exclusively in the feces of afflicted individuals. Another bovine pathogen, Mycobacterium bovis, had previously bridged the gap between humans and domestic animals using milk as the transport mechanism.

This threat to the public welfare was eliminated by the ability of pasteurization to inactivate M. bovis. Even when subjected to higher temperatures, MAP is not neutralized by pasteurization.

The 2001 United Kingdom Food Standard Agency Report stated that "There is undoubtedly sufficient cause for concern (relative to MAP being the cause of Crohn's disease) for further action to be urgently determined ..." Confronted with a possible threat to the public health constituted by the presence of MAP in pasteurized milk, infant formula, powdered milk, and related milk products, the U.S. Congress gave the responsibility of determining the validity of such a possibility to the Department of Agriculture (USDA).

Naser and co-workers at the University of South Florida isolated MAP from the breast milk of women with Crohn's disease and primarily, but not exclusively, from the blood of afflicted individuals [14-16]. In the United Kingdom, Dr. John Hermon-Taylor's group subsequently enhanced the possibility of a relationship between MAP and Crohn's disease by demonstrating the presence of MAP DNA in primarily diseased tissue from individuals with Crohn's disease [17-20]. By 2008, the circumstantial case linking MAP and Crohn's disease had developed such that the American Academy of Microbiologists stated that "the association of MAP and Crohn's disease is no longer in question. The critical issue today is whether MAP causes Crohn's disease or is incidentally present" [21].

The question of whether MAP infection caused Crohn's disease was crippled by four pertinent sets of data. When MAP produces gastrointestinal disease in domestic animals and human disease in immunocompromised individuals, MAP can be both isolated and, using special stains, visually identified. Despite the documented presence of MAP DNA, MAP can neither be isolated nor demonstrated by special stains from diseased tissue. The occasional identification of MAP DNA in non-diseased tissue or in the white blood cells of health control subjects represented a serious impediment to accepting causation. Finally, both steroids and biologics that can induce temporary remissions potentiate the pathogenicity of mycobacteria. If Crohn's disease is the consequence of MAP, the disease process would exacerbate rather than ameliorate.

MAP receptors line the entire small bowel [22]. Given the current widespread presence of MAP in milk, infant formula, cheeses and other milk-based products, it is more probable than not that the vast majority of individuals within industrialized nations have been infected by MAP. In 2007, the National Health Monitoring System study of 515 dairy farms identified that 31.2% of the participating dairy farms had bulk tank milk that tested positive for MAP DNA [23]. The probability of human MAP infection has become just a function of time and diet. The disparity between the number of individuals presumed to have been infected and the number of individuals afflicted with Crohn's disease supports the contention that MAP is a weak pathogen for humans with intact immunity. The occasional demonstration of MAP in normal gastrointestinal tissue reflects the prevalence of MAP in the food supply. The rare presence of MAP in the blood of a healthy individual identifies a person with recently acquired subclinical infection.

That powdered milk and infant formula can be adulterated by MAP is an established fact [24-29]. As early as 2005, 49% of 51 brands of baby formula manufactured by 10 different producers in seven different countries were demonstrated to contain MAP DNA [24]. The significant presence of MAP in powdered milk and infant formula answers the Whys? of 1. Why breastfeeding conferred protection against the future development of Crohn's disease and 2. Why the epidemic spread of Crohn's disease gained a foundation.

Breastfeeding reduces potential exposure of a baby to MAP within its period of incomplete acquired immunity. Aggressive marketing of infant formula coupled with USDA's failure to prevent the spread of MAP infection among the nation's milk-producing animals have been instrumental in the creation of the Crohn's disease epidemics within industrialized nations.

The protective effect of breast-feeding focused analysis on the neonatal period. What defines the immediate neonatal period is the absence of gut derived acquired immunity. Congenital and postpartum viral infections had documented the importance of cell-mediated immunity in determining the consequences of infection. If infection occurs in the absence of acquired immunity, viral infections that produce minimal or no symptomology or residual sequelae in individuals with complete immunity (rubella and the cytomegaloviruses) now resulted in widespread systemic disease and in organs of limited regenerative capacity, permanent alteration of structure and function.

