

## EDITORIAL

# True or False? The Hygiene Hypothesis for Crohn's Disease

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The "hygiene hypothesis" for Crohn's disease postulates that multiple childhood exposures to enteric pathogens protect an individual from developing Crohn's disease later in life, while individuals raised in a more sanitary environment are more likely to develop Crohn's disease. In this issue of the *American Journal of Gastroenterology*, two Canadian case-control studies come to diametrically opposed conclusions regarding the hygiene hypothesis for Crohn's disease. This difference may be partially related to differences in study population (population based vs hospital based), age of onset, different genetic determinants, urban/rural residence (40% rural vs principally urban), or different exposures from the putative causative agent. As of now, the veracity of the hygiene hypothesis for Crohn's disease is not confirmed.

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The pathogenesis of Crohn's disease is poorly understood, but is believed to involve genetic susceptibility, a triggering exposure, and unchecked mucosal inflammation. The "hygiene hypothesis" centers on the triggering exposure. Much work has been done to identify the inciting agent, whether it is a microbe, a dietary toxin, or a component of cigarette smoke, but investigations in humans and animal models have been inconsistent. With the hygiene hypothesis, it is theorized that a lack of exposures to enteric pathogens makes one susceptible to Crohn's disease (1–3). Conversely, multiple childhood infections and poor hygiene protects one from developing Crohn's disease by allowing the host to develop tolerance or immunity to agents that could trigger Crohn's disease later in life (4, 5). Interestingly, the first Crohn's disease gene identified, NOD2/CARD 15, is involved with the innate immune system and the response of monocytes to a bacterial challenge (6). The abnormal and unchecked inflammatory response that may occur in individuals with NOD2/CARD15 mutations is likely to be involved with the pathogenesis of Crohn's disease. Furthermore, countries with poor sanitary conditions have a low incidence of Crohn's disease (7). It is thought that endemic parasitic infections may favorably affect the immune system so as to prevent disease. Parasitic infections are known to stimulate T-helper type 2 (Th-2) cells, which could in turn downregulate Th-1 cells and prevent the exaggerated Th-1 response seen with Crohn's disease (8). Building on this theory, the ova of *Trichuris suis*, pig whipworm, have been successfully used to treat Crohn's disease patients (9).

In this issue of *The American Journal of Gastroenterology*, two separate Canadian case-control studies come to very different conclusions regarding the hygiene hypothesis and Crohn's disease. Bernstein and colleagues used the University of Manitoba IBD Research Registry to compare 364 adult Crohn's disease patients with a group of population-based controls using a postal survey (10). Crohn's disease patients were significantly less likely than controls to have

lived on a farm, to have drunk unpasteurized milk, to be a first-generation Canadian, and to have been exposed to cats before the age of 5 yr. The household size of Crohn's disease patients was significantly smaller than those of controls (4.5 vs 5, respectively). Even after controlling for other factors, the odds of developing Crohn's disease was reduced 67% by being a first-generation Canadian, reduced 34% by living with cats as a child, and reduced 13% for each additional household member during childhood. These findings support the hygiene hypothesis. Interestingly, infection with *Mycobacterium avium paratuberculosis* (MAP), an agent postulated by some as a possible causative agent of Crohn's disease, is often associated with living on a farm, particularly farms that raise cattle, and drinking unpasteurized milk (11). Whether or not MAP is a causative agent or a surrogate marker for another agent contracted from farms and contaminated food is yet to be determined, but the findings in this study would argue against the MAP hypothesis.

Alternative results are presented by Amre and colleagues from Montreal in a hospital-based, case-control study of 194 newly diagnosed Crohn's disease patients under the age of 20 yr and an equal number of controls from an orthopedic clinic matched on time period of visit and geographic area of residence (12). Potential exposures were ascertained by means of a structured interview of parents or older patients. Crohn's disease patients were more likely to have had pets and physician-diagnosed infections early in life and less likely to have had access to a personal towel. In multivariate analysis, access to a personal towel reduced the odds of Crohn's disease by 53%, while having pets or physician-diagnosed infections doubled the risk. Furthermore, the higher the ratio of household rooms to household members, the lower the risk for Crohn's disease. These results appear to directly contradict the hygiene hypothesis. In fact poor hygiene may contribute to the pathogenesis of Crohn's disease.

It is not obvious why these two studies should have such different results. The methodologies of each are similar, but minor differences exist. One is population based (10) (a preferred group of patients) and one is hospital based (12). One questionnaire was mailed (10), while the other was administered in person (12). The Manitoba study of patients of all ages may have been subject to a higher degree of recall bias than the Quebec study of pediatric patients because there was a longer interval between the exposure of interest and the study itself. There certainly could be differences in genetic determinants among these populations, but NOD2/CARD15 status was not assessed. There may have been important socioeconomic differences in these two populations—presumably the study from Montreal was principally from an urban population, while the Manitoba study was only about 60% urban. Finally, there may have been different rates of exposure of the putative causative agent, making it seem as though the hygiene hypothesis is supported or refuted, when in actuality it had no effect. Obviously, the question of the hygiene hypothesis in Crohn's disease is unsettled. Much work still needs to be done to determine if childhood exposures are truly important in the pathogenesis of Crohn's disease.

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