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World J Gastroenterol 2005;11(26):4127-4128
World Journal of Gastroenterology ISSN 1007-9327

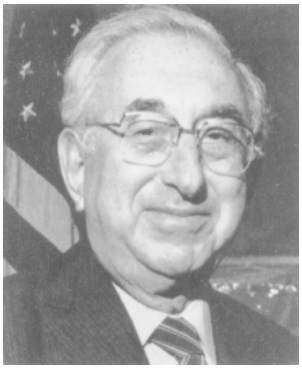
• *SCIENCE LIFE* •

Inflammatory bowel diseases: From the mystical to the cellular and now the molecular

Joseph B. Kirsner

Joseph B. Kirsner, The Louis Block Distinguished Service Professor of Medicine, Department of Medicine - Section of Gastroenterology, The University of Chicago, IL 60637, United States
Received: 2005-04-10 Accepted: 2005-05-23

Kirsner JB. Inflammatory bowel diseases: From the mystical to the cellular and now the molecular. *World J Gastroenterol* 2005; 11(26): 4127-4128
http://www.wjgnet.com/1007-9327/11/4127.asp



Joseph B. Kirsner, Evolution of our understanding of inflammatory bowel diseases: From the mystical to the cellular and now the molecular.

'Science (IBD) is moving but slowly, slowly creeping on from point to point'.
Alfred Lord Tennyson (1809-1892)

It is of interest in an era of increasing biomedical sophistication to recall that a relatively short time ago, early in the 20th century, 'simple' ulcerative colitis was an obscure 'medical curiosity' emerging slowly from an unknown past. Crohn's disease was yet unidentified as a separate entity although careful review of the IBD literature documented its early presence, masquerading as 'intestinal tuberculosis'. Into the 1930s, the etiology and pathogenesis of ulcerative colitis and Crohn's disease were unknown, and investigative hypotheses were scarce. Therapeutic resources were limited and treatment was primitive. At a time of limited biomedical knowledge and minimal clinical awareness, unsubstantiated views prevailed, including 'vague reactions to foods' (sugar, margarine, corn flakes), deficiency of a 'protective factor' in pig intestine, and psychiatric disease.

The position of inflammatory bowel diseases in the medical world today is vastly different. Ulcerative colitis and Crohn's disease are now recognized worldwide, are frequent subjects at medical meetings and increasingly provide the focus of important clinical and laboratory research. Indeed, few diseases in gastroenterology present as varied an array of investigative opportunities. This dramatic change began in the mid-20th century with the increasing support of biomedical research and the subsequent growth of the basic sciences, highlighted by the adiscoveries of sulfonamides in the 1930s, antibiotics in the 1940s, and ACTH and adrenocorticosteroids in the 1950s. The entry of young physicians into gastroenterology during the 1930s and 1940s, trained in the rigors of basic research and controlled clinical study, contributed to this advance. Progress accelerated following the establishment of the General Medicine Study Section of the National Institutes of Health in 1956, which subsequently provided a major source for support of research in gastroenterology, the growth of academic medicine, and the establishment of the Crohn's and Colitis Foundation of America. By the 1970s, sufficient new clinical and scientific information on IBD had been accumulated to justify a comprehensive publication on ulcerative colitis and Crohn's disease, the 1975 1st Edition of *Inflammatory Bowel Diseases,* a volume of approximately 400 pages, with contributions from 25 authors. Subsequent editions of *Inflammatory Bowel Diseases*, appearing approximately every five years, documented the increasing depth and sophistication of clinical and scientific knowledge of ulcerative colitis and Crohn's disease. The 3rd Edition of *Inflammatory Bowel Diseases* in 1985, involving 44 authorities, had doubled in size and included chapters on the nature of intestinal defenses, the M cell, early information on immunologic and genetic aspects of ulcerative colitis and Crohn's disease, as well as advances in the pathology, radiology and endoscopy of IBD, and its improving medical and surgical treatment. Psychiatric and other early 20th century hypotheses had been replaced by concepts based in the disciplines of epidemiology, microbiology, immunology and genetics.

Into the 1990s, with more investigators involved, knowledge of the inflammatory bowel diseases increased exponentially. Etiologic possibilities, as outlined by R Balfour Sartor, now were more definitive, including persistent pathogenic microbial infection, enhanced intestinal mucosal permeability, 'dysbiosis' or the altered balance of protective bacteria *vs* aggressive commensals, and 'dysregulated' immune responses, leading to loss of oral tolerance to commensal bacteria and aggressive cellular activation. Academically based IBD centers generated more focused research and controlled therapeutic trials. IBD research in the laboratory had advanced from the study of tissues and epithelial cells to cellular biology and cellular constituents. Chapters now included the biologic nature of the IBD tissue reactions, the gut mucosal immune system and more advanced immunological and genetic mechanisms. Ulcerative colitis and Crohn's disease had become features of national and international medical meetings attracting large audiences.

