15. Zakikhani M, Dowling R, Fantus IG, et al. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. Cancer Res 2006;66:10269–10273.
16. Evans JMM, Donnelly LA, Emslie-Smith AM, et al. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330: 1304–1305.
17. Bowker SL, Majumdar SR, Veugelers P, et al. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin [see comment]. Diabetes Care 2006;29: 254–258.
18. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 2002;94:972–980.
19. Fisher WE, Boros LG, Schirmer WJ. Insulin promotes pancreatic cancer: evidence for endocrine influence on exocrine pancreatic tumors. J Surg Res 1996;63:310–313.
20. Pour PM, Kazakoff K, Carlson K. Inhibition of streptozotocin-induced islet cell tumors and N-nitrosobis(2-oxopropyl)amine-induced pancreatic exocrine tumors in Syrian hamsters by exogenous insulin. Cancer Res 1990;50:1634–1639.
21. Stolzenberg-Solomon RZ, Graubard BI, Chari S, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 2005;294:2872–2878.
22. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 2004;127:1044–1050.
23. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes [see comment]. Diabetes Care 2009;32:193–203.

Reprint requests

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Conflicts of interest

The author discloses no conflicts.

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Infection, Inflammation, and Homeostasis in Inflammatory Bowel Disease

See "Increased short- and long-term risk of inflammatory bowel disease after *Salmonella* or *Campylobacter* gastroenteritis" by Gradel KO, Nielsen HL, Schønheyder HC, et al, on page 495; and "*Salmonella* induces flagellin- and MyD88-dependent migration of bacteria-capturing dendritic cells into the gut lumen" by Arques JL, Hautefort I, Ivory K, et al, on page 579.

The intestinal tract contains hundreds of different species of commensal bacteria and their phages, outnumbering our own cells by at least an order of magnitude. In recent years, our understanding of the importance of the intestinal microbiota has greatly expanded to include its roles in nutritional homeostasis and maintenance of normal immunologic function. This is an extremely exciting time as researchers elucidate the connections between bacteria, both commensal and pathogenic, and a variety of pathologies ranging from obesity to functional bowel disorders. Indeed, these topics are among several featured in a recent special issue of GASTROENTEROLOGY.[1] Although much remains unknown, including the factors controlling the structure of this population, its distribution, and its diversity between individuals, we are poised to learn a great deal as the human microbiome project moves forward.[2]

Among the most rapidly advancing areas of research are those related to the etiology and pathogenesis of inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (CD). These disorders are due likely to a derangement of the delicate balance between microbial flora and the host immune system, where an aberrantly aggressive response to commensals may occur.[3] For example, IBD predominantly affects portions of the gut with the highest concentrations of bacteria; genetically engineered mouse models of chronic IBD require the presence of bacteria for mice to develop inflammation, and IBD patients may improve with antibiotic treatment or diversion of the fecal stream. Cloning of IBD susceptibility genes also implicates the immune system: the *NOD2/CARD15* susceptibility gene for CD encodes an intracellular receptor for muramyl dipeptide and a number of studies suggest loss of *CARD15* function in this disease.[4] Genes involved in the interleukin (IL)-23 (IL23/T_H17) pathway and autophagy (ATG16L1 and IRGM) are candidates recently identified in genome-wide association studies of IBD,[5,6] Supportive data are already emerging for their role in IBD and, interestingly, the autophagy proteins may differentiate the diseases pathophysiologically as they are associated with CD and not UC.[7,8]

On the bacterial side, it has long been questioned whether specific culprit flora may precipitate the development of IBD and/or persistently colonize patients; additionally, whether and how an abnormal immunologic milieu may alter gut flora is not known. For instance, *Mycobacterium avium* subspecies *paratuberculosis* was cultured from patients in the 1980s; however, despite a number of studies, the etiologic relationship remains controversial.[9] An adherent and invasive *Escherichia coli* strain has been characterized in CD patients, and the B2+D phylogenetic group of *E coli* was also recently found to be over-represented in IBD patients.[10,11] The advent of large-scale sampling of bacterial communities has now allowed culture-independent studies demonstrating that microbial populations in IBD patients vary from those in healthy controls. For example, Frank et al[12] performed rRNA sequencing and phylogenetic analysis on samples from surgically obtained tissue in CD and UC patients as well as non-IBD controls.[12] Although this group did not find an individual bacterial species enriched to suggest it was an etiologic agent for IBD, a subset of the IBD patients had microbiotas that clustered separately from those of controls and the remaining IBD patients, and that were depleted for *Bacteroides* and *Lachnospiraceae*. Presence of the variant microbiota was correlated with abscesses in CD patients and younger age and may be a marker for more severe disease, although causation could not be addressed in this study.

