Post-hunter-gatherer era microbes' role in allergic/autoimmune diseases

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Abstract

Diverse hypotheses exist to explain allergic and autoimmune diseases. There are 3 factors common to most, if not all, of these diseases: 1. Microbial imbalances, microbial triggers and/or infections, 2. Allergy/hypersensitivity to food and/or environmental substances and 3. Stress. The post-hunter-gatherer era microbe hypersensitivity-enhanced colonization/infection (PHMHEC) hypothesis presented here proposes that these factors are part of a phenomenon that involves an extension of the altered microbiota hypothesis, which is the current leading hypothesis to explain the increase in allergic and autoimmune diseases in the last 75 years in association with westernization. The category of post-hunter-gatherer era microbes (PHM), as defined here, includes many microbes that are encountered much more frequently since humans ceased to live as nomadic hunter-gatherers and began living an agricultural or urban lifestyle. The microbial communities (microbiotas) that humans have been exposed to have changed as human activities have changed. It is postulated that the most intense and rapid changes in these microbiotas have occurred in recent decades in association with westernization. Human genetic makeup evolved largely during the 200 million years during which humans and their mammalian ancestors lived as hunter-gatherers or gatherers. It is proposed here that environmental microbes commonly encountered in association with that lifestyle in a pre-agricultural age would be the most coevolved with the human immune system, and thus the immune system would generally respond to these microbes without leading to debilitating chronic disease. In contrast, according to the PHMHEC hypothesis, at least some of the microbes newly encountered or encountered at higher levels during the post-hunter-gatherer era, the PHM, would be more likely to evade the immune system and cause hypersensitivity reactions. A mechanism called hypersensitivity-enhanced colonization/infection (HEC) is postulated to be one means by which low abundance microbes cause disease. Microbes sometimes cause hypersensitivity reactions in a manner that increases their virulence, and these reactions could be enhanced by increased exposure to similar or identical microbes in the environment. Slight differences between antigens of environmental and colonizing microbes could make the colonizing microbes even more difficult for the immune system to effectively target. Multiple secondary opportunistic infections resulting from PHM-induced immunosuppression and/or immune dysregulation could exacerbate disease processes. The long-term colonization/infection of multiple PHM and accompanying hypersensitivity reactions could contribute to physiological and psychological stress and tax the immune system and other systems of the body and be an underlying factor leading to many allergic, autoimmune and related diseases. The united holobiont disease hypothesis, which is analogous to the united airway disease hypothesis, is discussed, as well as the view that the concept of sterile inflammation needs revision and perhaps should be replaced with "inflammation without apparent infection" (IWAI) in light of the potential role of low abundance microbes. The relationship between the PHMHEC hypothesis and other hypotheses is discussed for a variety of diseases,

ending with a discussion of implications for research and treatment.

Keywords: Autoimmune, Allergy, Hypersensitivity, Microbiota, Hygiene Hypothesis, Cross-Reaction, Occupational Health, Plant-based Diet

Takeaway points

1. **Microbes in food, in the air and on the skin that humans have had greater exposure to since the hunter-gatherer period, especially in the last 75 years, may be contributing to the rise in allergic, autoimmune and related diseases associated with westernization.**
2. **Allergic and autoimmune diseases could stem from direct negative effects of PHM colonization/infection and/or the immune system's defensive reactions against PHM antigens that cross-react with food, pollen and other environmental antigens as well as self-antigens. Various treatments may be aiding the elimination of the PHM, e.g., dietary changes, anti-microbial treatments, microbiota manipulation, allergen avoidance, stress reduction methods and allergen-specific immunotherapy.**
3. **Research into mechanisms and treatments might benefit from investigating the potential role of PHM in light of the PHMHEC hypothesis.**

Introduction

Since the late 17^{th} century, when Anton Van Leeuwenhoek first discovered the teeming world of microscopic organisms that live everywhere from a drop of pond water to the surfaces of teeth, scientists have been exploring the diverse ways that organisms too small to observe with the naked eye have been affecting human beings. The power to observe the microbes, both directly and indirectly, has given us the ability to largely control many infectious microbes through both public health and medical interventions.

As many of the more obvious effects of microbes have already been uncovered, the more subtle, delayed and chronic effects have become the focus of increasing attention. Two well-known examples are the delayed effects of human papilloma virus in causing cervical cancer[1] and the ability of HIV to indirectly cause chronic illness through its detrimental effects on the immune system after years of latency[2]. Even more recently, there has been an examination of how sometimes relatively subtle imbalances in the microbial communities in various parts of the human body potentially affect disease susceptibility[3–5]. This trend toward more subtle, indirect and chronic microbial effects being the focus of attention is continued with the hypothesis presented here.

