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

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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.

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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 Helmy, 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 symbions 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...
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 straightforward 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...
affected by human culture. Thousands of years after the agricultural revolution, additional changes during the industrial revolution altered the microbiota, with infant formulas and modern medical practices in obstetrics profoundly altering the microbiota in early life [24]. Further, the diversity of the microbiota can be dramatically and chronically altered in some individuals as a result of the use of antibiotics [25]. However, the largest impact on the microbiota, seen in most individuals as a result of modernization (Fig. 2), is due primarily to a diet rich in fats and processed sugars but low in fiber and a diverse array of nutrients [26]. At the same time, advances in sanitation infrastructure, water treatment, and food preparation technology following the industrial revolution profoundly reduced the biodiversity of the microbiota in the human gut [19,27]. The components of the human biota most heavily impacted by these factors are helminths and protists [19], which are dramatically reduced in numbers and often completely eliminated by modern sanitation and hygiene [28] (Fig. 2).

It is evident that cultural factors affect the biota, which in turn affects the function of the immune system, leading to inflammatory diseases in Western society (Figs. 1 and 2). It is also apparent that specific elements of modern society do not affect all components of the biota in the same way. For example, while hygiene and sanitation have a limited impact on the normal gut microbiota [26], they dramatically reduce or even eliminate larger biota, including helminths (Fig. 2).

Similarly, the Westernized, inflammatory diet has no known effect on helminths, but substantially alters the composition of the microbiota (Fig. 2). With this in mind, it is difficult to conceive of an appropriate term that encompasses only one particular aspect of modern culture (e.g., hygiene) and still describes changes in the biota which affect public health.

Biota alteration is potentially more complex than those changes induced directly by cultural factors. For example, it now seems likely that microbial adaptation to the disease state (Fig. 3) may play a role in a vicious cycle connecting culture and disease. In this model, cultural factors affect the biota, which in turn affects inflammation, and the resulting inflammation feeds back to further affect the biota (Fig. 4). Although an emerging idea that is yet poorly understood, one potential mechanism underlying inflammation-induced microbial alteration may involve the selection of particular microbial communities by the disease state. For example, certain species of bacteria that are found in healthy non-human primates which have naturally occurring short intestinal transit times [29] are the same as those enriched in humans with short intestinal transit times (e.g., those with diarrheal disease) [30]. Thus, the disease state potentially leads to selection of bacteria that are compatible with and potentially "support" the disease state (Fig. 3) in ways that are largely not yet characterized. In addition, adaptation of bacteria to the disease state (Fig. 3) rather than simple selection of existing bacteria may be important and perhaps even more damaging. This idea is
exemplified in the case of obesity, where it has been postulated that microbial adaptation to an inflammatory diet has led to an increased ability of the microbiota to extract absorbable nutrients in some individuals, making those nutrients more available to the host [31]. Applying this principle of microbial evolution to inflammatory bowel disease (IBD), Hansen and Vison have postulated that “the environment of the inflamed intestine causes the bacteria to change/evolve to a more aggressive state that contributes to worsening disease and treatment failure” [32]. Studies evaluating the very rapid evolution of microbes in the mammalian gut support this view. Within a matter of a few years, laboratory bacteria newly introduced into the gut environment acquire new traits and an enhanced ability to live in the gut, while at the same time losing fitness for the laboratory environment [33]. Thus, not unexpectedly, microbiota have the capacity to adapt to environment of the gut. The mechanisms by which such adaptation may provide a “biological inertia” that supports the disease state and hinders efforts at treating disease (Fig. 3) remain a topic for future study.

