

## Translation of Hypothesis to Therapy in Crohn's Disease

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### Introduction

The ability of microbiological agents that downscale host immunity or block specific cytotoxic cytokines to achieve a remission is the foundation for the thesis that Crohn's disease is due to the body turning against itself. The labelling of Crohn's disease as an autoimmune disease has had a mind paralyzing effect on the more important issue of its prevention. The why that every epidemiological study done on Crohn's disease has identified that breast feeding prevents the subsequent development of the disease has been eclipsed by this proposed pathogenesis [1-6]. The central thesis of the Hruska Postulate is that Crohn's disease is an immune induced disease caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP). Disease production is theorized to be the concurrence of two synergistically functioning mechanisms: early MAP neonatal infection and frequent repeated re-exposure to MAP [7-9]. MAP is not neutralized by pasteurization. Milk, powdered milk, cheese, and infant formula have the potential to be adulterated by MAP [10-15]. If MAP infection occurs within the first few weeks of life when host's acquired immunity is grossly deficient, the pro-inflammatory cytokine response elicited by MAP is theorized to become fixed within immunological memory [8-9]. Upon re-exposure to MAP, rather than exhibiting immune tolerance to MAP's antigen, a pro-inflammatory response again manifests. The elicited cytotoxic cytokines attack MAP at its sites of epithelial attachment and antigen processing within the lamina propria. Despite the fact that MAP receptors lining the entire small bowel, the sites of diseased bowel correlate with those with maximum faecal stasis [16]. Given the remarkable regenerative capacity of the gastrointestinal mucosal lining, occasional re-exposure to MAP would be of limited significance. For immune mucosal challenges to effectively impair the anatomical barrier that separates the lamina propria from the gastrointestinal microbiota, they must be both numerous and closely spaced [8,9].

The quantity of the initial infectious challenge and the intensity/frequency of immune system re-challenge are thought to account for the divergent interims between neonatal MAP and subsequent manifestation of Crohn's disease. The requisite for translating neonatal MAP infection into disease was and is the widespread dissemination of MAP within a nation's food supply. Epidemiological studies involving relatively insulated populations have documented that widespread dissemination of MAP in the milk producing herds antedated the first appearance of Crohn's disease [8,9]. In 2007, USDA's National Animal Health Monitoring System estimated 70% of US dairy herds had been infected to an unspecified degree and that 31.2% of bulk tank milk collected from 515 dairy farms contained MAP DNA [17]. The contemplated pathogenesis of Crohn's disease is a foundation for the extension of the duration of remissions currently achieved with

biologics and antibiotics directed against the intestinal microbiota. The elimination from diet of foods potentially containing MAP is argued to be of paramount importance. Allowing continuation of MAP elicited immune challenges is counter-productive to neutralization of cytotoxic cytokines by biologics. In Japan, diet has been the first line of therapy for Crohn's disease. The ability to achieve remission with diet alone infers a synergistic interplay between elimination of immune challenges and dietary enhancement of nutrition/host immunity. As well as antimicrobial therapy directed against the invading gastrointestinal microbiota, specific therapy directed against MAP *per se* is advocated in order to sustain prolonged remissions. The subliminal presence of MAP has been postulated to be a requisite to maintaining the effector arm of the immune system primed against MAP's antigenic array. Using special media designed for the recovery of spheroclastic bacteria, MAP has been shown to be recoverable in low numbers from diseased tissues [18]. MAP's elimination through enhancement of cell-mediated immunity is thought to be the mechanism by which prolonged remissions have been achieved by diet alone. Because MAP persists in a spheroclastic form, antimicrobials that target ribosome should prove to be a valuable adjunct to dietary enhancement of cell-mediated immunity. That MAP can be actually destroyed by diet is inferred by one well studied experiment within veterinary medicine. A cow with far advanced Johne's disease due to MAP was removed from her herd and placed in a less stressful research environment in order to obtain added quantities of high titered anti-MAP serum. Under normal herd conditions, Holsteins with far advanced Johne's disease die within two to three weeks. To prolong her life, she was placed on diet supplements that targeted enhancement of cell-mediated immunity. Instead of dying, the cow flourished. When the animal was necropsied four months later, she had gained over 200 kg. Very comprehensive gross and microscopic analysis of the small intestines revealed that MAP could not be detected by special stains for mycobacteria. Gross and histological evidence of alteration of anatomical structure was absent [19]. Total eradication of MAP with total reversal of tissue damage had been achieved through stress reduction and dietary enhancement of immunity. Subsequently the mechanism used by the body for organism destruction was identified [20]. This observation adds to the short term objective of attaining clinical remission of symptomology the long term objective of cure.

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