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Is ulcerative colitis a disease of a dysfunctional microbiota?

Gilles R.G. Monif

Infectious Diseases Incorporated, 17121 Lakewood Drive, Bellevue, NE 68123-3954, United States

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ABSTRACT

Using the gross pathology literature and the prior decoupling of Crohn's disease from inflammatory bowel disease, IDI's White Paper puts into question the current understanding of what ulcerative colitis is and how it can be therapeutically addressed. The pathology literature, when coupled with the ability of fecal enema therapy to achieve a remission rate significantly superior to those documented for biologics, puts focus on the dominant role of the gastrointestinal microbiota in both disease induction and its recovery. The concept of endogenous enterotoxogenesis is introduced.

The term inflammatory bowel disease is but a description of a process. Yet, it has become the umbrella term under which disease entities of divergent pathogenesis have been lumped. The uncoupling of Crohn's disease from inflammatory bowel disease has renewed focus on the fact that ulcerative colitis is a diagnosis without firm foundation [1,2]. The rush to render complex into simplex may have prompted the lumping of diseases with diverging etiologies under a single label.

The lack of a specific diagnostic test necessitates the diagnosis of ulcerative colitis be based primarily on the clinical signs and symptoms of disease and site of involvement. Anatomical analysis of diseased specimens has only served to compound the ambiguity embedded in the diagnosis. The sites of inflammatory colonic involvement sites are sufficiently diversified that the designation of indeterminate colitis (IC) has been advanced when the gross and histological findings deviate from the anticipated spectrum of disease [3,4]. Evidence of active or prior inflammation can occur throughout the colon (pan colitis), have skipped areas of microscopic inflammation without mucosal involvement, present as focal ileal ulcers with patchy microscopic colitis, demonstrate severe inflammation of the transverse colon with relative rectal sparing, have disease focally involving both the ascending and sigmoid colon, present with left-sided colitis or have involvement restricted to the rectum and sigmoid colon [5].

Based upon the pathology of the disease selected observations emerge. Colonic inflammation may have a partial genesis within its extra colonic representation. Appendiceal orifice inflammation and its extension to adjacent mucosa have been advanced as the potential causation of right sided colitis [6–10]. Similarly, the extension of diverticular inflammation is thought to account the development of segmental colitis [11,12] which, in the elderly [11], has been shown to respond to antibiotics.

What appendices and diverticula share in common is a constricted mucosal line space. Microflora selection is a function of the prevailing microbiological environment. Anatomical compartmentalization potentially allows the prevailing microflora to differ from that of the intralumen gastrointestinal microbiota. As such, an appendix or compromised diverticula can serve as a potential reservoir of a microbial flora that is accelerated in terms of its status with respect to the anaerobic progression. Multiple epidemiological studies have documented the protective effect of appendectomy against the future development of ulcerative colitis [13–16]. All that is needed for disease induction is an additional change in the microbiological environment to release the dominant obligatory anaerobes from the remaining vestiges of competitive restraint. Cytotoxins are a function of logarithmic growth.

The role of bacterial infection in the genesis of "ulcerative colitis" is inferred by concomitant presence of inflammation in other area of the gastrointestinal tract. The occurrence of ulcerative duodenitis and/or gastritis accompanying ulcerative colitis is well-documented [17–20]. The microbiological environment of the stomach and duodenum is distinct from that within the colon and hence selects for a different spectrum of pathogens. In the 1950s, ulcerative gastritis or duodenitis would have been attributed to peptic ulcer disease, an infectious disease process due primarily to *Helicobacter pylori*. The question raised is why concomitant evidence of apparent infection within two dissimilar microbiological environments?

Pseudomembranous enterocolitis is a form of colitis whose pathogenesis is reasonably well grounded in science. Antibiotic therapy that included the drug clindamycin had induced an adverse outcome: pseudomembranous enterocolitis. The resultant disease entity was ultimately proven to be due to the production of cytotoxins by *Clostridium difficile*. Pseudomembranous enterocolitis delineates a mechanism by which, release from bacterial inhibition, allowed a toxigenic anaerobic bacteria to produce tissue destruction within the gastrointestinal tract.

E-mail address: gmonif@aol.com.

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In this set of circumstances, disease induction is due to role inversion between the previously dominant facultative anaerobes and the subordinate obligatory anaerobes. The mechanism by which pseudomembranous enterocolitis is induced is the same by which it is terminated. The antibiotic, metronidazole, targets the replication of the toxin producing *Clostridium difficile*.

