Decreased Breastfeeding as One Factor on a Short List That Causes Pandemics of Allergic and Autoimmune Disease

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Postindustrial society is plagued with pandemics of noninfectious, immune related illnesses. These diseases, which include allergic, autoimmune, and neuroinflammatory diseases, are not found in preindustrial societies, and are apparently caused by a limited number of environmental factors. These factors, essentially incompatible with human genetics, are each associated with a wide range of immune diseases. The most influential of these factors is a loss of diversity from the ecosystem of the human body, a condition termed "biome depletion." This state affects all postindustrial humans during and after fetal development, and remains the strongest challenge for modern medicine to overcome in the field of immunology. Fortunately, progress is being made. On the other hand, other factors associated with pandemics of allergic and autoimmune disease are within the control of each individual rather than the medical establishment. These factors include unrequited or chronic psychological stress, vitamin D deficiency, and substitution of breast milk with infant formula. Decreased breastfeeding in particular has a profound effect on immunity, probably through multiple mechanisms that involve increased stress levels, alterations of the human biome, and direct modulation of the immune system by mechanisms that remain largely uncharacterized. Given the synergism of these factors that adversely affect immunity in postindustrial culture, the importance of avoiding as many of these factors as possible is emphasized.

Keywords: breastfeeding, human biome, autoimmunity, allergy

Pandemics of Noninfectious, Immune-Related Diseases Limited to Postindustrial Culture

Postindustrial society faces an onslaught of diseases related to overreactive immune systems. This immune reactivity toward harmless foreign (extrinsic) or self (intrinsic) targets leads to allergic and autoimmune diseases, respectively. Consequently, up to 40% of the U.S. population suffers from allergic disorders (Arbes, Gergen, Elliott, & Zeldin, 2005; A. H. Liu et al., 2010), and another 3% suffers from autoimmune conditions (Jacobson, Gange, Rose, & Graham, 1997). Furthermore, several maladies that affect cognitive function—including migraine headaches, schizophrenia, and autism—may be induced by aberrant immune responses (Becker, 2007; Bilbo, Jones, & Parker, 2012; Fan, Goff, & Henderson, 2007; Parker, Perkins, Harker, & Muehlenbien, 2012; Patterson, 2009; Waeber & Moskowitz, 2005). Of critical importance is the observation that pandemics of this family of noninfectious, immune-related diseases do not occur in preindustrial societies (Bickler & DeMaio, 2008). Not only were the diseases not described in antiquity, but they also remain absent in preindustrial cultures of today (Bickler & DeMaio, 2008).

Given these observations, it can readily be concluded that these pandemics are not caused by genetics but are rather caused by changes in the postindustrial environment that are incompatible with human health. In other words, the rapid changes introduced by postindustrial culture are essentially incompatible with our genetics, which remain relatively unchanged since the beginning of the industrial revolution. This mismatch between our genes and our environment is widely appreciated as the cause of postindustrial pandemics of obesity, heart disease, and type 2 diabetes. Just as high-calorie diets without exercise lead to obesity-associated diseases, so does a handful of factors in our environment lead to noninfectious, immune-related diseases. These environmental factors are associated with both allergic and autoimmune disease, indicating that factors that lead to one type of disease also lead to the other. For example, substituting infant formula for breast milk not only increases the risk of many allergies, including eczema (Chandra, Puri, & Hamed, 1989; Merrett et al., 1988), it also increases the incidence of autoimmune diseases such as multiple sclerosis (Ryder et al., 1991) and type 1 diabetes (Fava,

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Leslie, & Pozzilli, 1994). Although substituting infant formulas for breast milk is an important factor leading to immune disease, this factor is joined by a handful of other factors that also drive postindustrial immune systems toward the same hyperreactive, pathogenic state.

Triggers for Disease and Associated Genetics Are Not the Cause of the Pandemics

Before describing postindustrial factors that cause pandemics of allergic and autoimmune disease, it is first important to point out that these diseases have two important contributors that are independent, or at least partially independent, of the postindustrial environment. The first of these two is called the "trigger." Triggers include a wide range of very common substances. For example, ragweed pollen serves as a trigger for hay fever, and viral infections can serve as a trigger for several immune-mediated conditions, including autism and multiple sclerosis. However, since ragweed pollen and viruses have been around for millennia without causing these diseases, and since these triggers are largely unavoidable, triggers are not generally a cause of postindustrial pandemics, and it is not the avoidance of triggers that is important for the prevention and, in many cases, the treatment of disease.

