Japanese Journal of Gastroenterology Research

www.jjgastro.com

*Short Commentary*

***Open Access, Volume 1***

# Crohn's disease and peptic ulcer disease: A personal comparative analysis

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Received: Jun 09, 2021
Accepted: Jul 15, 2021
Published: Jul 20, 2021
Archived: www.jjgastro.com


## Short commentary

Until the Hruska Postulate and its intellectual fulfillment [1-7], Crohn's disease was a disease entity without either cure or validation. The explanation put forward for its pathogenesis is that the body's immune system selectively turned against something within the gastrointestinal tract. That disruption of the immune system's pro-inflammatory Th1 response could produce evidence of mucosal healing and temporary abatement of disease was aggressively pushed as documentation of the concepts validity. Crohn's disease became the linchpin for 193 journals, 86 conferences and 15,631 articles about or related to autoimmunity. When sought for antibodies to a specific target organ could be demonstrated in a number of diseases. In congenital rubella, the presence of anti-islet cell antibodies introduced the hypothesis that autoimmunity was responsible for the higher incidence of abnormal glucose tolerance tests observed [9]. An equally plausible explanation was that the documented viral replication within islet cells of the pancreas sufficiently altered cellular structure so as to create cross-reacting antibodies. Most claims of autoimmunity have been based upon the demonstration of an antibody that cross-reacts with a cell or subunit within the target organ.

In Crohn's disease, disease involves primarily the small bowel of the gastrointestinal tract. The requisite antigen site was never demonstrated. That initial disease occurs at a specific site, the ileocecal area and its subsequent surgical removal does not prevent re-occurrence of disease ruled out cellular constituents of the gastrointestinal mucosa. Two decades of intense administration of anti-inflammatory drugs, steroid and biologics have yet to produce cures. When one adds the question mark to the word why, it becomes a four-letter word for those who have to answer.

History teaches us that, given the same set of circumstances, what happened in the past will re-occur. In the period from 1940-1960, the disease entity that dominated gastroenterology was "peptic ulcer disease". The explanation for its occurrence was the over-production of gastric acidity that was responsible for duodenal hemorrhage and/or upper small bowel penetration into the peritoneal cavity. The onus of responsibility for disease occurrence was on the individual. The pharmaceutical industry developed medication that could plicate but not cure the disease. The mass media of the period was inundated with product information. This two-decade fiscal marriage between industry and physician in the treatment of this chronic disease was interrupted when it was demonstrated that peptic ulcer disease

was an infectious disease that could be CURED by antibiotics.

In 2000-2020, a similar marriage between healthcare providers was in play. The responsibility for the disease was on the individual who somehow turned his or her body against something in the gastrointestinal tract. Just like with "peptic ulcer disease", if you had Crohn's disease, your body did something to create it. The autoimmune labeling of Crohn's disease had a mind-paralyzing effect of identifying the events that combine to produce disease. Autoimmunity could not answer why Crohn's disease is a relative new disease, why it has evolved into epidemics within industrialized nations, why Crohn's disease is rare to absent in selected subpopulations, why the site of initial disease, who does breast feeding provide protection against the future development of Crohn's disease, why infection with *Mycobacterium avium* subspecies *paratuberculosis* had to become wide spread in milking herds before Crohn's disease appeared in the general population, etc. These whys have been answered in detail by the Hruska Postulate and its extensions [8]. It took 18 years before autoimmunity was called out in the medical literature [9]. The one thing that biologics have provided circumstantial evidence that Crohn's disease involves an immune-mediated process.

There is a standing rule in medicine: "The exception defines the rule". The occurrence of "peptic ulcer disease" in individuals who produced little of no gastric secretion should have put into serious question its proposed pathogenesis.