The 1999 5th Edition included more than 70 authorities

submitting increasingly diverse chapters on epithelial cell function in health and disease (including heat shock proteins, and trefoil peptides), cytokines, chemokines, growth factors, eicosanoids and other bioactive molecules in clinical IBD and experimental intestinal inflammation, leukocyte-endothelial interactions, altered intestinal neuromuscular function, and the nature of oral tolerance. Genetic studies had identified susceptibility loci for ulcerative colitis and, most importantly, a locus (now identified as NOD-2) on chromosome 16 for Crohn's disease, particularly involving the ileum, the first gene linked with susceptibility to Crohn's disease. Transgenic and recombinatorial science now facilitated the creation of a variety of experimental animal models seeking to approximate human IBD, thereby enabling the more comprehensive study of intestinal tissue injury. The molecular nature of inflammation now became a prime area of investigation, with therapeutic dividends. After one hundred years of intermittent immunologic research led to the identification of tumor necrosis factor (TNF), an antibody to TNF proved to be a highly effective treatment, though not a cure, for Crohn's disease. Newly recognized bioactive molecules, IL-1, IL-2R, CAMS, addressins, defensins, flagellins, granulysins, selectins, claudins, annexins, guanilyns, laminins, intimins, aquaporins, and microsins now filled the IBD literature. Into the 21st century, additionbal bioactive molecules relevant to intestinal inflammation were identified at a rapid pace: adaptins, fibrillarins, syndecan-1, stromelysin, integrins, galanin-1, tropomyosin, fibroblast growth factor, epidermal growth factor, permeability-enhancing factor, neurotrophins, survivins, ubiquitins and zonulins.

The many pro-inflammatory and immunoregulation molecules, countless cytokines, and other biological substances, generated a series of novel biologic therapeutic agents (CP571, IDEC-131, OPC 6535, LDP02, CDP870 J695), creating a formidable, if not intimidating, array of terms and pathways for the IBD physician and investigator alike. How do these molecules relate to IBD and to each other? Where are the signaling mechanisms and pathways determining their coordinated action? Are they different in ulcerative colitis and Crohn's disease? Does NFκB have both pro-inflammatory and anti-inflammatory actions, also involving trace elements (boron, selenium, vanadium, zinc)? Are there other dominant pro-inflammatory molecules analogous to TNF which can be successfully blocked? What is the possible role of the Peyer's patch microenviroment in the regulation of T cell function? Since the intestinal bacterial flora play a critical role in the pathogenesis of IBD, what might be the abnormalities in the commensal mucosal flora or the defects in the intestinal epithelium barrier leading to chronic intestinal inflammation? The role of human regulatory T cells? The 5q31 cytokine gene cluster? The role of the M cell in the entry of protective or detrimental antigens? The pivotal regulatory role of AP_{20} in intestinal inflammation? The role of the intestinal epithelial barrier in the development of intestinal immunity? The possibility of increasing the production of local secretory IgA antibodies as a protection against bacterial infection and inflammation? The possible involvement of nitric oxide in the inflammatory responses and immune reaction of IBD? The possible role of maternal immunologic memory in predisposing children to IBD and the genetic regulation of the intestinal epithelium? Important clinical issues similarly await resolution: the nature of the environment associated with urban industrialization and its relationship to IBD; and the role of today's 'hygienic home environment' in the vulnerability to IBD among children? Jewell and his colleagues recently have pointed out 'the importance of NOD-2/CARD 15 and the HLA region in determining clinical subgroups of Crohn's disease, which may provide the initial basis for the construction of a molecular classification of Crohn's disease.'

The discovery of new therapeutic approaches, in addition to currently available methotrexate, cyclosporine, antimicrobial compounds, thalidomide, and the adhesion molecule inhibitor heparin, including: growth factors, anti NFκB transcriptional agents, the prostaglandin receptor EP4, anti-A4 integrin antibody, inhibitors of stress-activated MAP kinases, antisense oligonucleotides vasoactive intestinal polypeptide and heterologous hemopoietic stem-cell transplantation. Sartor has raised the possibility of more effective local treatment of IBD via 'targeted delivery of biologically active immunosuppressive molecules by recombinant bacteria colonizing muscosal surfaces.' More immediately available microenvironmental approaches include the resurrection of 'old' treatment probiotics, live microbial food ingredients (lactobacilli, bifidobacteria species) and prebiotics (germinated barley and nonabsorbed carbohydrates) and their newly recognized actions: production of antimicrobials and short chain fatty acids, inhibition of microbial adherence to the intestinal epithelium and restoration of normal intestinal permeability. In classic Karl Popper fashion, the expanding IBD research has generated many new important IBD questions and new research opportunities, necessitating a new IBD 'road map.' Despite the extraordinary progress in scientific information, more fundamental knowledge awaits discovery as the pace and the dimensions of IBD research continue to increase.

The impressive scientific advances in IBD, illuminating fundamental biologic and physiologic aspects of intestinal function, accentuate the importance of the 6th Edition of *Kirsner's Inflammatory Bowel Diseases*, and also defines its purpose: to clarify the new intestinal biology, its relevance to the clinical situation, and provide a launching pad for the remarkable advances towards etiology and the cure of IBD yet to come. *Kirsner's Inflammatory Bowel Diseases*-6th Edition, provides the currently indispensable 'road map' guiding IBD physicians and scientists through the multi-complex IBD labyrinth. Co-editors, Dr. R Balfour Sartor, Professor of Medicine, Microbiology and Immunology at the University of North Carolina, and Dr. William J Sandborn, Professor of Medicine at the Mayo Clinic, have assembled a superb panel of national and international authorities and a 'cutting edge' array of IBD scientific and clinical topics. This book, *Kirsner's Inflammatory Bowel Diseases,* since 1975, has played a vital part in assembling and expertly analyzing for the medical world the increasing 'basic' science and the expanding clinical information and will continue this important role, befitting the status of *Kirsner's Inflammatory Bowel Diseases* as 'the best book in the IBD field.'