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RESEARCH ARTICLE

The Neglected Second Mechanism of Pathogenicity in Crohn's disease: Infectious Diseases Incorporated's Perspective

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ABSTRACT

Crohn's disease is an immune-mediated disease which results from the persistence of a pro-inflammatory cytokine response to *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and MAPs widespread presence in the food supply of industrialized nations. Over time, the destructive antigen/cytokine interaction overwhelms the regenerative capacity of the gastrointestinal mucosa. The resultant focal destruction of mucosal integrity creates a portal for invasion by the gastrointestinal microbiota; the second mechanism of pathogenicity for Crohn's disease. Failure to effectively address polymicrobial submucosal infections has resulted in 25% of Crohn's afflicted individuals requiring one or more operations within their lifetimes.

Infectious Diseases Incorporated is an infectious disease think tank established in 1973.

Crohn's Disease

Crohn's disease is a zoonotic food-borne disease due to *Mycobacterium avium* subspecies *paratuberculosis* (MAP) that translates itself into an immune-mediated disease when MAP becomes widespread in the food supply (1). Because of veterinary mismanagement, MAP became widespread in milk-herds. Infected animals could shed MAP into their milk (2,3). Once in milk, MAP was not effectively neutralized by pasteurization (4). As early as 2005, research investigators at the Veterinary Research Institute in the Czech Republic documented the presence of MAP DNA in 49% of 51 samples of infant formula manufactured by 10 different producers in seven different countries (4,5). At birth, a newborn is analogous to a germ-free entity. Its acquired immunity has yet to develop. If a newborn is sufficiently challenged by MAP, to abort continued mycobacterium replication, its inherent immunity's proinflammatory response could become fixed within immunological memory. Every time the immune system is again confronted with MAP's antigen array, rather than exhibiting immunological tolerance, it re-initiates its original pro-inflammatory cytokine response against MAP at its sites of mucosal attachment. Repeated and concentrated MAP/cytokine interaction at a future date overwhelms the regenerative capacity of the gastrointestinal tract mucosa which allows bacterial invasion of the lamina propria and underlying tissues to become the second operative mechanism of Crohn's disease (6,7). The loss of mucosal integrity and the resultant alterations of the local oxidation-reduction potential allow commensal bacteria to attain pathogenic status via the anaerobic progression (8).

The regenerative capacity of the gastrointestinal tract is responsible for the long interim between creation of a fixed pro-inflammatory response directed against MAP and the focal loss of mucosal integrity. MAP receptor sites line the entire small bowel, yet the initial lesions involve just the ileocecum (9). The fact that the ileocecum is the site of maximum fecal statis argued for the density as well as frequency of antigen challenges being critical in determining of the site of mucosa destruction.

Gastrointestinal Tract and Microbiota

The microbiota of the gastrointestinal tract functions as an independent entity whose confines and constituency are defined by the imposed anatomical and environmental elements. The gastrointestinal microbiota is a highly regulated hierarchy that functions to assure its stability and its survival. With disruption of microflora stability by pathogenic bacteria or enterotoxins, the gastrointestinal microbiota will ultimately self-regulate.

Through the evolutionary process, humans and entrapped microbes have developed a successful commensal and symbiotic inter-relationship. Owing to the greater destructive firepower that reside with the microbiota, the stability of this relationship is somewhat fragile. Some 70-80% of the human immune system is dedicated to the defense of the gastrointestinal mucosa from effective organismal invasion.

Microbial Pathogenicity in Crohn's Disease

Barring submucosal fibrosis, the immune-mediated part of Crohn's disease is resolvable with restoration of mucosal integrity using biologics or diet. If left unaddressed, the infectious disease part of Crohn's disease (fistula, surgical removal of inflamed bowel, loop-to-loop anastomosis, and septic deaths) are permanent consequences due to physician failure to treat or adequately treat the gastrointestinal microbiota.

The initial oxygen-rich environment created by lamina propria infection allows the more facultative anaerobic bacteria to initially dominate. If a tissue-adherent stain of *Escherichia coli* is present, submucosal extension of infection may result in submucosal healing by fibrosis (10). If the anaerobic progression is not arrested, transmural penetration occurs. The inflammatory process can cause adherence of ileocecum to the lining of the cul-de-sac. This apposition of surfaces permits continuation of the process into the body's underlying soft tissues, creating a fistulous tract.

Crohn's afflicted individuals often have had one or more operations for the removal of diseased bowel within their lifetime. Surgical removal of the ileocecum displaces the site of maximum fecal stasis. Once repositioned, recurrence of transmural inflammation can cause agglutination of one loop of bowel to another loop of small bowel and creation of a loop-to-loop anastomosis. If not sealed by another loop of small bowel, fecal material is delivered directly into the peritoneal cavity.