Although at least some allergic and autoimmune diseases have apparently been observed for thousands of years[6–8], there has been a rapid increase associated with westernization in the last 75 years[9]. The term westernization will be used here to include a number of factors that have been proposed to be associated with health effects. It includes a westernized diet, increased exposures to both indoor and outdoor pollutants associated with petrochemicals and other products that are manufactured according to relatively recently developed processes, often made from substances that humans have only come in contact with in the last few hundred years. New exposures from western medicine, like antibiotics, are also included. The westernized diet typically includes increased consumption of animal products, fat (especially saturated animal-derived fat and vegetable oils), sugar, fast foods, processed foods/beverages, salt and food additives. At the same time, there has been reduced consumption of whole foods, high fiber foods and traditional plant-based diets.

A sedentary lifestyle is also often associated with westernization, however, it will not be discussed further here.

There are a number of hypotheses attempting to explain the rapid increase in disease rates. A hypothesis regarding changes in the normal human microbial inhabitants arising from westernization[10–12] is the explanation that has probably gained the widest level of acceptance. The hypothesis presented here is essentially an extension or elaboration of this altered microbiota (aka microflora) hypothesis. Several other hypotheses, including those related to the role of environmental chemical/pollution or occupational triggers, are compatible with the hypothesis presented here, and will be discussed further in later sections.

The Genetic Sequencing Revolution Provides a Window on Microbiotas over the Millennia

Great advances have been made in recent years in understanding the microbes that live in and on a wide array of plants and animals. Much of this has been learned due to advances in technology arising from the Human Genome Project, which allowed the complete sequencing and mapping of all the genes in the human genome in the early 2000s[13]. Soon, many microbial, plant and animal species genomes were sequenced.

Just as for computer technology, advances occurred rapidly, and the cost of sequencing dropped dramatically. What previously took 13 years and more than a billion dollars can now be accomplished in an hour for under a $1000, and the costs will likely continue to drop[13]. This has led to the generation of large amounts of data and much greater understanding of many diverse microbial communities, including those associated with humans.

We now know that many species of microbes play beneficial roles in the human intestinal tract[14,15]. Some are pathogenic, while others are only a problem under certain conditions, such as in a person with a suppressed immune system.

Area after area in the human body that was thought to be sterile in healthy individuals has been reported to contain microbial communities, including the blood[16–18], the lungs[19], the synovial fluid[20], the placenta[21,22] and even the brain[23–26]. Although arguments have been made contesting some of this research, claiming laboratory contamination issues are responsible for the findings, the differences typically observed between controls and individuals with a number of different diseases and the use of methods that control for contamination argues in favor of microbial presence in these tissues[22,27].

Humans and their mammalian ancestors spent more than 200 million years as nomadic hunter-gatherers or gatherers and have coevolved with microbes living in and on the body[28]. Changes in the human microbiota likely did occur for a variety of reasons, such as climatic changes or moving to a different habitat. And at certain points, cultural changes occurred, like the advent of tool use and cooking, and these changes caused alterations in early humans' microbial exposures[29].

One of the examples of cultural change that provides a preview of later changes, was the beginning of food processing in populations that were at least partially sedentary but still pre-agricultural. In North Africa, in the Pleistocene, early humans ground up acorns and pine nuts and the resulting change in food consistency is thought to have led to one of the first populations to suffer from dental decay due to the bacteria Streptococcus mutans[30]. This is just one early example of changes in lifestyle having detrimental effects due to changes in microbial communities.

When cultural changes were significant, such as the change to an agricultural society, the microbial exposures also changed significantly[31]. Interestingly, there are indications that early agricultural populations were less robust and it is thought that this might be related to nutritional deficiencies[32], but possibly could be related, in part, to different microbial exposures. The microbes associated with agricultural crops and

their storage would have been PHM in the sense that there would be much higher exposure to certain agriculture-associated microbes. (Note: PHM in this article is singular or plural, depending on the context).

An interesting example that has likely played a historical role is the growth of mold on crops causing a condition called ergotism[33]. In fact, there is some evidence that the Salem witch trials in colonial America in the 17^{th} century were a result of the hallucinations and other effects of the toxins from a type of fungus that grows on grains[34]. Some doubt has been cast on this theory, however there have been many outbreaks of ergotism throughout history that are not disputed[33].