4. Biota alteration as a more accurate modern replacement for hygiene hypothesis

Our understanding since 1988 has now evolved to the point that discontinuation of the use of the term hygiene hypothesis is warranted except in a historical context [34,35]. Strachan used the phrase originally for its catchy sound much more so than for any nuanced meaning [5]. Indeed, as explained above, the term had already been applied earlier by Barker in a different context. However, at present, the term is inaccurate, misleading, and potentially detrimental to public health efforts [34,35]. The term cannot accurately be applied to current thinking regarding “biota alteration”, or alternatively “biome depletion”, since it is not actually hygiene that is currently causing the primary changes in the biota (as discussed above and in Fig. 1). Further, the complex relationship between hygiene, culture, biota alteration, and disease precludes the use of a term that is both accurate and based strictly on hygiene. For example, personal hygiene and the infrastructure associated with the development of hygiene (sewer systems and water treatment facilities) were historically some of the major drivers of inflammation-induced biota alteration, including loss of helminth colonization. However, in the current Western environment, it would be essentially impossible to acquire long term colonization with most helminths that were historically common in humans (e.g., the giant roundworm, hookworm, human whipworm, or bovine tapeworm) even if an individual completely abandoned all practices of what we think of as hygiene, including house cleaning, bathing and changing clothes. At the same time, decreased hygiene in the current Western environment increases the incidence of crowd...
infections and the abundance of insect-derived antigens, both of which can act as drivers for inflammatory disease. Thus, not only is hygiene only one factor among several that affect biota alteration, but the role of hygiene in biota alteration has changed through time. With this in mind, it seems that for the sake of accurate communication of current ideas regarding science and medicine, it is appropriate to abandon the term “hygiene hypothesis”. Instead, biota alteration is both accurate and descriptive, and can account for a wide range of factors affecting the biota, including those leading to inflammation and those diminishing it.

The hygiene of a century ago resulted in biota changes that can induce inflammatory disease, but hygiene today helps us avoid inflammation-causing factors such as acute crowd infections (e.g., the flu), mold, and insect allergens. This brings to the fore the most compelling reason for abandoning the “hygiene hypothesis” as a term used to describe current thinking in immunology: The idea that hygiene is a driver for inflammatory disease in the public consciousness has potentially damaging ramifications for the public health [35], which is necessarily dependent to an extent on proper hygiene. This point has been expounded upon in some detail by Bloomfield, Rook et al. [35]. It is counterproductive for scientists to use a phrase which is both misleading and dangerous. The fact that it is eye catching and recognized publicly is becoming more of a disadvantage than an advantage. As Strachan pointed out, the term is now an “enfant terrible” [5].

5. From hygiene hypothesis to biota alteration theory

Biota Alteration Theory is supported by numerous epidemiologic studies showing that the incidence of hyper-immune related diseases is drastically higher in populations and in individuals with Westernization-induced biota alteration compared to those without such alterations [14,36]. Conclusive evidence supporting this theory, obtained from direct experimental evidence in animal models and in humans, shows that restoration of the biota prevents or even treats disease [37]. Thus, what began as a hypothesis received with disdain has now evolved in terms of both ideas and unequivocal support. Given the number of studies confirming, for example, that multiple sclerosis is attenuated by the presence of helminths [38–40], it is apparent that biota alteration is indeed one factor that affects inflammatory disease. At the same time, as pointed out above, the theory is not intended to state that biota alteration is the only cultural factor leading to increased inflammatory disease.

6. Biota alteration theory and public health: principles of restoration

The fact that culture-induced biota alteration is an underlying cause of inflammation is extremely encouraging from the perspective of the public health. The underlying problem in this case appears to be vastly more manageable.
than rapidly mutating pathogenic viruses leading to immune syndromes, or sociopolitical conditions leading to poverty, malnutrition, chronic stress, and pollution. Indeed, a very wide range of relatively benign helminths and protozoans have been put forth as potential agents to reverse the effects of biota alteration [41], and apparently healthy microbiota are readily available following routine screening of healthy donors.

Treatment of fundamental causes of disease is preferable to treatment of more proximal causes, and offers the hope of eliminating disease in an efficient and benign manner. Some therapies, including helminth therapy and fecal transplants for recurrent Clostridium difficile colitis [42–47], are designed for replacement of lost components of the biota, and therefore do indeed deal with underlying causes of disease. However, not all biota-based therapies deal with fundamental causes of disease (Fig. 4). Controlled exposure to soil bacteria [48] potentially operates based on the same principle of replacing what was lost, although the potential of restoring exposure to soil bacteria for health and treatment of disease has not been explored. Probiotics and some fecal therapies, on the other hand, operate on a different principle. These therapies generally involve repeated exposures to microbiota in patients whose disease state (e.g., inflammatory bowel disease) was not evidently caused by a loss of their native microbiota. As such, these therapies do not deal with fundamental causes of disease. However, they may interact with the disease process at a level more distal than do typical pharmaceutical interventions (Fig. 4).

We argue that several principles should guide our application of biota alteration theory to the public health. The first and foremost principle is to deal with ultimate causes of disease when possible, as described above. The second principle that should be considered when applying biota alteration theory to the public health is to avoid reductionism. While reversing the effects of biota alteration on human immune function must be a high priority, it should be conducted in conjunction with effective campaigns to mitigate other fundamental causes of inflammation. With that in mind, public policy needs to aggressively address not only the root causes of biota alteration, but also the factors which drive low levels of vitamin D, sedentary lifestyles, chronic psychological stress, and inflammatory diets.

