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EDITORIAL

# Environmental factors associated with Crohn's disease in India—there's more to it than meets the eye

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Inflammatory bowel disease (IBD) has traditionally been considered a Western disease. However, the last 2 decades have seen an increase in the reports of both ulcerative colitis (UC) and Crohn's disease (CD) from Asian countries [1]. Most of these reported series have been hospital-based with only one population-based survey by Sood et al. [2]. Time-trend data from Japan and China indicate a dramatic increase in the incidence of UC and a more gradual increase in that of CD [1]. In addition, a higher incidence of UC has been noted amongst second-generation Asian migrants in the United Kingdom [3]. This increase in the incidence and prevalence of IBD in Asia mirrors the epidemiological trend in the Western world that occurred 50 years ago Though increased awareness of IBD, better diagnostic facilities, and the growth of the specialty appear to have played a major factor for this increase in reported incidence, there is probably also a genuine increase in the incidence of both UC and CD [1].

The role of the changing environment in the pathogenesis of IBD is likely to be a major contributory factor for the increase in this condition in Asian countries. Improvement in sanitation and public health, while inevitably leading to a decrease in the burden of infectious diseases, have been shown to be associated with an increase in autoimmune and chronic inflammatory diseases [4]. The environmental factors which are well-recognised as associated with IBD include smoking, diet, stress, microbial agents, appendicectomy, social status and intestinal permeability to fermentable oligo-, di- and mono-saccharides and polyols (FODMAPs).

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In this issue of the *Journal*, Pugazhendhi et al. [5] from a tertiary referral hospital in southern India report a case–control study that looked at the association of surrogate markers of environmental hygiene in patients with CD compared to age-linked healthy controls. They found that urban residence, safe drinking water and availability of piped water (all indicators of better hygiene) were positively associated with CD whereas consumption of fish (a source of ω-3 polyunsaturated fatty acids) and exposure to cattle (an indicator of poor hygiene) were negatively associated with CD. The message of the study is clear—improved hygiene was associated with a higher prevalence of CD in this area.

The 'hygiene hypothesis' [6] of IBD is based on the observation that incidence of IBD has increased in both developing and developed countries with improvements in hygiene during the 20th century. It claims that raising children in extremely hygienic environments negatively affects immune development and tolerance to a variety of antigenic challenges, which in later life predisposes them to develop chronic inflammatory diseases such as IBD. However, the evidence for the contribution of several factors included in this hypothesis has never been analyzed in a systematic manner. In the present study too, except for diet (fish oil), all the other factors found to be correlated with the development of CD, can be linked to gut microbiota and immune tolerance.

The mucosal surface of the human gastrointestinal tract is approximately 200–300 $m^2$ in area and is colonised by $10^{14}$ bacteria of more than 1,000 different species and subspecies [7, 8]. The phylogenetic diversity of the human gut microbiome allows an individual microbial fingerprint to be created. This adult profile is usually well established by the age of 2 years [9, 10]. Though it remains unclear whether the overall microbial fingerprint of the gut flora in patients with CD is different from controls, the relative

numbers of at least certain bacterial strains have been shown to differ in this disease [11–13]. Though a single pathogenic organism has never been found in patients with CD, adherent invasive *Escherichia coli*, AIEC, have been detected in some patients [14]. In addition to *E. coli*, an increase in anaerobic bacteria such as Bacteroides spp. has been shown in patients with CD.

Furthermore, an imbalance in the normal gut microbiota without actual acquisition of a particular infectious organism may be responsible for the development of IBD. In fact, metagenomic studies have shown that entire classes of bacteria are lost or over-represented in patients with IBD [15]. In animal models of colitis, the exposure of germ-free animals to bacteria has been clearly shown to induce intestinal inflammation. In addition, timing of exposure of an individual to various bacteria may also be important. For instance, exposure to a pathogen in a small dose during early childhood may be associated with induction of immune tolerance, since regulatory dendritic cells may fail to induce a proliferation of the regulatory T cells in the terminal ileum. In addition, there is a complex interplay between mucosa-associated bacteria, mucosal immunology and mucosal barrier permeability, whereby an increase in mucosal permeability (well known in patients with CD and their relatives) often leads to a continuous, persistent antigenic challenge resulting in an exaggerated and prolonged/persistent inflammatory response in the mucosa.

So what do the results of the present study add to the knowledge that is already available? Being an observational study, it does not achieve much, except that it supports the previous studies that have looked at various aspects of the hygiene hypothesis. Further, the impact of environmental deprivation in the developing world on CD may be difficult to compare with that in the western world. A definitive answer is likely to come from bacterial fingerprinting studies on the gut flora from patients with CD and age-matched controls, both of whom have been exposed to similar environmental conditions, and by linking these data to genetic susceptibility, disease phenotype, smoking etc. Some initial data using pulsed-field gel electrophoresis profiles of *E. coli* strains from patients with CD, UC and controls show a well-defined clustering, supporting the idea of a disease-associated gut microenvironment [16]. With the recent developments in sequencing techniques for gut microflora, and microRNA arrays the next few years should be quite exciting, and lead to newer clues to the role of environmental factors in the etiopathogenesis of IBD.

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