



Opinion

Crohn's Disease: The infectious Disease Incorporated's Perspective

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Abstract: Infectious Diseases Incorporated (IDI) is an infectious disease think-tank, established in 1973. Crohn's disease (CD) is a chronic, recurrent disease of the gastrointestinal tract that has reached epidemic proportions within industrialized nations. CD is said to be without cure. Since 2003, therapeutic interventions have focused on disruption of the pro-inflammatory Th1 response against an unknown antigen. In 2015, the Hruska Postulate was introduced and, in so doing, explained how, in the absence of acquired immunity, newborn infection by *Mycobacterium avium* subspecies *paratuberculosis* could cause fixation of the immune system's Th1 response against the organism. The Hruska Postulate was utilized to answer all the documented epidemiological facts embedded in the natural history of Crohn's disease and, in particular, why breastfeeding confers protection against the future development of Crohn's disease. It is Infectious Diseases Incorporated's (IDI) stated opinion that Crohn's disease is both preventable and curable if treated appropriately in its early stages.

Keywords: Crohn's disease; Hruska Postulate; *Mycobacterium avium* subspecies *paratuberculosis*; autoimmunity



Citation: Monif, G.G.R. Crohn's Disease: The infectious Disease Incorporated's Perspective. *Gastrointest. Disord.* **2021**, *3*, 138–141. <https://doi.org/10.3390/gidisord3030015>

Academic Editors: John F. Mayberry and Andrew Day

Received: 21 June 2021

Accepted: 13 August 2021

Published: 25 August 2021

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The natural history developed over the past 89 years explains what Crohn's disease (CD) is. The challenge is in explaining WHY it occurs. The specific facts that define the natural history of disease are:

1. Prior to 1936, disease occurrence was a rare event.
2. The overwhelming preponderance of retrospective studies have shown that breastfeeding confers protection against the future development of CD.
3. Currently, CD has reached epidemic proportions within industrialized nations.
4. Prior to the introduction of a Western diet, CD was, at best rare, unknown in subpopulations for whom breastfeeding constituted the prime source of nutrition for newborns.
5. Initial disease primarily involves the ileocecal area of small bowel.
6. Up to 25% of individuals afflicted with CD will require one or more operations.
7. Therapy directed at disrupting Th1's pro-inflammatory arm often induces temporary remission; less frequently, mucosal healing is documented, but not permanent remissions (cures)
8. Rare permanent remissions were achieved by rigid dietary manipulation or by selective antimicrobial therapy.

The current CD therapy was developed through therapeutic trial-and-error. A demonstration that pharmacological disruption of the immune system's Th1 proinflammatory response could induce temporary remissions on drug therapy, but not cures, allowed for CD to be enshrined as a chronic disease entity with no known cure. Fact #7 became the foundation for the postulate that CD was due to autoimmunity. The embarrassing questions of how and why it occurs were left unaddressed. The label of autoimmunity has had a paralyzing effect on the search for a cause.

In 2000, John Herman-Taylor proposed the concept that *Mycobacterium avium* subspecies *paratuberculosis* (MAP) was the causation of CD [1]. Sechi et al. [2], Bull et al. [3], and Autschank et al. [4], identified a positive correlation between the presence of MAP

DNA in diseased tissue from CD [2–4]. Scana et al. [5] presented similar evidence that MAP was involved in the pathogenesis of subgroups with “irritable bowel syndrome”. Almost invariably, MAP DNA was also identified in a small number of individuals without CD.

In 2008, the American Academy of Microbiology summary stated that “the association between MAP and CD (Crohn’s disease) is no longer in question. The critical issue is not whether MAP is associated with CD, but whether MAP causes CD or is incidentally present” [6].

In 2009, three separate diagnostic laboratories confirmed a strong positive correlation between CD and the demonstration of MAP DNA in human blood. MAP could be recovered from a small number of allegedly normal individuals. In 2005, the University of Florida/Infectious Disease Incorporated collaborative team documented that MAP receptor sites lined the entire small bowel [7]. The presence of MAP receptor sites throughout the entire small bowel, coupled with the high prevalence of MAP within the food supply of industrialized nations, have suggested that MAP is a non-pathogen for individuals with intact immunity. The finding of MAP DNA within circulating, human white blood cells confirmed MAP’s ability to cause human infections [8,9].

The postulate that MAP, as an organism, causes disease in humans as it did in cattle, was aborted by MAP’s failure to be cultured from diseased tissue containing MAP DNA or demonstrated by special stains. The infectious disease postulate argued for guilt by association.