7. Shaping therapy around biota alteration theory versus traditional pharmaceutical-based drug discovery and development: Is there a compromise?

The advantage of biota-based therapies over pharmaceutical-based approaches is grounded in the ability of biota-based therapies to address relatively more distal causes of disease, as described above (Fig. 4). As with effective exercise regimens, embracing a healthy diet, and supplementation with vitamin D, biota based therapies are typically directed at restoring a healthy ecosystem to the human body, eliminating “environmental mismatches” that cause disease [37]. Thus, these approaches attempt to recapitulate the environment that humans require for health. As such, they are not as prone to adverse side effects that come from blockade of proximal causes or blockade of symptoms as is typically accomplished by pharmaceutical intervention [49].

Considerable effort and attention has been directed toward an obvious half-way point between biota-based therapies and traditional pharmaceutical drug discovery/development: The development of symbiont-derived drugs. Efforts directed at developing microbe-based drugs abound. Intriguingly, the development of an isolated and stable helminth-derived molecule is one of the clearest examples of a potential therapeutic that could, if it works, mimic the beneficial effects of the naturally occurring organisms while yet holding several potential advantages over the organisms themselves. Such a hypothetical drug would easily fit into the current drug pipeline, avoiding the problems that intact therapeutic helminths encounter because they do not fit well with current regulatory policy [49] or with current financial incentives for drug development [50]. Further, the stigma associated with all helminths, widely assumed to be intestinal parasites even if they don’t induce disease [51,52], can be avoided. We, however, have contended that such efforts to develop helminth-derived drugs are misguided [19]. Our view is that exquisitely complex interactions between two biological systems cannot be recapitulated by pharmaceutical intervention. Helminth-derived molecules with specific biochemical targets may in some cases work as an immunosuppressive drug, perhaps attenuating the symptoms of a particular disease. However, no drug can train and modulate immune function as do host–symbiont interactions [49]. Thus, it is our view that even ideal results from attempts to develop helminth-derived drugs will be disappointing compared to results that can be obtained using intact organisms. Further, as we and others have maintained [20,53], humankind eventually needs to move beyond the idea that helminths are best used as a drug or a therapy. Rather, we need to embrace the view that helminths are a necessary component of the ecosystem of a healthy body, and that helminths should be cultivated for population-wide biota restoration. Attempts to develop helminth-derived drugs are, by intent, designed to treat disease, not to restore health to the population. As such, efforts to produce helminth-derived drugs will not help achieve the long-term goals of disease prevention, and may indeed provide a distraction from such goals as they divert resources that could be used for biota-based restoration and maintenance.

8. Biota alteration theory and public health: where do we stand?

The simplest approach to alleviating inflammatory disease resulting from biota alteration is relatively straightforward in design: restore what is lost. Although biota replacement is a straightforward approach and is scientifically sound, progress has been shockingly slow. Perhaps the best characterized example of such an approach is the replacement of fecal...
bacteria for patients with recurrent \textit{C. difficile} colitis, a debilitating and sometimes deadly disease that occurs when the microbiota fails to recover after medical use of antibiotics. Fecal replacement from a healthy donor was first shown to effectively rescue patients in 1958 [54] in a study that was ground breaking for Western medicine. In that landmark study, Ben Eiseman, founding Chief of Surgery at Denver General Hospital [54], argued that “reintroduction of the bacteria, viruses, and bacteriophage normally found in the colon might re-establish the balance of nature.” Eiseman contended that his procedure, which would eventually become known as the fecal transplant, would lead to a decrease in the growth of potentially harmful and antibiotic-resistant organisms. Eiseman’s successes with the fecal transplant were corroborated by several independent hospitals in California in the early 1960s [55].

Despite the early success of fecal transplants in resolving an otherwise deadly disease, fecal transplants are only now becoming widely accepted. Although the 60-year old procedure was named one of the top ten medical innovations for 2014 by the Cleveland Clinic, the procedure is still not the standard of care for patients with recurrent \textit{C. difficile} colitis, and many patients still die of the colitis without being aware that an effective therapy exists.