An Under Addressed Issue

The practice of gastroenterologists deals directly or indirectly with the microbiota of the gastrointestinal tract. Gastroenterologists are positioned to be the mediators between the gastrointestinal tract per se and its microbiota. Yet, there is little in the formal education of gastroenterologist to prepare them for dealing with the complex microbiological and immunological issues embedded within the gastrointestinal tract and its microbiota.

For three decades, peptic ulcer disease constituted a significant part of the clinical practice of gastroenterologists until peptic ulcer disease was documented to be a curable infectious disease. With Crohn's disease, history is repeating itself. Crohn's disease is a preventable and curable disease (11,12). More likely than not, ulcerative colitis is not a single disease entity, but rather, a collection of disease entities with somewhat divergent pathogenesis (13). Ulcerative disease is another example of a disease entity that whose therapy is more influenced by the pharmaceutical industry than scientific knowledge (14).

Gastroenterologists need to pay appropriate intellectual homage to the gastrointestinal microbiota, less individuals continue to pay a terrible price for that failure (15,16).

REFERENCES

1. Monif G. R. G. 2015. Hruska postulate. Med Hypothesis 85:878-881. dx.doi.org/10.1016/j.mehy.2015.09.019
2. Millar, D. Ford, J. Sanderson, J. et al. 1996. IS 900 PCR to detect *Mycobacterium avium* subspecies *paratuberculosis* in retail supplies of whole pasteurized milk in England and Wales. Appl. Environ Microbiol. 62:3446-54
3. Grant I. R., Ball H. J., Neill S. D., Rowe M. T. 1996. Inactivation of *Mycobacterium paratuberculosis* in cow's milk at pasteurization temperatures. Appl. Environ. Microbiol. 62:631-636
4. Millar, D. Ford, J. Sanderson, J. et al. 1996. IS 900 PCR to detect *Mycobacterium avium* subspecies *paratuberculosis* in retail supplies of whole pasteurized milk in England and Wales. Appl. Environ Microbiol. 62:3446-54
5. Grant I. R., Ball H. J., Neill S. D., Rowe M. T. 1996. Inactivation of *Mycobacterium paratuberculosis* in cow's milk at pasteurization temperatures. Appl. Environ. Microbiol. 62:631-636
6. Hruska K., Barto M., Kralik P., Pavilik P. 2005. *Mycobacterium avium* subsp. *paratuberculosis* in powdered infant milk: paratuberculosis in cattle – public health problem to be solved. Veterinarni Medicina 2005:327-335 http://vri.cs/dos/vetmed/56-5-226.pdf
7. Botsaris G., Swift B. M. C., Slama J. et al. 2016. Detection of viable *Mycobacterium avium* subspecies *paratuberculosis* in powdered infant formula by phage-PCR and confirmed by culture. Intern. J. Food Microbiol. 216:91-94
8. Monif G. R. G. 2017. An infectious disease process within an immune-mediated disease process: Role of the gastrointestinal microbiota in Crohn's disease. Adv. Res. Gastroenterol. Hepatol. *5* (5):1-2 doi.10.19080/ARGH 2017.*05555675*
9. Monif G. R. G. 2018. Are the permanent sequelae of Crohn's disease a failure to treat the gastrointestinal microbiota. Med. Hypothesis. 122:198-199
10. Gorbach S. L., Bartlett J. C.1974. Anaerobic infections. N. Engl. J. Med. 290:1280-1294
11. Schleig P. M., Buergelt C. D., Davis J. K. et al. 2005. Attachment of Mycobacterium avium subspecies paratuberculosis to bovine intestinal organ cultures: method of development and strain differences. Vet. Microbiol. 108:271-279
12. Gorbach S. l.: 199. Clinical aspects of anaerobic infections. J. Infect. 1:25s-37
13. Monif G. R. G. 2019. Is ulcerative colitis a disease of a dysfunctional microbiota Med. Hypothesis 131 (2019) 199300. Doi.org/10.1016/j.mehy.2019.1009300
14. Lichenstein G. R., Loftus E. V. Jr., Isaacs K. l. et al. 2018. ACG Clinical Guidelines: Management of Crohn's disease in adults. Am. J. gastroenterol. 113:481-517. Doi 10,1038.ajg.2018.27
15. Monif G. R. G. 2021. The Crohn's disease: The Infectious Disease Incorporated's Perspective. Gastrointest. Discord. 2021 3:138-141, doi.org/10.3390/gdiscord3030015
16. Monif G. R. G. 022. Crohn's disease: A curable disease held hostage? Chapter20. eBook ISBN: 978-93-*5547-537-4* 20