What's in a name? The (mis)labelling of Crohn's as an autoimmune disease

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Scientists constantly generate new factual information that they use to derive models of the processes they study. This knowledge often requires the generation of new terms. In medical science, disease labels help to guide research priorities by informing funding agencies of the kinds of investigators and types of studies that are likely to be successful for a specific disorder. In clinical medicine, disease names provide pertinent information that helps to explain why patients are sick, what they can expect, and how treatments are predicted to modify the outcome. For this reason, criteria have been defined to establish that a microorganism is the cause of an infectious disease (Koch's postulates) or that something is a carcinogen (Hill's causality criteria).[1,2] Therefore, putative autoimmune diseases should be subject to a similar degree of scrutiny before we conclude that the disease process is caused by a self-directed host immune response.

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Crohn's disease is referred to as an autoimmune disorder in a large amount of published work—ie, textbooks, internet, or review articles by opinion leaders.[3–5] The acceptance of this disease as an autoimmune disorder is the basis for subsequent rhetorical links (eg, NOD-like receptors have a role in autoimmunity,[6] and autoimmune diseases are increasing as part of the hygiene hypothesis[7]), and is the premise for investigation of what autoimmune diseases have in common (eg, genetics of autoimmunity[8]). Notably, the word autoimmune is not mentioned on some websites about inflammatory bowel disease, and evidence suggests that patients with Crohn's disease have an impaired innate immunity.[9–11] With the widespread use of autoimmune terms for the description of Crohn's disease, with some exceptions, the autoimmune definition might be described as a prevalent viewpoint with incomplete penetrance.

For more on **inflammatory bowel disease** see http://www.ccfa.org/; http://www.nacc.org.uk/

Erroneously, the term autoimmunity is often used for any disease in which the immune response causes tissue injury. The development of autoimmunity requires, as an initial step, the recognition of self-antigens by antigen-specific autoreactive lymphocytes, followed by their expansion to effector cells that then bring about tissue injury. Therefore, in the study of autoimmune diseases the aim is to understand how self-tolerance collapses, enabling the activation of autoreactive lymphocytes. To establish that a disorder is caused by autoimmunity, a set of criteria have been proposed. These criteria, known as Witebsky's postulates, require the demonstration of autoreactive lymphocytes against autologous antigens; identification of the corresponding self-antigen; and the experimental demonstration that this autoimmune process produces a disease that resembles the human condition.[12] In view of the widespread characterisation of Crohn's disease as an autoimmune disorder, we sought clinical data for the first two postulates and experimental data for the third. However, the first criterion has not been met, since only a few patients with Crohn's disease have autoantibodies (atypical antineutrophilic cytoplasmic antibodies 5–25%, pancreatic autoantibodies 27–37%, and thrombophilia-associated antibodies 3–37%[13–15]). The second criterion only applies to a subset of these autoantibodies; the third criterion has not been met for any of these antibodies.

Autoimmune diseases often occur at mucosal surfaces. At such sites, the co-existence with microflora requires a delicate balance of tolerogenic versus effector immunity, and dysregulated responses to colonising microbes might result in autoimmune processes. Autoantibodies are commonly detected in ulcerative colitis, a mucosal disease,[16] in which an estimated 60–70% of patients are positive for atypical antineutrophilic cytoplasmic antibodies.[17] By contrast, Crohn's disease is a transmural disease, in which the pathological changes in the gut wall were originally thought to result from submucosal inflammatory changes.[18] Therefore, although there is good reason to study autoimmune mechanisms in ulcerative colitis, there is little evidence to support a similar primary process in Crohn's disease.

For several reasons, including ambiguous clinical diagnosis, medical specialisation and research funding, Crohn's disease and ulcerative colitis can be pragmatically grouped under the rubric inflammatory bowel diseases. For instance, people with ulcerative colitis can be used as controls in studies of the genetics of Crohn's disease, and vice versa, and this design is equally useful in the investigation of microbial exposures that differ between the two groups. However, there is little reason to believe that these diseases share a common cause. We might risk creating an artificial construct that is not pathophysiologically valid by researching the cause, genetic basis, or microbiota of inflammatory bowel disease. Just as bringing together tuberculosis and asthma as inflammatory lung diseases is unlikely to lead to a new vaccine against tuberculosis or a new treatment for asthma, we argue that joining together Crohn's disease and ulcerative colitis for the purpose of research into inflammatory bowel disease will not mean that knowledge about one disease (such as autoimmunity in ulcerative colitis) can be attributed to the other disease, without a factual foundation.

