LETTERS TO THE EDITOR

What caused the increase of autoimmune and allergic diseases: A decreased or an increased exposure to luminal microbial components?

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Received: 2006-12-06 Accepted: 2007-01-16

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Key words: Autoimmune disease; Allergic diseases; Hygiene hypothesis; Intestinal permeability; Luminal microbial components

Qin X. What caused the increase of autoimmune and allergic diseases: A decreased or an increased exposure to luminal microbial components? *World J Gastroenterol* 2007; 13(8): 1306-1307

<http://www.wjgnet.com/1007-9327/13/1306.asp>

TO THE EDITOR

The dramatic increase of allergic and autoimmune diseases such as asthma, atopic dermatitis (eczema), allergic rhinitis, inflammatory bowel disease (IBD, including both Crohn's disease and ulcerative colitis), multiple sclerosis, and insulin-dependent diabetes mellitus (type I diabetes) in the developed countries in the last century^[1-3] is a big puzzle. "Hygiene Hypothesis" was proposed more than two decades ago and it suggested that the increase in these allergic and autoimmune diseases is caused by the aberrant development and response of the immune system due to a reduced exposure to microorganisms along with the improved hygiene^[2-4]. Interestingly, recent studies revealed that these allergic and autoimmune diseases are closely related to the microbes in the gut^[5]. For instance, even asthma, an allergic reaction of the lung to inhaled antigens, is closely related to a reduced exposure to foodborne and orofaecal microbes, rather than the amount of allergens in the air or the exposure to airborne microbes^[5-7]. It is known that bacteria in the gut could be 10 times in number of the eukaryotic cells of the body^[8]. Therefore, it would be not too surprising that microbes in the gut may have a great impact on these autoimmune and allergic diseases.

On the other hand, many studies revealed that an

increase in intestinal permeability was shown in patients with these autoimmune and allergic diseases, such as those with IBD^[9,10], multiple sclerosis^[11], type I^[12,13] (but not type II^[14]) diabetes, asthma^[15,16], and atopic eczema^[17,18]. The increased intestinal permeability in these patients seems to be a prerequisite rather than a consequence of these diseases, as it could precede the clinical onset of these diseases^[12,19,20]. In addition, increased intestinal permeability was also seen not only in healthy relatives^[10,21], but also in spouses of these patients^[10,22]. An increase in intestinal permeability would result in an increased infiltration of the luminal components. Therefore, it would be reasonable to ask what have caused the increase of these autoimmune and allergic diseases: is it a decreased exposure to luminal microbial components due to the improved hygiene, or an increased exposure to luminal microbial components due to the increased intestinal permeability?

There is a large amount of microbes in the gut. The endotoxin in gut bacteria could be enough to kill the host thousands of times over^[23]. Therefore, it would be more likely that the tightness of the gut barrier would have played a more important role in determining the extent of exposure rather than the absolute number of microbes in the gut. Actually, there could be an intrinsic link between the increased intestinal permeability and improved hygiene. An effective inactivation of the digestive proteases depends on gut bacteria^[24,25]. The increased intestinal permeability could be a result of the improved hygiene and a reduction in gut bacteria, by a mechanism such as the impaired inactivation of digestive proteases by gut bacteria, and thus an over-digestion of gut barrier. A reduction in gut bacteria not only can be the result of improved sanitary conditions, along with the more clean food and water, it also can be caused by an inhibition of gut bacteria by factors such as the widely used sweetener saccharin^[26]. Interestingly, saccharin consumption correlated well with the ups and downs of the IBD, and probably had played a causative role in IBD^[27,28]. This would lead us to raise a more general question: Will the improved hygiene and thus a reduction in gut bacteria necessarily result in a decreased exposure to luminal microbial components, the fundamental assumption of the "Hygiene Hypothesis"^[29,30]. Further study in this area would be worthwhile. It would help better understand why both Th1 type diseases such as Crohn's diseases and type I diabetes, and Th2 type diseases such as ulcerative colitis and atopic diseases increase with the improved hygiene^[29,30].

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