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Microbes and Infection xx (2017) 1–9

www.elsevier.com/locate/micinf

Review

Evolution of the hygiene hypothesis into biota alteration theory: what are the paradigms and where are the clinical applications?

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Received 7 August 2017; accepted 2 November 2017
Available online ■ ■ ■

Abstract

For thousands of years, changes in human cultures have altered the biota associated with the human body, and those alterations have strongly influenced human health. The hygiene hypothesis has evolved over the past 30 years into a nuanced biota alteration theory, but modern medical priorities and regulatory policies have resulted in tragic underutilization of the acquired knowledge.

Keywords: Biota; Biome; Helminth; Hygiene hypothesis; Microbiota

1. Hygiene hypothesis: historical views and origins of the term

The term “hygiene hypothesis” has been used for decades to describe one of the causes of inflammatory disease in Western culture. David Barker coined the term in 1988 and used the term more than once [1,2] that year to explain an increasing incidence of appendicitis in rural communities. Besides coining a new term, Barker's papers in 1988 provided a potential explanation for an increased incidence of appendicitis. Barker's explanation for appendicitis utilized the widely held view in 1988 that the primary problem leading to allergic disease was *delayed* exposure to infectious agents. According to that model, exposure to infectious agents relatively late in life caused immune disease [3,4]. In 1989, David Strachan again used the term “hygiene hypothesis”, but Strachan changed the paradigm; rather than simply delayed infection, the problem was the absence of specific infections during a critical period of immune development.

Strachan's line of reasoning was at first received with “disdain on grounds of implausibility” [5], but eventually moved thinking in the field into a new and productive direction. The working paradigm has continued to evolve, with the more recent scientific literature showing an appreciation for the role of broad, culturally-induced changes to the life associated with the human body, the human biota, in the induction of inflammatory disease. As Bloomfield et al. noted, “A consensus is beginning to develop round the view that more fundamental changes in lifestyle have led to decreased exposure to certain microbial or other species, such as helminths, that are important for the development of immunoregulatory mechanisms” [6]. Thus, as Bloomfield and others, including Helmby, Maizels, Shoenfeld, Okada, Yazdanbakhsh and Wills-Karp have concluded [7–12], it is not so much a lack of infection, as it is dramatic changes in the symbionts normally associated with the human body that are connected with inflammatory related disease. But as Shoenfeld et al. have pointed out [13], not all infections are created equal, with some infections promoting disease and others preventing

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https://doi.org/10.1016/j.micinf.2017.11.001
1286-4579/

disease. Further, work considering the various components of the biota (e.g., bacteria and helminths) and their relationship to inflammatory disease suggests a complex connection between culture, biota, and human health. In this review, current thinking regarding this connection between culture, the biota, and disease will be discussed.

2. The human biota as one factor among several in the context of culture and inflammatory disease

Alteration of the human biota in modern society has been linked to an array of hyper-immune related diseases involving chronic inflammation [14–17]. This phenomenon can be described by a "biota alteration theory" (or, alternatively, biome depletion theory), which states that alteration of human biota constituents in post-industrial societies leaves the immune system unstable and overly reactive toward harmless and even self-antigens [18–20]. This over-reactivity leads to a wide range of debilitating conditions that include autoimmunity, allergy, digestive disorders, cancer, heart disease, and neuropsychiatric disorders. However, these pandemics of inflammation-related problems in modern culture are certainly not caused by any one factor alone. That is to say, biota alteration theory is not meant to be a stand-alone explanation for the inflammatory diseases of Western culture. Major cultural factors, largely independent of biota alteration, that affect pandemics of inflammatory disease include indoor work environments leading to vitamin D deficiency [21], changes in social structure and other factors that lead to chronic psychological stress [22], sedentary lifestyles, and inflammatory diets. Further, genetic factors and environmental stimuli also contribute to inflammatory disease, as shown in Fig. 1.

3. Complexity in the connection between culture, the human biota, and disease

Numerous components of modern human culture have profoundly altered the array of life associated with the ecosystem of the human body, the human biota (Figs. 1 and 2). Modification of the biota by culture is not as straight forward as decreased infections due to current practices of hygiene. Rather, alteration of the biota began approximately 10,000 years ago, with the development of agriculture, resulting in increased population densities and the rise of "crowd infections" [23]. Although modern hygiene has alleviated that burden to an extent, most crowd infections either did not exist or were extremely rare in the hunter–gatherer tribes that existed prior to the agricultural revolution [23]. Thus, civilization as we know it still has potentially more, not fewer, infections than our hunter–gatherer ancestors, despite the use of modern hygiene practices. The agricultural revolution and urbanization also resulted in a dramatic increase in colonization with various symbionts such as helminths (Fig. 2). Helminths and crowd infections are not the only organisms