When a person first encounters a microbial organism, the body's immune system aggressively takes its inventory. When the host is re-exposed to it, the immune system gives the bacteria a pass from Th1 responsiveness. The absence or ineffective acquired immunity makes aborting an organism's replication more difficult, particularly if the organism is a documented pathogen. If the MAP challenge load is sufficient, the resident inherent immune system may become so taxed, that in order to suppress continuing MAP replication, its pro-inflammatory attack response to MAP becomes fixed in immunological memory. When again challenged by MAP, the body's immune system finds itself locked into a perpetuation of its initial pro-inflammatory response against MAP. Upon re-exposure to MAP, the now complete immune system's response is still one of attack rather than one of "so-what" (immunological antigen tolerance). The Hruska Postulate argues that, in the absence of effective acquired immunity, the immune system elaborates a cascade of substances that attack MAP at its sites of attachment and antigen processing [30]. Disease is contingent on MAP antigen overload. For the resultant immune-mediated mechanism to overcome the regenerative capacity of the gastrointestinal mucosa, MAP challenges need to be sufficiently repetitive and concentrated in order to create a localized loss of mucosal integrity [31].

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What is underappreciated is that the clinical spectrum of Crohn's disease is the composite of two inter-related disease processes: an immune-mediated disease and an infectious disease [32]. Once focal mucosal integrity is lost, the intra-luminal gastrointestinal microbiota has sustained open access to the lamina propria and submucosa. The invading gastrointestinal microbiota creates a polymicrobial infection. The mechanisms by which polymicrobial infections produce divergent patterns of disease follow the dictates of the anaerobic progression. Submucosa infection dominated by the Enterobacteriaceae results in healing by fibrosis. If antibacterial therapy is not comprehensive, bacteria whose spectrums of susceptibility are not addressed will re-align themselves within the anaerobic progression. As long as the gastrointestinal microbiota has open portal access, antibiotic administration has the potential to select for antibiotic resistance. Stricture formation, submucosal fibrosis, loop-to-loop fistula, and bowel perforations are not the consequence of the immune-mediated disease, but rather documentation of infectious disease induced tissue damage. Twenty-five percent of afflicted individuals developed fistula.

Using the Hruska Postulate, a number of the four- lettered whys embedded in the natural history of Crohn's disease become answerable.

a) Why the sudden appearance of a new disease: The combination of neonatal MAP infection in the absence of acquired immunity and widespread prevalence of MAP in a nation's food supply.

b) Why the long period between initial MAP infection and disease: The regenerative capacity of the gastrointestinal mucosa.

c) Why the initial localization of disease in the ileocecal region: The ileocecal area is the site of maximum fecal stasis thereby increasing the probability of MAP binding to its complimentary intestinal binding site.

d) Why the efficacy of steroids and biologics to effect temporary remissions through mucosal healing: Steroids and biologics prevent the cytokines elaborated by the host's immune system from affecting their targets.

e) Why do biologics fail to achieve permanent remissions: They do not destroy the immune template that sustains a dysfunctional immune response.

f) Why do selected anti-MAP drugs produce apparently sustained remissions and other anti-mycobacterium drugs do not? Persisting in its spheroclastic form, MAP is the template for the dysfunctional pro-inflammatory response. To affect spheroclasts, drugs must disrupt ribosomal function, Current anti-MAP therapy include compounds impact on ribosomal function (

g) Why biologics can't cure Crohn's disease: Biologics fail to destroy the immune template that sustains the dysfunction pro-inflammatory response against MAP.

h) Why do only selected a limit number of anti-mycobacterial drugs appear to induced sustained remissions: The MAP DNA identified in disease tissue represents MAP in its spheroclast form (an organism without its cell wall). The absence of a cell wall is why MAP can't be identified with special stains Anti-mycobacterial compounds whose mechanism of action is contingent on disruption of cell wall synthesis have minimal efficacy. The anti-MAP regimens now advocated include agents that that inhibit selected critical internal cell functions within MAP spheroclasts.

i) Why have exclusion diets with targeted supplementation produced rare, sustained remissions: Reduction of MAP embedded in adulterated foods coupled with the upgrading of host immunity.

j) Why is it not an ethical imperative to move therapy beyond plication of disease to its cure; Why?

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