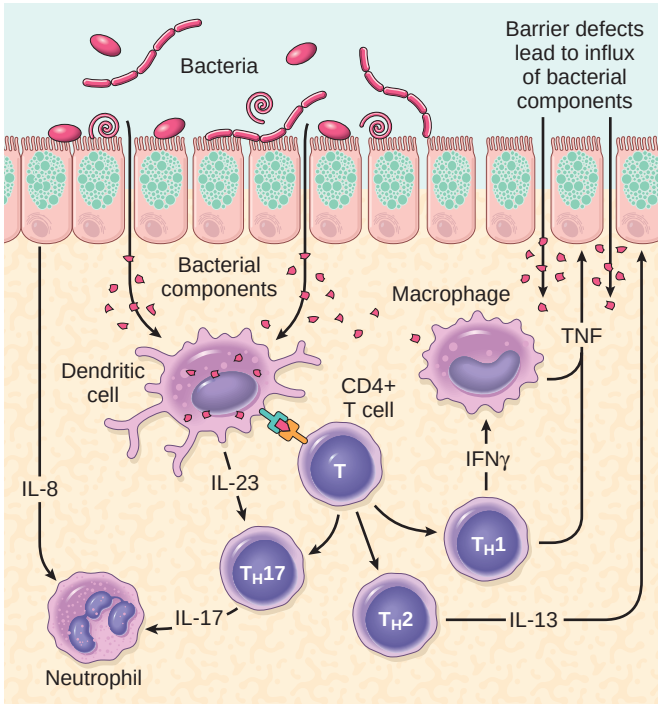

Figure 17-33 One model of IBD pathogenesis. Aspects of both Crohn disease and ulcerative colitis are shown. See text for details.

three are involved in recognition and response to intracellular pathogens, supporting the hypothesis that inappropriate immune reactions to luminal bacteria are an important component of IBD pathogenesis.

- **Mucosal immune responses.** Several observations support a role for mucosal immune responses in the pathogenesis of IBD. Some of these are:
  - T helper cells are activated in Crohn disease and the response is polarized to the T_H1 type (see Chapter 6)
  - T_H17 T cells most likely contribute to disease pathogenesis. Consistent with this, certain polymorphisms of the IL-23 receptor, which is involved in the development and maintenance of T_H17 cells, confer marked reductions in the risk of both Crohn disease and ulcerative colitis.
  - Many other pro-inflammatory cytokines, including TNF, interferon-γ and IL-13, as well as immunoregulatory molecules such as IL-10 and TGF-β, appear to be play a role the pathogenesis of IBD. The role of IL-10 is supported by the observations that autosomal recessive mutations of the IL-10 and IL-10 receptor genes are linked to severe, early onset IBD.

  Overall, while details remain to be defined, it is clear that deranged mucosal immune activation and defective immunoregulation contribute to the development of ulcerative colitis and Crohn disease. Immunosuppresive agents remain the mainstay of treatment for these conditions.
- **Epithelial defects.** A variety of epithelial defects have been described in both Crohn disease and ulcerative colitis. Some examples follow:
  - Defects in intestinal epithelial tight junction barrier function are present in Crohn disease patients and a subset of their healthy first-degree relatives. In patients with Crohn disease and their relatives, this barrier dysfunction is associated with specific disease-associated *NOD2* polymorphisms; experimental models demonstrate that barrier dysfunction can activate innate and adaptive mucosal immunity and sensitize subjects to disease.
  - Some polymorphisms, such as those involving *ECM1* (extracellular matrix protein 1), which inhibits matrix metalloproteinase 9, are linked to ulcerative colitis but not Crohn disease. In this context it is notable that inhibition of matrix metalloproteinase 9 reduces the severity of colitis in experimental models.
  - Certain polymorphisms in the transcription factor *HNFA* are associated with ulcerative colitis but not Crohn disease. These *HNFA* polymorphisms are also strongly associated with maturity onset diabetes of the young (MODY), which like IBD, is associated with reduced intestinal barrier function.

  Together these data suggest that, derangements in epithelial function is an important component are critical to IBD pathogenesis.
- **Microbiota.** The abundance of microbiota in the GI lumen is overwhelming, amounting to as much as 10^{12} organisms per milliliter in the colon and 50% of fecal mass. In total, these organisms greatly outnumber human cells in our bodies, a sober reminder that at a cellular level, we may be only about 10% human. A sampling of data that supports the notion that microbiota play a role in the evolution of IBD follows:
  - As mentioned earlier, linkage to NOD2, points to the involvement of microbes in the causation of Crohn disease.
  - The presence of antibodies against the bacterial protein flagellin are most common in Crohn disease patients who have disease associated *NOD2* variants, stricture formation, perforation, and small-bowel involvement. In contrast, anti-flagellin antibodies are uncommon in ulcerative colitis patients.
  - Microbial transfer studies are able to induce or reduce disease in animal models of IBD, and clinical trials suggest that probiotic (or beneficial) bacteria or even fecal microbial transplants from healthy individuals may benefit IBD patients.

One model that unifies the roles of intestinal microbiota, epithelial function, and mucosal immunity suggests a cycle by which transepithelial flux of luminal bacterial components activates innate and adaptive immune responses. In a genetically susceptible host, the subsequent release of TNF and other immune-mediated signals direct epithelia to increase tight junction permeability, which causes further increases in the in flux of luminal material. These events may establish a self-amplifying cycle that gives rise to maladaptative and injurious immune responses.

Crohn Disease

Crohn disease, an eponym based on the 1932 description by Crohn, Ginzburg, and Oppenheimer, has existed for centuries. Louis XIII of France (1601-1643) suffered relapsing bloody diarrhea, fever, rectal abscess, small intestinal and colonic ulcers, and fistulae beginning at age 20 years, most likely due to Crohn disease.