On the other hand, toxins and pollutants can also trigger immune disease (Rea, 1988); and these are associated with industrialization. However, it is the postindustrial society, typically less polluted than societies in the peak of their industrialization, which has the most immune disease. Thus, it is expected that toxins and pollutants are not the actual cause of disease, although they can serve as triggers. The fact that inflammation associated with immune disorders can impair toxin metabolism (Bilbo et al., 2012) further exacerbates the roles of toxins in immune disease; but based on the epidemiology of disease, it is probably not these toxins that cause the pandemic of disease.

Independent of triggers, genetics has also been identified as a contributor to pandemics of postindustrial, immune related diseases. Almost all allergic and autoimmune diseases are linked to one or more genetic factors present in the population. However, genetics, like many triggers, is essentially independent of the postindustrial environment, and thus cannot be the causative factor for any postindustrial pandemic. Thus, in a very real sense, the search for genetic links to postindustrial immune disease is of little practical use. Not only is genetics not the cause of the pandemic, but effective treatment of many mutation-induced diseases (e.g., cystic fibrosis, sickle cell anemia, Tay-Sachs disease, and color blindness) has proven extremely difficult for modern medicine.

Cultural Factors Leading to Pandemics of Noninfectious, Immune-Related Diseases

Looking beyond long-established triggers and genetics, assessment of the scientific and medical literature points toward a very limited number of factors that appear to be the cause of recently emerging diseases. These factors involve changes in our culture so that human genetics no longer match the human environment. These changes have profoundly affected the "ecosystem of the human body," and all of the organisms associated with that ecosystem, called "the human biome."

At present, four cultural factors have been identified that alter the human biome, making it susceptible to allergic and autoimmune disease. Data from anthropologic, immunologic, epidemiologic, and clinical studies support these cultural factors as underlying causes of allergic and autoimmune disease (Bilbo, Wray, Perkins, & Parker, 2011; Parker et al., 2012). In all cases except one, causal links have been unequivocally demonstrated by clinical studies. These four are as follows:

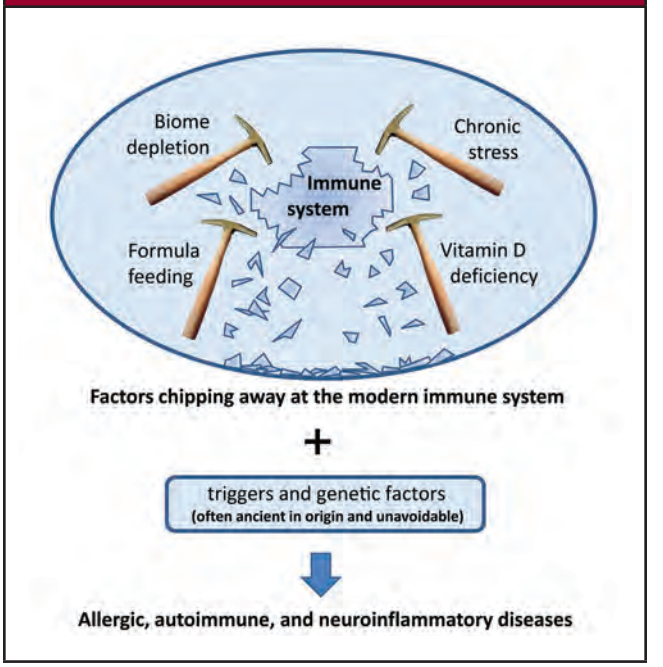
1. *The alteration or complete loss of living species normally associated with the human biome* is the primary factor leading to pandemics of allergic and autoimmune disease. The use of modern toilets, water-treatment facilities, and modern medicine is largely responsible for this factor called "biome depletion." For example, the use of toilets has eliminated most symbiotic helminths (worms) from the human body. Although generally thought of as parasites, some of these helminths are in fact harmless when found in postindustrial culture, and modulate the immune system effectively, preventing immune-related disease. A vast body of scientific evidence, including data from clinical studies, studies in animal models, and studies in basic-science laboratories, strongly supports this view in a manner that is overwhelming. This information has been reviewed in detail recently (Bilbo et al., 2011; Parker et al., 2012) and will be summarized only briefly here.

   The introduction of sewage systems, water-treatment facilities, and modern medicine into postindustrial society all but eliminated many infectious diseases and parasites. Unfortunately, this vitally important advance in public health has produced an unexpected and profoundly negative backlash: The human immune system, which has leaned into an onslaught of infectious parasites for all of human existence, is now destabilized by the sudden removal of its old adversaries.

