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Crohn Disease

SUMMARY OF THE ORIGINAL ARTICLE

Regional Ileitis, A Pathologic and Clinical Entity

Burrill B. Crohn, MD; Leon Ginzburg, MD;
Gordon D. Oppenheimer, MD

JAMA. 1932;99(6):1323-1329

This article describes, in clinical and pathologic detail, a disease of the terminal ileum characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration is reported to be accompanied by a dispro-

portionate connective tissue reaction of the involved intestinal wall, which frequently leads to stenosis of the lumen and is associated with the formation of multiple fistulas.

The disease is clinically featured by symptoms resembling those of ulcerative colitis, ie, fever, diarrhea, emaciation, and a mass in the right iliac fossa usually requiring surgical resection. The etiology is unknown.

See www.jama.com for full text of the original *JAMA* article.

Commentary by Richard S. Blumberg, MD

IN A 1932 ISSUE OF *JAMA*, CROHN, GINZBURG, AND OPPENHEIMER¹ brought into clear focus a new clinical entity with characteristic pathologic features that were previously only anecdotally recognized with uncertain meaning.² This disease, originally called *regional ileitis*, has now assumed Crohn's name to recognize the bellwether nature of these published findings¹ and to account for the now recognized protean manifestations of this clinical syndrome that may involve the entire gastrointestinal tract without restriction to the ileum as originally described.

Perhaps most importantly, it is apropos to describe the clinical entity as Crohn disease (CD) given the remarkable degree of accuracy in its original description,¹ such that it remains the basis for diagnosis 75 years later. In their description of 14 cases, Crohn and colleagues described a chronic disease of young adults that presented with fever, diarrhea, and dull to cramp-like right lower quadrant abdominal pain, together with anemia and constitutional symptoms. This was pathologically characterized by transmural and segmental inflammation of the intestines with granulomas, linear ulcerations, and a "cobblestone" appearance. Perhaps most presciently, they categorized the now well-accepted subtypes of disease behavior as ulcerative (or inflammatory), (fibro)stenotic, perforating (with abscess), or fistulizing.

This landmark article¹ launched an intense interest worldwide in this disease and especially in understanding the etio-pathogenesis that, in the past 2 decades, has reached a remarkable intensity of investigation—with a level of success

that would astound Crohn and his numerous disciples. Early investigations (1930s-1950s) focused attention on the familial nature of the disorder, the environment of the intestines, the burgeoning understanding of intestinal immunophysiology, and similarities between CD and many infectious diseases. By the early 1980s, studies permitted a disallowance of numerous concepts of etiology (eg, food allergy, psychogenic). Also at this time studies introduced the emergence of a yet to be tested model that involved the primacy of genetics and its relationships to the uniquely constructed immune system that was associated with the intestines and their relationship to the normal commensal microbiota.

An understanding of the nature of inflammatory bowel disease (IBD) that included CD and ulcerative colitis, a related clinical entity that shares similar biological mechanisms, experienced a quantum leap forward due to the serendipitous observation that genetic deletion of the antigen-specific T-cell receptor or the cytokine interleukin 2 (IL-2) led to spontaneous colitis that resembled IBD.^{3,4} Since that nascent observation, dozens of other genetic manipulations in mice have shown an effect, either on the intestinal epithelial cell barrier or the immune system that results in spontaneous intestinal inflammation resembling IBD.^{5,6} Importantly, in all models studied, development of IBD-like inflammation in mice was dependent on the commensal mi-

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crobiota and specifically its bacterial components.⁶ Investigation of the inflammation mechanisms of these mouse models has further revealed a detailed understanding of immunopathogenesis in which innate immune cells (ie, dendritic cells) inappropriately recognize commensal microbial antigens as if they were pathogenic. These same innate immune cells drive the activity of 1 or more types of differentiated and aggressive T cells, which secrete constellations of class-specific cytokines (helper T cells [T_H1, T_H2, or T_H17]) that lead to IBD-like disease resembling CD (type 1 and type 17 cytokines) or human ulcerative colitis (type 2 cytokines).^{5,6}

Under normal, noninflamed conditions, these mouse models have also shown that innate immune cells (ie, dendritic cells) drive other classes of T cells that are anti-inflammatory or tolerogenic (T-regulatory cells). Thus, a tug-of-war between anti-inflammatory and pro-inflammatory pathways that is more-or strain dependent in mouse models and thus genetically determined is at play in IBD and specifically in CD. Furthermore, over the last 15 years, the extensive research in IBD animal models has provided a concise blueprint for IBD pathogenesis—one that shows that in a genetically susceptible host, CD results in an inappropriate recognition of the normal commensal microbiota by the innate (dendritic cell) and adaptive (T cell) components of the gut-associated lymphoid tissue.

Simultaneous clinical investigations in humans have corroborated the importance of inflammation derived from innate immune cells, T_H1 cells, and likely T_H17 cells in the pathogenesis of human CD. This occurs by virtue of the induction of therapeutic responses through the administration of monoclonal antibodies that target tumor necrosis factor, emerging from innate immune cells and T_H1 cells, and IL-12 and IL-23—innate immune factors derived from dendritic cells that drive T_H1 and T_H17 cells and their entry into intestinal tissues.⁷⁻⁹ The synonymous observations in mouse and human studies are remarkable and underscore the future added value of mouse models in translating biological pathways into human therapies for this disease.

It was not, however, until 1996 and finally in 2001 that a genetic basis for human CD could be substantiated as originally hypothesized by Crohn in 1934,¹⁰ with the identification of an innate immune response gene that was involved in bacterial recognition (nucleotide-binding oligomerization domain 2 [NOD2]).^{11,12} In only a short time, leveraging the recent description of the human genome, geneticists worldwide have identified approximately 12 CD-associated genes¹³ and in the near future an anticipated 24 to 36 will be identified that confer risk for the development of CD. In fact, among several polygenic common diseases (bipolar disease, coronary artery disease, hypertension, rheumatoid arthritis, type 1 diabetes mellitus, type 2 diabetes mellitus), CD appears to be the polygenic disease in which host genetic composition is the greatest contributor to susceptibility.¹⁴

This not only confirms the centrality of genetic risk in the development of CD but also identifies and confirms the

major immunobiologic pathways, as originally identified, in animal models of IBD that underlie the development of this disease. These pathways include abnormalities of intestinal epithelial cell barrier function, innate immunity (eg, NOD2), adaptive immunity (eg, IL-23R), autophagy (eg, autophagy-related 16-like 1 gene; *ATG16L1*), and each of their respective relationships with the microbial milieu.

The therapeutic implications of these discoveries are profound and amazingly may be outdistanced as investigators worldwide currently race to complete the first sequencing of the human intestinal microbiome (akin to the sequencing of the human genome), which has been largely driven by the need to understand IBD pathogenesis. Since the number of cells in the human body is 10% human and 90% intestinal bacterial, the opportunities for understanding CD and numerous other clinical entities (eg, obesity) at an even deeper level are just on the horizon.

In summary, Crohn et al¹ had not “witnessed the evolution of a Frankenstein monster” as Crohn² wrote in 1957, but rather a profound initiation of investigations to understand and thus treat not only CD but a large number of other immune- and bacterially mediated clinical problems that will be benefited by insights derived from the intense investigation of the etiopathogenesis of the disease described by Crohn et al.¹

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