It is well-known that many epidemic diseases accompanied the introduction of agriculture and the concentration of people and domesticated animals[28]. In fact, many of the microbes causing epidemic diseases that arose during this period (e.g., typhus, smallpox) could be seen, in a sense, as part of the post-hunter-gatherer microbial environment. However, they would not often be part of the human microbiota and are not the focus of this hypothesis. The current hypothesis is focused on typically less virulent environmental microbes, often with more subtle, cumulative and/or chronic effects.

The introduction of different materials, for instance, copper, bronze and iron, as part of human cultural evolution would likely have introduced new microbes associated with the materials being used. Microbes are found living in virtually all materials studied, even at great depths and inside of rock[35,36]. Later, petroleum and coal would have introduced new microbes that would be extracted with them[37]. And in other cases, products made from new materials could have provided unique selective pressures for microbes, thus potentially increasing the number of novel species and strains[38].

Currently, it is not known to what extent these past cultural developments changed microbial exposures and led to disease, although interesting studies are beginning to be done using ancient DNA[39]. It seems likely that some human genetic variants would have been more compatible with the new microbial exposures and natural selection would have occurred to select the more compatible genes. Thus, evolution is likely to have occurred, at least to some extent, to allow toleration of the newer microbes. Some microbes actually evolved to produce vitamins and have many other beneficial effects[40,41], further supporting the idea of coevolution between humans and many of their microbial inhabitants.

Recently, many changes in the human microbiota have been observed and associated with diseases, and rapid progress has been made. Particular microbes in the intestinal tract have been associated with certain diseases[42]. Antibiotics have been seen to deplete the normally diverse microbial communities to varying degrees[12], and probiotics have been found to be helpful in some diseases[43,44]. Diet can have dramatic effects, and a diet depleted of fiber, which is a fuel for many microbes, has been seen to lead to a loss of microbial diversity in the intestinal tract[45].

Despite these recent advances, a problem that has become increasingly recognized is the difficulty of detecting rare species/strains[46]. In 2008, Dethlefsen et al[41] extended the numbers of microbial taxa found in stool samples, and others have followed[47–49]. Better culturing methods and other improved methods are beginning to find even rarer microbes[50,51], but still, there is inadequate information regarding the rare or low abundance microbes that inhabit the body. Lagier et al[52] depicted the situation as similar to an iceberg with a large portion of the microbial diversity under the surface, still undetected, and not yet detectable with current methods.

In addition, with most genetic sequencing methods, the species must already be known and present in the sequence libraries in order to be identified, and certain practices commonly used (limited primers, discarding singletons, rarefaction) tend to bias the results and/or limit detection of rare and unusual species[4,41]. Efforts are currently being made to rectify these problems, and improvements are already occurring[53], but it is still not possible to detect many rare microbes.

On the surface, this limited knowledge of rare species may not seem important, since abundant species may be thought to be more important. However, as Lagier et al points out[50], the low abundance oral bacteria Poryphyromonas gingivalis has been implicated in bone loss in gum disease, and recent research suggests it

is involved in Alzheimer's disease and other diseases[54].

So, what might make up the diverse community of rare microbes, sometimes called the rare biosphere[41], in and on the human body? Presumably at least some are microbes from the environment that are able to colonize the human body but are not so well-adapted to living in humans so as to become very abundant, or there may be other reasons for their being less abundant[55]. The whole vast biosphere of environmental microbes that we inhale, ingest and that come into contact with our skin on a daily basis should be considered in relation to this question. Some are likely common soil and plant microbes and are known. The less abundant, often unknown ones that are changing with human cultural practices, are one of the main focuses of this hypothesis. It is known from ecological studies of diverse environments that there are typically many rare species[56,57], often with very patchy distributions[55,58].

The PHMHEC hypothesis proposes that colonization/infection by at least some of these PHM could be significantly contributing to the pathogenesis of allergic/autoimmune and related disorders and many of them could have been missed by current methods. The period of exposure to many of these PHM has likely not lasted long enough for coevolution between the PHM and their human hosts to have occurred. It is proposed here that the lack of sufficient coevolution means at least some PHM are likely to be contributing to chronic disease through colonization/infection and hypersensitivity.

In addition to explaining the rapid recent increase in disease rates, this hypothesis can explain why some of these diseases were apparently present at least to some degree in early civilizations[6–8]. Significant changes in the PHM likely accompanied the advent of agriculture and other cultural changes occurring at the time and could have been involved in disease causation.