In ecological terms, the species we lost from our body's ecosystem turned out to be "keystone": without them, the system destabilizes. Fortunately, this realization suggests that "biome reconstitution," the controlled reintroduction of appropriate organisms, could effectively combat immune disease. Unfortunately, there is very little to be done about this problem now by the average person. Not only would abandonment of hygienic practices in postindustrial culture lead to widespread infectious disease but also the needed organisms are already gone. Worse hygiene will not establish helminths that are entirely absent in the population, and even if it could, no one envisions curing allergic and autoimmune disease by restoring widespread infectious disease. Thus, short of obtaining organisms outside the bounds of traditional medical practice (a practice increasing in popularity) or participating in experimental clinical trials, a cure for immune disease involving biome reconstitution must wait on modern medicine to re-introduce the missing organisms in a controlled and safe fashion (references).

Fortunately, this factor is only one of four factors, and the other three factors listed in the following text (Figure 1) can be controlled by the typical individual. Because this first factor is out of our immediate control, it is extremely important to control the other three. The immune system already has one big strike against it, so further strikes should be avoided if at all possible.

Figure 1. Postindustrial Factors Undermining Immune Function



Various factors associated with postindustrial culture undermine immune function and increase the chances of a wide range of inflammatory diseases, including allergic and autoimmune diseases. Biome depletion, as described in the text, is probably the single most important factor undermining immune function, and modern medicine is still grappling with an approach to resolve this problem. On the other hand, other factors known to undermine immune function are largely avoidable and include the lack of breastfeeding in a substantial portion of the population.

2. *Unrequited or chronic psychological stress* is well established as a factor that increases the incidence of both allergic and autoimmune disease in postindustrial cultures (Bagnasco, Bossert, & Pesce, 2006; Bailey et al., 2009; Buret, 2006; Glaser & Kiecolt-Glaser, 2005; Gouin, Hantsoo, & Kiecolt-Glaser, 2011; Ippoliti et al., 2006; Kiecolt-Glaser et al., 2009; Moylan et al., 2013; Reiche, Nunes, & Morimoto, 2004; Stojanovich & Marisavljevich, 2008). Using experimental models, the causal link between chronic psychological stress and immune dysfunction, as well as some of the underlying biochemical/immunological pathways involved, have been established (Bailey et al., 2009).

   However, it is unclear whether Western culture is particularly prone to psychological compared to preindustrial (agrarian and hunter-gatherer) cultures, but it is clear that increased psychological stress is bad for our immune health. Thus, various stress-reduction strategies are recommended for restoring immune health and combating allergic and autoimmune disease.

3. *Vitamin D deficiency*, like the other factors described earlier, causes an increase in the incidence of both allergic and autoimmune conditions (Cannell, 2008; de Borst et al., 2011; N. Q. Liu et al., 2011; Lucas et al., 2011; Mark & Carson, 2006; Sharief, Jariwala, Kumar, Muntner, & Melamed, 2011; Wagner, Taylor, & Hollis, 2008). Hossein-Nezhad, Spira, and Holick (2013) have solidly established the link between immune dysfunction and vitamin D deficiency, probing a wide range of immune factors impaired by vitamin D deficiency and demonstrating that normalization of vitamin D levels can reverse disease. As stated recently by Holick (Hossein-Nezhad et al., 2013):

   Our data suggest that any improvement in vitamin D status will significantly affect expression of genes that

have a wide variety of biologic functions of more than 160 pathways linked to cancer, autoimmune disorders and cardiovascular disease that have been associated with vitamin D deficiency. This study reveals for the first time molecular finger prints that help explain the non-skeletal health benefits of vitamin D.

Inadequate levels of vitamin D were probably relatively rare before the industrial revolution, when sunlight was the main source of light for almost all human activity. In contrast, the use of windows that block ultraviolet (UV) light, sunscreen, and indoor lighting devoid of UV light has left more than half of the postindustrial population lacking in adequate vitamin D (Holick, 2006). Although sporadic exposure to the sun, which causes severe sunburn and subsequent skin cancer, is not a recommended means of avoiding this problem, vitamin D supplements are readily available and quite effective (Hollis, Johnson, Hulsey, Ebeling, & Wagner, 2011). At present, the primary hurdle in overcoming this factor is educational in nature. Even many healthcare professionals are unaware that vitamin D deficiency puts individuals at risk for anything more than bone density problems, despite the preponderance of evidence (Staud, 2005; Wagner et al., 2008) supporting the view that vitamin D deficiency increases the risk for immune-related disease.