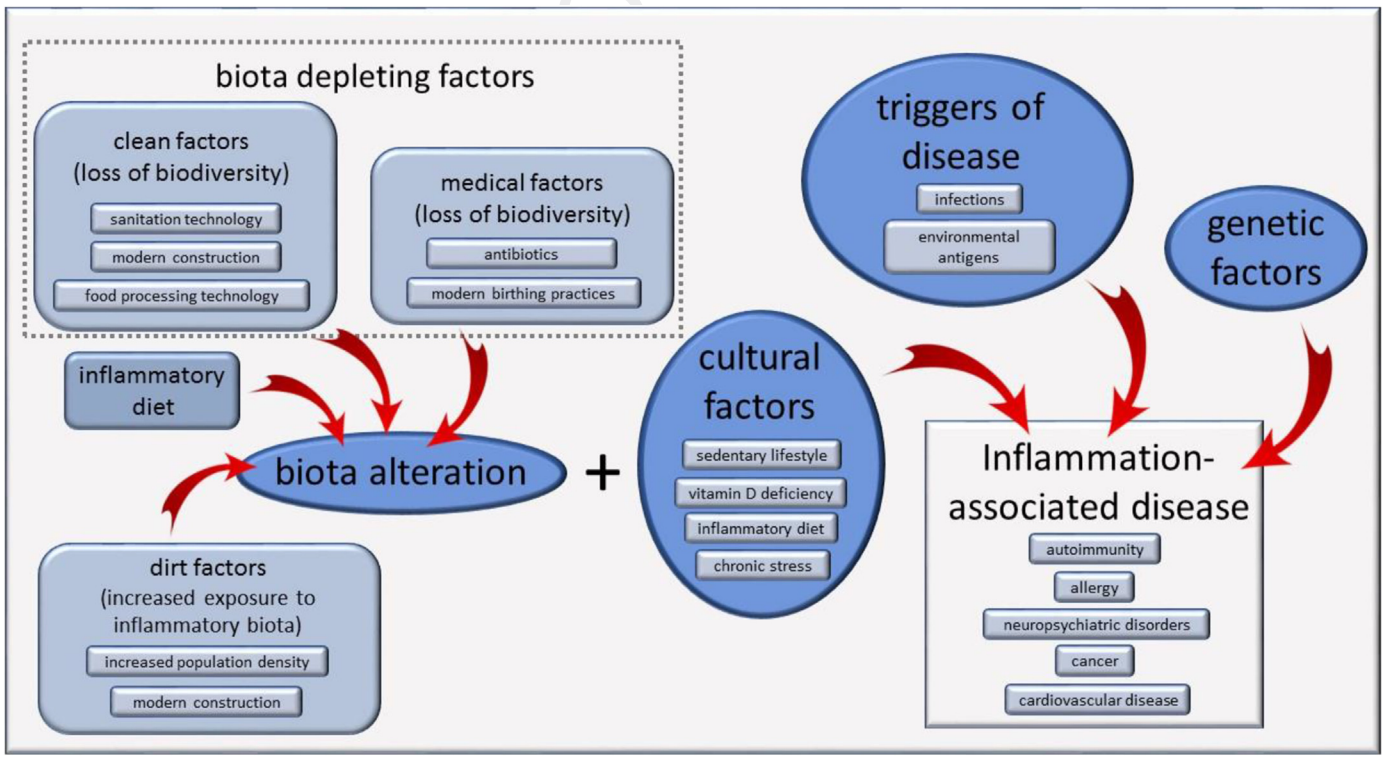

Fig. 1. Complex relationship between culture, biota alteration, and disease. In this model, biota alteration along with other culture-associated factors such as vitamin D deficiency and a sedentary lifestyle are considered to be mediators of inflammatory disease, along with "triggers" of disease (e.g., acute infections or environmental antigens) and genetic predisposition. Diet, however, enters the equation in two places, both acting independently of the biota and also being a primary mediator of biota alteration. Modern sanitation also enters the model in two opposing positions, contributing to biota depletion (promoting inflammation) and contributing to reduced crowd infections (reducing inflammation).

Please cite this article in press as: Villeneuve C, et al., Evolution of the hygiene hypothesis into biota alteration theory: what are the paradigms and where are the clinical applications?, Microbes and Infection (2017), https://doi.org/10.1016/j.micinf.2017.11.001