Is *Mycobacterium paratuberculosis* or Any Other Infectious Agent Involved in the Pathogenesis of IBD?

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Mycobacterium paratuberculosis is not a cause of either ulcerative colitis (UC) or Crohn's disease (CD); however, other microbial agents may be. UC is a disease of the epithelium—a very superficial process. Colonic crypt epithelial cells undergo necrosis, granulocytes aggregate in crypts and adjacent lamina propria, and the inflammatory process extends, undermining additional crypt units, causing ulcers. Attempts at healing result in a hyperplastic response, misshaped or branched crypts, and ultimately dysplasia. There are autoimmune elements to this disease, autoantibodies against colonic epithelium and lymphocytes occurring in a variable proportion of patients, and perinuclear antineutrophil cytoplasmic antibodies in 60%–80%.[1]

Appendicitis that occurs before the age of 20 is protective against UC, whereas appendicitis after the age of 20 is not,[2] suggesting that having childhood appendicitis (or lymphadenitis of an adjacent lymph node) confers some level of protective immunity. Childhood appendicitis is very often viral, whereas adult-onset appendicitis is most often bacterial in origin. Hypothetically, exposure to a "colitis virus" during the late teen years, adolescence, or early adult years might be expected to result in 1 of 3 outcomes: little or no clinically manifest disease, acute appendicitis, or, if later, UC.

Selective damage to crypt epithelium occurs in several important viral gastroenteric diseases, e.g., gastrointestinal coronavirus infections, parvovirus infections, and pestivirus diarrheas.[3] The chronic or relapsing epithelial disease of UC may be analogous to that of chronic hepatitis. Persons exposed to the hepatitis B virus may experience little or no clinical disease, some have acute disease and recover, and others suffer the consequences of persistent viral infection, with or without superimposed autoimmune elements. Just as the virus of non-A, non-B hepatitis eluded medical research for so many years, a viral etiology for UC may be eluding us currently. The disease lacks the appearance of a bacterial process and does not respond to treatment with antibiotics.

CD is another matter. The disease is chronic, transmural, and segmental, with features of mucosal and submucosal lymphangitis,[4] the latter often underappreciated. In the past, an experimental animal model of "regional enteritis" was created by injecting sclerosing agents into regional intestinal lymphatics. The result was segmental bowel wall thickening, sclerosis, granulomas, mucosal ulcerations, and fistulas.[5]

A number of important features of CD are well-recognized elements of infectious small bowel diseases, such as, salmonellosis, *Yersinia* infections, and tuberculosis. The earliest lesions in these diseases occur in the lymphoid follicles of Peyer's patches. These "tonsils" of the lower gut are concentrated in an incomplete circumferential ring at the distal end of the ileum, and distributed at "skip" intervals in more proximal intestine.[6] Bacteria and viruses are taken up regularly by the M cells in the epithelium overlying the lymphoid follicles, for the sampling of antigens that occur in the intestinal lumen. Many organisms use Peyer's patches as portals of entry, including even the prions of transmissible spongiform encephalopathies. Thus, the place of onset and the distribution of lesions suggest that CD is microbial in origin. Loop-to-loop adhesions, localized peritonitis, abscesses, granulomas, and fistulas are all evidence of bacterial invasion.

What causes us to doubt that bacteria are the primary causative agent of CD is the failure to reproduce disease by animal inoculation (a standard method for the demonstration of bacterial diseases), failure to consistently culture a pathogen from diseased tissue, failure to find antibodies or cell-mediated immunity against a causative bacterium, and failure to cure with short or even long courses of antibiotics. There is also the absence of a spontaneously occurring animal model. Spontaneous regional enteritis of pigs is bacterial in origin and has many features of CD,[7] but few investigators recognize the comparative aspects of the disease or study its origins and pathogenesis.

Attempts to find bacteria that might be responsible for CD have yielded conflicting and controversial results. Polymerase chain reaction (PCR) seems to have compounded the problem, with various laboratories reporting positive evidence of *M. paratuberculosis, Yersinia, Listeria*, and *Escherichia coli*. Results cannot be confirmed among laboratories, and when broad-based searches for 16S rDNA are done on tissues, none, save perhaps *E. coli*, can be demonstrated. This author has reviewed the many reasons why Johne's disease and CD are not equivalent,[8] and recently suggested that *E. coli* may be the most relevant bacterium demonstrated in CD.[9]

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There is evidence that some strains of *E. coli* induce lepromatous granulomatous disease, of meninges, urinary tract, intestine, and gall bladder. In Hjarres disease of fowl the intestinal response to *E. coli* is tuberculoid granulomas.[9] Immunohistochemistry has demonstrated *E. coli* antigen in the diseased tissues of patients with CD,[10] *E. coli* DNA has been detected in microdissected granulomas,[11] and patients have been shown to have higher antibody titers and titers directed against a greater variety of *E. coli* than in controls.[12]

The age of onset of CD prompts consideration of the viruses of adolescence, i.e., those responsible for tonsillitis, appendicitis, mononucleosis, and Hodgkin's disease. Given the age group affected most frequently, it may be important to recognize the possibility that CD could be the result of 2 pathogens, a persistent or recurring virus, which initiates disease (with a short episode of gastroenteritis) and then flares in activity from time to time, and an *E. coli* of the granuloma-inducing kind. Such 2-pathogen sequences are well recognized in pneumonias of all species, albeit these being acute, and in chronic respiratory disease of fowl, in which a respiratory coronavirus or paramyxovirus is accompanied and abetted by *E. coli*.[13] Antibiotics help patients with CD and there may be resolution of some clinical manifestations, but antibiotics do not cure the condition. A persistent viral agent such as Epstein–Barr virus (EBV), or one that commonly recurs, such as influenza or the enteroviruses, may ultimately be shown to initiate CD. That multiple cases occur within families and even in spouses suggests exposure to a shared environmental agent.[14]

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