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Hygiene hypothesis in inflammatory bowel disease

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The word "hygiene" is defined as "conditions or practices conducive to maintaining health and preventing disease, especially through cleanliness" [1]. The etiology of inflammatory bowel diseases like ulcerative colitis (UC) and Crohn's disease is unknown. We will focus on UC. The lack of complete penetrance of UC among monozygotic twins and the absence of a family history in the majority of UC cases has always implied that factors in the environment must play an important causative role. Furthermore, the disease has always been more common in the developed than in the developing countries. This geographic difference in the prevalence of UC has spurred the hypothesis that reduced exposure to childhood infections (enteric antigens) might lead to improper development of the immune system in those residing in developed countries. It is believed that modern living conditions cause defective maturation of regulatory T cells and regulatory antigen-presenting cells. Subsequently, chronic intestinal inflammation evolves after an alleged microbiological insult in genetically susceptible individuals [2]. Various proxy markers of hygiene have been proposed to explain the geographical difference of UC incidence. Controlled studies in UC patients over the last twenty years have examined possible associations with such interrelated factors as access to running water, hot water taps, sanitation, overcrowded living conditions, family size, pregnancy and perinatal factors, lack of breast-feeding, sibship birth order, sharing of bedrooms, rural environment, childhood bacterial infections and parasites, household pets, swimming, diet (including fast food), exposure to antibiotics, immunization, medications, dental care, income, education, industrialization, indoor occupation, and so on, with varying results. Nonetheless, the increased presence in Crohn's disease patients of NOD2/CARD15 that codes for a protein involved in innate immunity responses to bowel bacteria, and the inability to provoke inflammatory bowel disease in sterile animal models, does strengthen the possibility of the hygiene hypothesis being in operation, also in UC patients.

Several detailed reviews of studies of the hygiene hypothesis have been published in recent years [2-4]. The studies have recurring limitations. Cross-sectional studies of this subject are inherently retrospective over many years or decades, and are thus subject to a strong recall bias. Furthermore, lack of accessible medical documentation can mask important differences between subjects and controls, and this is quite likely in third world countries with limited budgets. Many of the factors studied are interrelated and impossible to separate. Sample size may be a major problem where UC is uncommon or where access to specific populations is limited. For example, an impressive Israeli study of a 400,000-strong cohort of army recruits showing that male gender, urban upbringing, and small family size were significantly associated with a higher incidence rate of UC eschewed the inclusion of a large population of orthodox women likely raised in more crowded conditions from the studied population [5]. The evidence for a causal link between diet and UC is tenuous since dietary histories from the childhood years are often inaccurate [3]. Breastfeeding however protected against UC onset in most studies, possibly through the antibacterial effect of lactoferrin on gut *Escherichia coli* [4]. Birth order hierarchy associated with UC has given conflicting results [5,6]. Early-life exposure to respiratory and gastrointestinal infections had a strong negative association with UC development in a Spanish cohort [7]. However, in a nine-country case study with 197 UC cases where childhood respiratory infections were more common, it was not clear whether the infections preceded the onset of UC [8]. *Helicobacter pylori* (*H. pylori*) infection is rife in crowded communities. The low seroprevalence of *H. pylori* of 18% in UC cases compared with 43% in controls was suggestive evidence for a protective role of exposure to childhood infections [9]. The fault in this theory is that *H. pylori* is not a microbe of the intestines and its association with other infections was not determined. Nonetheless, *H. pylori* DNA was found in tissues from UC patients [10]. A comprehensive retrospective population-based controlled study from Manitoba in Canada compared 217 UC patients with 433 healthy controls but yielded negative results [11]. Thus, it was found that UC patients had a similar birth order to controls, family size was smaller than controls, and a history of having quit smoking did not reach statistical significance. In a different theme, attention has been focused on soil-borne helminths that play an immunoregulatory role in the intestinal microbiota in animal models. Of note, helminths were postulated to have a protective role in the development of UC, that disease being more common in societies where helminth infestation has become rare. Indeed, administration of *Trichuris suis* (pig whipworm) ova has been proposed as a therapy for UC patients [12], but its efficacy is debatable and much further study is indicated. Taken together, the many works on the hygiene hypothesis in UC give suggestive but

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often conflicting data and as yet the causal role for most of these factors remains unclear. Given the preponderance of environmental over genetic factors in the pathogenesis of UC, there is clearly a need for more investigation in this area.

We therefore compliment Sood *et al* [13] who in this issue of the *Annals of Gastroenterology* have examined the possible relevance of the hygiene hypothesis in an area in northern India where an increasing incidence of UC has been observed alongside a rise in the standard of living conditions. This is an interesting study where a structured questionnaire was administered to 518 consecutive UC patients attending a tertiary care hospital in Punjab and 188 matched controls derived from a variety of sources during the years 2005 to 2009. The questionnaire was administered by a blinded trained medical officer in an interview with the patients or controls. For participants under 18 years of age the questionnaire was administered to the parent or guardian. Recall information was limited to items that would be easy to remember, such as the number of siblings etc. 90% of patients were Sikhs and Hindus. For religious reasons there were few smokers in the study, preventing analysis of smoking patterns. As confounding factors, there were significantly more females in the UC group and the education status of patients was higher than in the controls. Univariate analysis indicated that UC cases had less access to private beds, were less likely to wash their hands before eating, had less access to flushing toilets, and owned a pet more often. Interestingly, there was no apparent difference in the sources of drinking water. Upon multivariate analysis however, after allowing for confounders, having a personal bed and flushing toilet facilities were inversely related to the onset of UC, which refuted the hygiene hypothesis. Possessing a pet however was linked with an increased risk of having UC in later life, as was having a death in the family. Large family size was not associated with risk for developing UC. Overall, there was little evidence to support the hygiene hypothesis. Nonetheless, the merit of this study lies in the fact that it was carried out in the very sort of area that is desired in such studies, as the authors rightly point out: areas undergoing rapid economic improvement and showing a rise in the incidence of UC.

Returning to environmental factors in general, only active cigarette smoking [14] and having an appendectomy (or more likely appendicitis) in early life [15] have been shown consistently to impact negatively on the later incidence of UC. As indicated, multiple other factors have given erratic results. Thus, much further work is required to determine whether the lesser potential of exposure to microorganisms and its adverse effect on the development of innate immunity, as expounded by the hygiene hypothesis, is valid in UC.

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