The autoimmune postulate of causation documented that the mechanism of disease production involved the production of proinflammatory cytokines. Using developmental immunology, infectious diseases and pathology principles, the Hruska Postulate created a pathogenesis for Crohn’s disease that linked the two other postulates into a synthesis that addressed all eight facts embedded in the natural history of Crohn’s disease [10].

The Hruska postulate states that if a newborn lacking acquired immunity becomes infected with MAP, depending on the challenge dose and organismal virulence, the newborn’s inherent immune system can be so stressed as to become locked into its Th1 pro-inflammatory response. Every time the individual’s immune system is challenged by MAP, it will again respond by elaborating a pro-inflammatory set of cytokines (absence of immunological tolerance). The evidence for viral enhanced pathogenicity in the absence of acquired immunity has long been in evidence.

As early as 2005, MAP adulteration of infant formula was documented. Hruska et al. demonstrate MAP DNA in 49% of 51 brands of infant formula, manufactured by 10 different producers in seven different countries [11]. Newborn MAP infection creates an immune-mediated mechanism for potential disease production. For disease to develop, MAP challenges had to be both repetitive and dense to overwhelm the regenerative capacity of the gastrointestinal mucosa. MAP had to become prevalent in the food supply for Crohn’s disease to manifest [12–17]. The need for repetitive MAP challenges to overcome the regenerative capacity of the gastrointestinal mucosa accounts for the interim between infection and disease. The density of MAP challenges ultimately dictates the location of initial disease. Maximum small bowel fecal stasis occurs in the ileocecum.

Why the initial rarity of Crohn’s disease in breastfed infants: At the turn of the century, breastfeeding newborn infants was the traditional means of providing initial newborn nutrition. MAP had not become widespread among milk-producing herds.

Why does breastfeeding confer protection against the future development of Crohn’s disease: Breastfeeding precludes the newborn from being infected with milk or infant formula that has been adulterated by the presence of MAP [18–20].

Why the global epidemic of Crohn’s disease exists: Two factors contribute to Crohn’s disease having grown from a medical rarity to epidemic status. First, the progressive failure of governmental agencies to limit the spread of MAP within milk-producing herds [12]. Secondly, the progressive adulteration of powdered milk and infant formula [16,17].

Why was Crohn’s disease very rare among economically challenged populations until the introduction of a western diet: In third-world countries, breastfeeding was

nearly the primary means of providing newborns with nutrition during the first months of life, Crohn's disease slowly appeared, in association with the aggressive marketing of infant formula and introduction of MAP adulterated foods.

Why does disease initially involve the ileocecal region: The gastrointestinal mucosa is continually renewing itself. The interim between acquisition of the mechanism for disease induction and the development of clinical disease is governed by the integrity of the gastrointestinal tract and the frequency and density of MAP antigen challenges. MAP receptor sites line the entire small bowel [7]; however, disease occurs where the ileocecal valve controls the transit time of small bowel contents.

Why do individuals with Crohn's disease develop stricture, loop-to-loop anastomosis, bowel perforation, perineal fistula. Intense focus of the suppression of inflammation has partially masked the importance of treating the gastrointestinal bacterial microbiota once mucosa integrity has been breached [21].

In science, the exception defines the rule. For Crohn's disease, two exceptions exist. In isolated instances, individuals have a self-induced permanent remission through dietary manipulation or received selected antimicrobials.

Dietary manipulation entails removing diet foods that possibly contain MAP and, in so doing, reduce the MAP antigen load. Studies of animals with advanced Johne's disease have demonstrated that, through dietary immune system enhancement, one can go beyond immunological capture of MAP and attain total organism destruction [22,23].

Why only selected anti-mycobacterial drugs achieve a permanent remission/sustained remission: The dysfunctional proinflammatory response to MAP is driven by an MAP template that resides within the body as cell-wall-free organisms. To affect MAP in its cell-wall-free form, a drug must impact the organism's ribosomes [24].

Both dietary manipulation/immune system enhancement and selected antimicrobials target the MAP template.

Why is Crohn's disease still without recognized cures when the science indicates that they are probable: The U.S. FDA is wedded to "evidence-based" data, which translates to placebo-controlled, double-blinded comparative studies. Such studies cost tens-of-millions of dollars, thus surrendering the therapeutic dialogue of Crohn's disease to those who can sponsor such studies.

As long as the developing science is unaddressed, Crohn's disease will remain a disease without a cure. What is most disappointing is that the global epidemic can be stopped by women breastfeeding their newborns for the first four weeks of life or use an infant formula that is MAP-free.

Funding: There is no external funding.

Conflicts of Interest: The author declares no conflict of interest. Infectious Diseases Incorporated is an infectious disease thinktank that is internally funded.

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