4. *Replacement of mother's milk with infant formula*, as mentioned earlier, is yet another factor that apparently affects both allergic and autoimmune disease (see details in the following text). Indeed, the potential ramifications of replacing breast milk with infant formula for human biology are vastly complex. However, unlike the first three factors described earlier, the effect of substituting formula for breast milk cannot readily be subjected to controlled clinical trials and has not been investigated using experimental-animal models. Nevertheless, the role of breastfeeding in immunity is supported by a wide range of evidence, and, from several perspectives, that evidence points toward a lack of breast milk as a contributing factor in the pandemics of immune disease.

The Impact of Human Milk on Immune Function

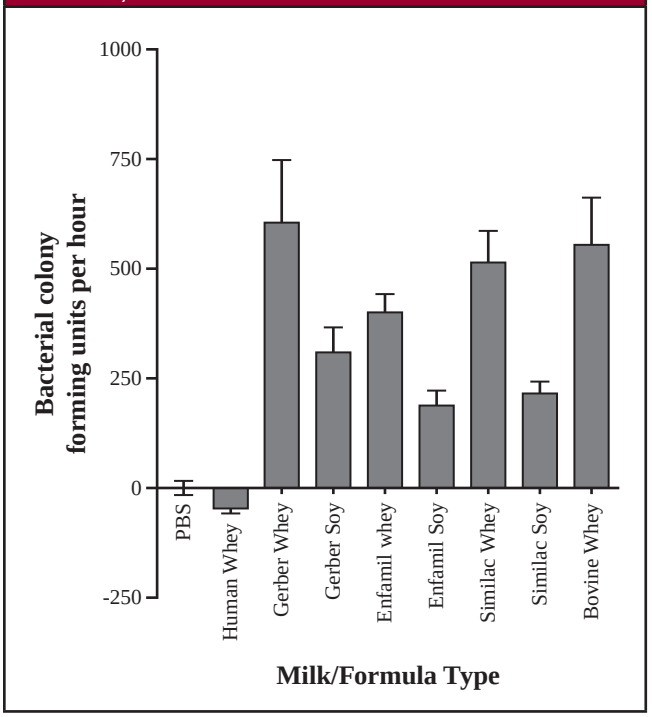
Clinical studies demonstrate conclusively that human milk is vitally important for immune function. At the same time, immunological and biological studies lag behind, and our understanding of the role of breast milk in human biology is in its infancy. Nevertheless, current research suggests that the impact of human milk on immune function is multifactoral. One key point of impact appears to be the importance of human milk in establishing the bacteria within a baby's gastrointestinal tract. It is upon these bacteria that the development of the immune system is critically dependent (Gaskins, Croix, Nakamura, & Nava, 2008; Tsuji, Suzuki, Kinoshita, & Fagarasan, 2008). Human milk and infant formulas lead to a much different microbial population in the infant digestive tract (for a review, see Guaraldi & Salvatori, 2012). In general, the bacteria in the gut of babies fed infant formula more closely resemble the bacteria found in adults rather than those found in normal (breastfed) infants (Mackie, Sghir, & Gaskins, 1999). Thus, babies fed infant formula rather than breast milk are essentially bypassing steps in the development of their bacterial symbionts, called the microbiome. This alteration of the microbiome may be important for immune function because the development of the microbiome is very closely tied to the development of immunity. For example, animals that are raised with no microbiome have an immune system that is grossly underdeveloped (for a review, see Tlaskalová-Hogenová et al., 2002).

Simple in vitro experiments readily show the profound differences between human milk and infant formulas in terms of their interactions with bacteria (Zhang, Lee, Truneh, Everett, & Parker, 2012). Human milk facilitates the clumping of bacteria, reducing the numbers of free-floating bacteria, whereas infant formulas have the opposite effect: they induce the rapid proliferation of free-swimming bacteria. The results of a typical experiment are shown in Figure 2.

Both nutritional sources induce bacteria to grow, but they cause the bacteria to grow in profoundly different ways. The copious quantities of secretory IgA (SIgA) in human milk, but not infant formulas, are probably responsible at least in part for this observation (Bollinger et al., 2003). Evidence suggesting that SIgA supports the growth of living films of bacteria, called biofilms, in the normal, healthy gut was first uncovered about a decade ago (Bollinger et al., 2003). For example, artificial models of the human gut containing both human gut cells and bacterial biofilms were first successfully created using a nutrient broth containing SIgA (Bollinger et al., 2006). Previous attempts at creating the artificial system without SIgA were unsuccessful.