The protective role of the gastrointestinal microbiota has been less than properly understood [21–24]. The ability of salmonella species to induce clinical disease as opposed to transient subclinical infection is largely a function of the magnitude of the challenge dose. If the resident gastrointestinal flora is significantly altered through antibiotic administration, a challenge dose, previously incapable of disease induction, now converts subclinical infection to its disease counterpart.

Polymicrobial bacterial florae are highly regulated through a complex interaction of enzymes, hydrogen peroxide and bacterocins that allow a bacterium within a given species to quantitatively regulate the degree of replication of all other bacteria within its grouping: king of a mountain [25–27]. If any of the conditions supporting its dominance become altered, a new king is crowned.

The bacterial florae identified in ulcerative colitis represent a departure from its protecting counterpart [24]. By altering the intralumen microbiological environment, if induced, mucosal inflammation can set into motion a mechanism by which previously suppressed bacteria attain progressively greater representation within the gastrointestinal microbiota. What has been put in question is not the deregulation of the gastrointestinal microbiota, but rather, what is the set of events that deregulates the protection afforded by gastrointestinal bacterial flora?

In 1989, a prolonged remission was achieved when a physician self-administered fecal enemas to treat his ulcerative colitis [28]. Fecal enemas have since received non-FDA sanctioned acceptance as therapy for *Clostridium difficile* toxin induced enterocolitis.

Fecal enemas (fecal microbiota transplantation) are applications of unquantified bacterial communities administered in an attempt to disruption the prevailing bacterial dominance structure. To date, the remission rates attainable with fecal enemas are only two to three times better than those reported with biologics [29]. Given the lack of precise knowledge of the diversity of bacterial constituents and their quantitative representation, the fact that fecal enemas have produced any positive results speaks well for the implied mechanism of action, competitive bacterial interference. As should have been anticipated, some sources of fecal enemas are more efficacious than others. Based upon the mechanism of action in play, added selection strategies need to be implemented if fecal enemas are to attain their maximum potential.

The degree to which diet influences the composition of the gastrointestinal microbiota is an embarrassingly understudied area. One experiment in nature comes from beef cattle. In contrast to animals pastured on grass, cattle fattened with corn have an enhanced presence of potentially pathogenic *Enterobacteriaceae* in their feces. Diet needs to be considered pre-biotic in that pre-biotics skew the microbial dominance patterns achievable.

Fecal transplantation is slowly evolving into a more precisely defined therapeutic tool [29,30]. The fact that competitive bacterial inhibition works to the degree that it does without adjunct refinement corroborates the probability that most, if not all, of what is termed ulcerative colitis, may be a result of endogenous enterotoxogenesis whose triggers await discovery. The postulate of endogenous enterotoxogenesis is consistent with the ability of compounds that disrupt the effector arm of the immune response to provide a degree of clinical benefit without addressing the underlying mechanism of disease induction.

The 2019 Infectious Disease Incorporated White Paper states that the therapy and probability of long-term remission of “ulcerative colitis” is contingent upon:

1. The exclusion of other causes of infectious colitis as well as colitis mimickers;
2. The administration of antibiotics that are target group specific in order to effect microbial dominance reversal. Broad spectrum antibiotic therapy, as one might use initially in Crohn’s disease, can be effective [31], but in terms of re-establishing an optimal gastrointestinal microbiota, they can potentially be counter-productive;
3. The number of fecal enemas required is that necessary to achieve permanent remission. Selection of donor is very important. The ideal donors are healthy individuals who are vegetarians or who have been certified as optimal fecal donors;
4. The colon is the site of selected vitamin synthesis and absorption. Deficiency of particularly water-soluble vitamins is to be anticipated. Superimposition of previous latent cytomegalovirus infection is a partial function of disease-induced, impaired host immunity [32,33]. Aggressive dietary supplementation is needed to restore optimal immunological function;
5. Attention to diet is critical in order to maintain long-term benefits of a re-established protective gastrointestinal microbiota. Diet dictates the long-term character of the gastrointestinal microbiota. To be excluded from diets are foods known to enhance anaerobic bacterial replication [34]; and
6. Biologics and steroids have very limited roles with the therapy of infection-based diseases.

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Declaration of Competing Interest

None.

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