In the work described above, a convincing role for common conventional pathogens in the development of IBD has not yet been established. In this issue of GASTROENTEROLOGY, Arques et al[13] and Gradel et al[14] present 2 very different studies related to the complexity of events during bacterial infection and its possible etiologic relationship to both UC and CD. The work from Gradel et al is an epidemiologic study conducted in 2 Danish counties from 1991 through 2003. The authors utilized a study cohort of 13,148 patients exposed to *Salmonella* or *Campylobacter* gastroenteritis, and 26,216 control patients, who were followed for a mean of 7.5 years and up to 15 years. Among the patients who were exposed to *Salmonella/Campylobacter* gastroenteritis, there was a significant increase in IBD incidence over the first year postinfection, with a continuation of this trend so that by the end of the study period 1.2% of exposed versus 0.5% of unexposed patients carried a diagnosis of IBD. The study benefited from the comprehensive registry and long-term follow-up of patients, and builds on prior, more short-term studies that suggested an increased risk of IBD after these infections.[15–17] Although the authors point out the challenges in assessing patients diagnosed with IBD in the short term—for example, similarities in endoscopic appearance between infectious colitis and IBD, or the likelihood of more detailed investigations in patients with more severe illness—the incidence of IBD in the exposed versus control patients was increased in the long term as well, although it is not yet understood how this might occur pathophysiologically.

The study by Arques et al presents data that extend our understanding of the early mucosal immune response to *Salmonella* infection in mice. Utilizing both oral infection and introduction of bacteria into isolated intestinal loops, the authors found evidence of transepithelial bacterial sampling as well as dendritic cell (DC) migration into the intestinal lumen in response to infection. Their reference strain was noninvasive *S enterica* serovar Typhimurium lacking *Salmonella* pathogenicity island 1 (SL1344-ΔSPI1). At 5 hours postinfection, the researchers detected CD11c+ cells containing GFP-labeled *Salmonella* in the gut lumen. Subsequently, a more detailed analysis utilizing flow cytometry and additional markers revealed that the *Salmonella*-containing cells were a specific subpopulation of DCs, $CD11c^{+}CX_3CR1^{+}$ $MHCII^{+}CD11b^{-}CD8\alpha^{-}$, that are specific to the small intestine. DC migration was dependent upon the presence of bacterial-associated flagellin as well as the SPI2 pathogenicity island, as intraluminal DC migration was not induced significantly in response to ΔSPI1-Δ*fliC*Δ*fljB* and ΔSPI1-Δ*ssrA* strains, nor in response to purified flagellin. DC migration was also not elicited by *E coli* K12, and furthermore was minimal in MyD88 mutant mice lacking this adaptor molecule central to Toll-like receptor (TLR) signaling pathways. The DCs internalized bacteria as observed by confocal microscopy and recovery of the bacteria after purification of the DCs; however, the DCs were not observed to migrate back across the mucosa when labeled with diI and injected into fresh ileal loops. We still have much to learn about DCs, which sample bacterial antigens, monitor the environment, and coordinate the appropriate responses of the immune system through the actions of discrete DC subsets with specific addresses and functions. Arques et al have demonstrated that they can also undergo wholesale migration into the gut lumen in response to specific bacterial stimuli.

These 2 disparate studies present an opportunity to speculate further about how infection with common bacterial pathogens may predispose some patients to later development of IBD. First, the susceptible immunologic substrate may respond differently to these bacteria. CX3CR1 deficiency in DCs reduces their ability to sample luminal bacteria and take up pathogens, and the early phase of infection with a *Salmonella* type 3 secretion system 1 mutant required DCs for invasion across the epithelium.[18,19] DCs from IBD patients seem to be phenotypically distinct and have increased expression of TLR2 and TLR4, as well as the activation marker CD40.[20] Although polarization of the immune response depends on the interaction between epithelial cells and DC, which