A second means by which breast milk alters immune function is probably through the modulation of

Figure 2. Effect of Infant Nutrition on Friendly Bacteria



Human milk proteins have a profoundly different effect on the growth of growth of non-pathogenic *E. coli* compared to other forms of infant nutrition. The increase in colony forming units per hour was measured following a 2-hr incubation at physiologic temperature (37 °C). Phosphate buffered saline (PBS) was used as a "control" (the number of bacteria present after incubation with a nutrient-deficient liquid), and the number of colony forming units under those conditions were set at zero. Whereas human milk proteins (Human Whey) caused an actual decrease in the number of bacterial counts, other forms of infant nutrition caused a dramatic increase. These experiments and a larger series of related experiments have been described previously (Zhang et al., 2012), and demonstrate that human milk supports the growth of *E. coli* but that it supports it in a fashion much differently than does other forms of infant nutrition. Importantly, the decrease in colony counts because of human milk proteins was caused by clumping of growing bacteria, not by killing of bacteria.

psychological stress. As pointed out earlier, chronic psychological stress is one of a very limited number of factors that leads to allergic and autoimmune disease (Figure 1). Breastfeeding not only reduces psychological stress in the infant but is also associated with reduced stress in the mother (Groër, 2005; Hahn-Holbrook, Holt-Lunstad, Holbrook, Coyne, & Lawson, 2011; Mezzacappa, 2004). In this case, the act of breastfeeding may be as important as the breast milk itself. The idea has recently, but strongly and convincingly, emerged that skin-to-skin contact between mother and newborn, a usual component of breastfeeding, is by itself extremely important for both infant and maternal psychological well-being (Acolet, Sleath, & Whitelaw, 1989; Gray, Watt, & Blass, 2000; Ludington-Hoe et al., 1999; Ludington-Hoe, Hashemi, Argote, Medellin, & Rey, 1992).

In one dramatic example, Morgan and colleagues found that the simple act of separating mothers from their newborns for only one-hour apparently induces a substantial increase in psychological stress in the newborn (Morgan, Horn, & Bergman, 2011). In that study, the authors evaluated healthy infants with and without a 1-hr separation from their mother, providing convincing evidence suggesting that separation from the mother is not compatible with human biology. The authors conclude that such separation "may not be benign."

To what extent skin-to-skin contact with the mother versus the actual breast milk affects maternal and infant well-being remains largely unknown and presents an extremely important area for future investigation. However, it is evident that, especially in the infant, breastfeeding reduces psychological stress, one of the leading factors associated with allergic and autoimmune disease.

Conclusions

By the time a human baby is born in postindustrial society, he or she has already been exposed to an environment (the womb) affected by biome depletion. In addition, there is a substantial possibility that the same infant has already been exposed to the effects of chronic psychological stress and vitamin D deficiency in the womb. To be deprived of breast milk at this point adds further to the potential milieu of insults already suffered by the infant's immune system, and seems worth avoiding if at all possible.

Breastfeeding involves a vastly complex connection with mother and infant, affecting the entire body, including the immune, endocrine, nervous, and digestive systems. Perhaps just as importantly, breastfeeding affects establishment of the human biome, particularly the microbiome, which is intimately tied to the immune system development. Given that breastfeeding has been the established method of providing infant nutrition for as long as humanity has existed, it seems unsurprising that alteration of this process leads to an increased incidence of disease.

Although the biochemical and physiologic reasons that breastfed babies have a reduced risk for noninfectious

immune-related disease remain largely unknown, studies are beginning to emerge that explain, at least in part, this connection. Perhaps one of the most important considerations regarding the modern decrease in breastfeeding should be that other factors associated with postindustrial society operate synergistically with deprivation from mother's milk to induce immune-related disease. Fortunately, some of those factors can be avoided using vitamin D supplements as needed and by reducing chronic stress as much as possible. On the other hand, biome depletion, caused by necessary developments in sanitation and medical practice, remains uncontrolled at present, and work toward reversing this problem is in its infancy. The ubiquitous nature of biome depletion in postindustrial society and the potent damage this factor has on immune function argues strongly in favor of avoiding, if at all possible, factors such as deprivation from mother's milk which further damage immune function.

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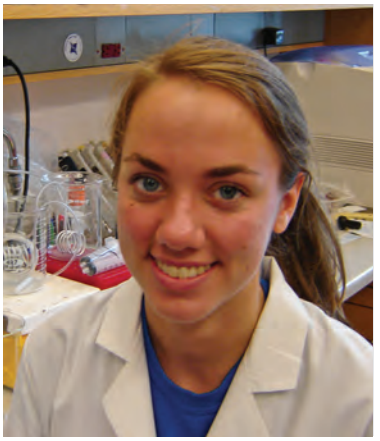

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