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Opinion

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Infectious Diseases Incorporated's Perception of the Japan's Crohn's Disease Epidemic an Old Therapy Redefined

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1. Opinion

Crohn's disease's evolution from a rare clinical entity into a global pandemic within eighty years underscores the conceptual paralysis engendered when a problem has a partial solution and it appears to address the problem. The questions of why the sudden emergence of a global Crohn's disease pandemic and why the pandemic is limited to industrialized nations have been left unaddressed. Once Crohn's disease was identified as an immune-mediated disease, analytic focus went from macro- to micro-analysis and in so doing distorted the understanding of the events that combine, not to produce disease, but to produce its pandemic spread and its implied therapy. In this to-the-point opinion paper, Infectious Diseases Incorporated (IDI) revisits what was once Japan's first line therapy for Crohn's disease. In 2015, The Hruska Postulate was first introduced into the medical literature [1]. It stated that Crohn's disease is the product of two, interacting elements: fixation of a dysfunctional pro-inflammatory response directed against *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and an over-abundance of MAP in a nation's food sources.

Fixation of the immune system's pro-inflammatory response is the consequence of a MAP infectious challenge occurring in the effective absence of host acquired immunity which occurs in the first weeks of life. In order to combat MAP replication, the baby's inherent immunity may become so stresses as to become fixed within immunological memory. To convert a dysfunctional Th1 response to MAP to disease status takes prolonged and concentrated MAP antigen challenges before the regenerative capacity mucosal capacity of the ileocecum is finally overwhelmed. The Hruska Postulate has effectively explained the key epidemiological characteristics of Crohn's disease [2,3].

The sudden transformation from a rare disease to one of pandemic status is a function of a newborn becoming infected with a sufficient MAP challenge. The rise in the number of cases of Crohn's disease parallel, but lags slightly the shift in infant nutrition from breast feeding to infant formula. As early as 2005, the significant presence of MAP in infant formula was documented. The Veterinary Research Institute (VRI) in the Czech Republic identified that 49% of 51 brands of infant formula manufactured in 10 different countries contained MAP DNA [4]. The probability that MAP-adulterated infant formula has globally fueled the Crohn's disease global pandemic is substantiated by the near total absence of Crohn's disease in nations whose primary source of infant nutrition is breast milk. Why the widespread dissemination of MAP in the food supplies of industrialized nations? USDA allowed the licensing of MAP diagnostic tests which masked the true prevalence of infection and refused to made mandatory of an animal's MAP serological status on its Certificate of Health. In protecting agribusiness, USDA allowed infected animals to be shipped across regional and international boundaries. McKenna et al. showed that the commercial MAP ELISA tests identified only 6.8% to 8.8% of tissue positive cattle [4]. In 2011, 54% of MAP infected/disease cows imported into Japan came from the United States [5]. Before the advent of biologics, di-

etary manipulation had been the first-line of therapy in Japan before the introduction of immune system Th 1 response disrupters [6]. Successful diets producing clinical amelioration of symptomology or temporary disease suspension often paralleled those utilized by vegetarians. The tragedy in the therapy of Crohn's disease is that dietary manipulation was but ameliorative and not curative. This fact opened the door for pharmacological interventions whose ultimate performances may not have matched those achieved with blinded dietary manipulation. In its FDA submission for approval, the manufacturer of adalimumab demonstrated that 40% of study subjects administered adalimumab attained temporary remissions at 26 weeks versus 17% for the subjects receiving placebo [7]. At 56 weeks, the percentage of treatment subjects in remission slipped a little to 36%. In contrast Sigall-Bonehet et al. reported that 70% of individuals with Crohn's disease achieved clinical remissions using exclusion diets [8]. Chiba et al. reported that 94% of Crohn's disease afflicted individuals who remained on a semi-vegetarian diet (that excluded milk protein) maintained their clinical remission whereas 33% who returned to a regular diet relapsed [9]. What dietary manipulation unknowingly did was to lessen the quantity of oral MAP antigenic challenges that were embedded in MAP adulterated milk-based products and meat from grass-fed animals. Why they failed is a lack of knowledge as to what foods were potentially adulterated by MAP. When adalimumab works, it does so by effectively precluding the immune system's Th 1 response to MAP challenge from developing which, in time allows for mucosal healing and restoration of mucosal integrity. Those remissions which are attained with biologics will ultimately fail. From 2003-2022, biologics have yet to demonstrate the ability to induce permanent remissions. Knowledge within the pathogenesis of Crohn's disease stands to make dietary manipulation again a gold therapeutic standard for Crohn's disease [10] and possibly its cure [11]. Infectious Diseases Incorporated is an infectious disease think tank founded in 1973.

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