When a disorder like Crohn's disease responds to anti-inflammatory treatment but does not meet accepted criteria of autoimmunity, we submit that it should preferably be called a chronic inflammatory disorder of

unknown cause, in which case nothing is implied and nothing is assumed. Emerging genetic and immunological data suggest that Crohn's disease is not an autoimmune disorder, and represents instead either an immune deficiency[19] or a secondary immune response to altered intestinal microbiota.[20] Researchers need to weigh the evidence for these new hypotheses with care, before pursuing clinical and laboratory investigations on the basis of the latest label.

Contributors
MAB, MD, and JDL contributed to the literature search and writing of this Viewpoint.

Conflicts of interest
We declare that we have no conflicts of interest.

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References

1 Lowe AM, Yansouni CP, Behr MA. Causality and gastrointestinal infections: Koch, Hill, and Crohn's. *Lancet Infect Dis* 2008; **8:** 720–26.
2 Rothman KJ, Greenland S. Causation and causal inference in epidemiology. *Am J Public Health* 2005; **95** (suppl 1)**:** S144–50.
3 Lettre G, Rioux JD. Autoimmune diseases: insights from genome-wide association studies. *Hum Mol Genet* 2008; **17:** R116–21.
4 Dinarello CA. Interleukin-18 and the pathogenesis of inflammatory diseases. *Semin Nephrol* 2007; **27:** 98–114.
5 Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. *Annu Rev Immunol* 2002; **20:** 495–549.
6 Stetson DB, Medzhitov R. T helper 17 cells get the NOD. *Immunity* 2007; **27:** 546–48.
7 Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347:** 911–20.
8 Sirota M, Schaub MA, Batzoglou S, Robinson WH, Butte AJ. Autoimmune disease classification by inverse association with SNP alleles. *PLoS Genet* 2009; **5:** e1000792.
9 Smith AM, Rahman FZ, Hayee B, et al. Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease. *J Exp Med* 2009; **206:** 1883–97.
10 Seidelin JB, Broom OJ, Olsen J, Nielsen OH. Evidence for impaired CARD15 signalling in Crohn's disease without disease linked variants. *PLoS One* 2009; **4:** e7794.
11 Cooney R, Baker J, Brain O, et al. NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. *Nat Med* 2010; **16:** 90–97.
12 Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 1993; **14:** 426–30.
13 Lidar M, Langevitz P, Barzilai O, et al. Infectious serologies and autoantibodies in inflammatory bowel disease: insinuations at a true pathogenic role. *Ann N Y Acad Sci* 2009; **1173:** 640–48.
14 Seibold F, Mork H, Tanza S, et al. Pancreatic autoantibodies in Crohn's disease: a family study. *Gut* 1997; **40***:* 481–84.
15 Desplat-Jego S, Johanet C, Escande A, et al. Update on anti-*Saccharomyces cerevisiae* antibodies, anti-nuclear associated anti-neutrophil antibodies and antibodies to exocrine pancreas detected by indirect immunofluorescence as biomarkers in chronic inflammatory bowel diseases: results of a multicenter study. *World J Gastroenterol* 2007; **13:** 2312–18.
16 Das KM, Biancone L. Is IBD an autoimmune disorder? *Inflamm Bowel Dis* 2008; **14** (suppl 2)**:** S97–101.
17 Schoepfer AM, Schaffer T, Mueller S, et al. Phenotypic associations of Crohn's disease with antibodies to flagellins A4-Fla2 and Fla-X, ASCA, p-ANCA, PAB, and NOD2 mutations in a Swiss Cohort. *Inflamm Bowel Dis* 2009; **15:** 1358–67.
18 Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathological and clinical entity. *JAMA* 1984; **251:** 73–79.
19 Marks DJ, Harbord MW, MacAllister R, et al. Defective acute inflammation in Crohn's disease: a clinical investigation. *Lancet* 2006; **367:** 668–78.
20 Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009; **9:** 313–23.