In Crohn's disease, the fact that stringent diet and selected antimicrobials produced an occasional permanent remission should have similarly put into question the explanation of causation. Intense advertising and possible strategic investments in medical leadership precluded focus on anything that countered the myth of autoimmunity and biologics forever. The American College of Gastroenterologists 2018 Guideline (singular) for Crohn's disease reads " *…there still remains a large group of patients who do not respond adequately to our current medication armamentarium. …. We will certainly expand our war chest and uncover effective biologics with different mechanisms of action to treat our patients. If the initial drug (biologic) fails, the patient will be able to switch to another agent and even combination biologics may be reality* [10]". In 2019, the makers of the leading biologic made 19.94 billion dollars. Inflammatory bowel disease, which includes Crohn's disease, has made gastroenterologist second only to cardiologists among subspecialists in internal medicine in terms of financial compensation. Gastroenterologist's over focus on inflammation has resulted in non-treatment or undertreatment of the invading gastrointestinal microbiota which in turn resulted in strictures, loop-to-loop intestinal anastomosis, bowel perforation and fistula, Twenty-five percent of individuals afflicted with Crohn's disease had one or more surgery to remove diseased bowel.

In 2015, the Hruska Postulate stated that the dysfunctional pro-inflammatory response of Crohn's disease was the consequence of newborn infection by *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in the relative absence of acquired immunity [1]. The timing of infection is primarily created by the presence of MAP in infant formula or milk [11-14]. As early as 2005, Hruska et al. documented that 49% of 51 brands of infant formula manufactured by 10 different producers in seven different countries contained MAP DNA [11]. For Crohn's disease to manifest, the MAP antigen needed to become widespread in the food supply. In 2002, USDA estimated that 20-30% of the milk producing herds in the United States contained one or more MAP infected animals. By 2007, the FDA's estimate was 70% (15). In 2012, 54% of animals identified in quarantine as being MAP infected came from the United States [16]. That same year, the World Health Organization for Animal Health (OIE) contemplated removing paratuberculosis due to MAP, the Terrestrial Animal Health Code because "*MAP infection is so widespread, continued recognition of MAP as an animal pathogen would only cause economic losses through restriction in international trade*".

The Hruska postulate states that in the absence of acquired immunity and, depending on the challenge dose and organismal virulence, a newborn's inherent immune system response to MAP infection can be so taxed that the elicited anti-MAP pro-inflammatory response becomes fixed within its immunological memory [1]. Every time the individual's immune system is again challenged by MAP, it will again respond by elaborating a pro-inflammatory set of cytokines (absence of immunological tolerance). Repeated and concentrated antigen exposure is required to overwhelm the regenerative capacity of the gastrointestinal mucosa.

Major differences between "peptic ulcer disease (PUD)"and Crohn's disease are the financial and societal costs of disease.

The cost of treating "peptic ulcer disease" was modest. No one subgroup within medicine administered care to the majority of afflicted individuals. Individuals with PUD rarely had to leave the work force of change employment to accommodate their disease.

In contrast, the nature of Crohn's disease forced afflicted individuals to change or leave their employment to accommodate their disease. When launched in 2003, Humira carried the list price of $522 per a 40-milligram syringe. In 2020, f Humira cost was $2,984 per syringe [17]. The cost of therapy has become such that, without insurance coverage, individuals are forced to leave the workforce in their prime earning years to go on disability in order to attain a reasonable quality of life. The direct and indirect costs to the federal government are estimated to be between 12-16 billion dollars. The U.S. is unable to directly negotiate for lower prices for its Medicare beneficiaries, thereby making the American taxpayer a cash cow.

The digital age has radically altered the genesis of medical information. Publication in a medical journal, requires the investigators to pay "publication costs" which can be as high as several thousands of dollars. Case reports involving therapy have become rare to non-existent. Their deletion from the medical literature removes the sharing of unusual experiments in nature.

FDA requires that for information to be recognized, the data be evidence based. The problem resides in the definition of what constitutes evidence-based information: placebo controlled, blinded comparative studies. Having applied the evidence-based doctrine to Crohn's disease effectively surrendered the control of information to those entities that could afford the multi-million-dollar price tag.

With PUD, infectious causation triumphed over gastric acidity. This "medical truth" was not established by evidence-based comparisons, but the straight forward curing of disease. With Crohn's disease, the ability to achieve permanent resolution of disease through the destruction of the MAP template stands to have history repeat itself [18].

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