Other biota-based therapies have not fared better. Helminth exposure was shown in preliminary studies to be effective for the treatment of IBD resistant to pharmacological therapy [56,57] and of multiple sclerosis [58] in 2005 and 2007, respectively. Yet, the follow-up has failed to evaluate the potential of helminth therapy. Subsequent efforts have been primarily limited to the testing of only one helminth, and those tests were eventually halted, apparently due to technical problems associated with the storage of the helminth that may have rendered it ineffective [59]. Our own studies suggest that helminth therapy may be effective for the treatment of Parkinson’s disease and for such common inflammation-associated conditions as migraine headaches and anxiety disorders [59,60], but the effects of helminths on these conditions have not been examined in clinical trials. At present, no helminth is available for approved therapeutic use, and commercial development of helminths for therapeutic use is minimal, despite more than 10 years having passed since the first studies indicated that the organisms may be effective for the treatment of diseases that are otherwise difficult to treat or even untreatable.

The origins of the probiotics concept dates back to 1907, predating helminthic therapy and even fecal transplants [61]. Experiments using \textit{Lactobacillus acidophilus} as a dietary supplement were conducted in the 1920s and 30s. However, despite this long history, use of probiotics in clinical practice is not standard of care, even for situations where probiotics are known to impart benefit to the patient. For example, even though certain probiotics are known to attenuate some of the potential adverse effects of antibiotic use [62], co-administration of probiotics with antibiotics is not the current standard of care.

\section{Biota alteration theory and public health: what needs to be done?}

Biota-based therapies face significant hurdles because they do not fit well with current regulatory policy [49]. Our naturally occurring symbionts, when used for therapeutic effect, occupy a dead zone between human tissue and pharmaceuticals. Attempts to regulate the organisms as pharmaceuticals using laws written with a profit-driven pharmaceutical industry in mind are some of the major hurdles at the present time [49]. Current financial incentives for drug development and even for medical practice are difficult to apply to naturally occurring organisms [50,63]. We have suggested that major legislative correction needs to occur [49]. Laws need to be written which effectively weigh and consider the potential harm of biota-based therapies with the ongoing harm occurring as a result of biota alteration. The laws and regulations must take into account the view that health rather than profit should drive the biomedical research system [49]. We argue that the goals of health and profit can be diametrically opposed in biomedical research, and that this opposition is currently damaging the public health [63].

\section{Biota alteration theory: research that needs to be conducted}

At present, with clinical application of knowledge lagging sometimes decades behind the clinical application of Biota Alteration Theory, the scientific community is in danger of being seen as conducting biomedical research for the sake of science, without the public health in mind. Certainly this is far from reality. Scientists developed the hygiene hypothesis almost 30 years ago and are considering Biota Alteration Theory today because we are profoundly interested in attenuating pandemics of inflammatory disease that afflict Western society. Indeed, the basic science of biota alteration theory would likely receive no attention in the absence of any disease. Interest in studying multiple sclerosis would be limited, for example, if everyone was colonized with a benign helminth and, as predicted, the disease was eradicated. Indeed, a vast array of fascinating phenomena exist in this universe and await our study, but have largely been put on a back burner for the moment as we study a much less interesting but pressing concern: organisms that are unhealthy because their environment has been dramatically altered in readily apparent and easily reversible ways. Although we have observed dozens of differences between biota-depleted and biota-enriched animals [64–66], we posit that the most urgent questions in the field are clinical in nature [20] rather than molecular/genetic. Which organisms work best, which therapies work for treatment, and which approaches can only be used for prevention? Other questions that likely need to be addressed include whether genotype affects the need for particular components of the biota. For example, is it possible that groups whose ancestors lived in tropical climates for many millennia have different requirements for...
helminths that those whose ancestors lived in temperate, arid, or polar climates?

11. Summary

In this review, we summarize the evolution of thinking surrounding the induction of disease as a result of culturally-induced biota alteration. The term hygiene hypothesis was used initially because increased hygiene was identified as the major factor associated with inflammatory disease and simply because the phrase was catchy. But numerous subsequent advances in thinking have led to a far more detailed and nuanced picture of biota alteration and how that alteration has affected human health. Unfortunately, advances in our understanding of biota alteration theory have far outpaced clinical practice. While the vast majority of biomedical research drives at pharmaceutical interventions that address proximal causes of disease or even only symptoms, patients often wait for literally decades for the application of knowledge regarding biota alteration that addresses more distal causes of disease. It is suggested that changes in policy and regulation will be important innovations for future application of biota alteration to the field of medicine, and that biota restoration and maintenance will eventually become an important aspect of disease prevention and public health work.

Conflict of interest statement

The authors declare no conflicts of interest.

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