Man-made products and harsh chemicals might not seem conducive to microbial survival. But new discoveries continue to highlight the remarkable adaptability of microbes – the more they are studied, the more extreme conditions they are found to tolerate. Probably the only sterile places on earth, besides a few laboratory cleanrooms, are hot springs, volcanoes and other areas so deep in the earth that they reach over 150 degrees Centigrade[36]. There also might be areas in Antarctica too salty for microbes, though this is questionable[59]. Otherwise, microbes are likely everywhere and in everything on earth[36]. Autoclaves used for sterilization do not kill all microbes but are thought to kill all those able to cause infections[37]. Hospitals attempt to sterilize needed items with multiple sequential methods but can only make probabilistic statements regarding sterility and cannot directly determine if the items are truly sterile[60]. NASA is required to minimize the chance of transferring microbes to other planets, but it cannot afford to do its work at the highest level cleanrooms. Recently, scientists at NASA have found new microbial species living in their cleanrooms[61] and some species that have been found to "feed on" the cleaning products used to disinfect the rooms[62]. In hospitals, despite frequent cleaning, microbial contamination is widespread, leading to investigation of alternative anti-microbial copper surfaces[63].

How could many of the PHM that likely are not generally adapted for survival in animals persist in humans? It is now recognized that some environmental microbes that may be thought of as not being able to generally infect healthy humans may still survive within human cells and sometimes cause disease due to "dual use" virulence factors[64]. That term has been used to describe how microbes can avoid being destroyed by larger microbial predators in the environment, such as amoeba, and actually can survive inside of their predators. And the adaptations that allow this survival also allow survival within human cells. So, this might be one means by which PHM might be able to colonize/infect animal tissues.

So, the PHMHEC hypothesis proposes that at least some PHM that are part of a westernized lifestyle and are associated with substances inhaled, ingested and contacting the skin/mucosal surfaces may be significantly contributing to allergic and autoimmune diseases. Some of these PHM may be so low in abundance in the human body that they are below current detection limits, however they may still be part of the altered microbiota associated with the last 75 years of westernization. Not all of the PHM are so rare as to be undetectable, however, and examples will be given of microbes that fit the definition of PHM and that are involved in a number of diseases. The mechanisms by which they are proposed to contribute to disease

will be discussed in more detail in later sections. These proposed mechanisms are intimately connected with inflammation that occurs in response to allergens/antigens and is observed in conditions like allergy, asthma, autoimmune diseases and related conditions.

The hypothesis presented here is by no means the first to propose that hard-to-detect, slow infections may be causing many chronic inflammation-related diseases. Some of the proposals in the second half of the 20th century arose from research by Mattman[65–67], Brown[68], Tedeschi et al[69] and Domingue et al[70]. Others have followed, some emphasizing microbes in the blood and/or tissues[23,71–77] and others emphasizing the oral and/or gut microbiota[78,79]. What distinguishes the PHMHEC hypothesis is its proposal regarding the sources of the microbes that are the primary underlying cause and their relationship with allergy/hypersensitivity, cross-reactivity, stress, chemicals/pollution (xenobiotics) and opportunistic infections.

Allergy and Hypersensitivity

Allergies have been known since ancient times and have puzzled observers, from patients to doctors to researchers. Why would one person have such a dramatic negative response to a food or inhalant that is tolerated well by others? At a basic mechanistic level, researchers learned that the immune system's B cells produce immunoglobulins, aka antibodies (for instance IgE in classical allergic responses), that bind to substances called antigens. The antibodies match particular antigens like a key fits a lock. Once binding occurs, many other immune system responses can occur. The term allergen is used for antigens that lead to an allergic immune response.

Allergic reactions are just one of 4 major types of hypersensitivity reactions (immediate, cytotoxic, immune complex, cell-mediated) that can result from the immune system recognizing and responding to an antigen. This section will focus primarily on immediate IgE-mediated reactions, however, much of what will be described also may apply to other types of immune hypersensitivity reactions, as discussed later. In this article, the word hypersensitivity will refer to the 4 major types of immune reactions or newer types being elucidated[80,81]. The term allergy/hypersensitivity will be used to emphasize that allergy as well as one or more of the other immune hypersensitivity reactions is being referred to. Non-immune mechanisms associated with adverse reactions that are often called intolerances are not the focus of this article.

The assumption for most of the history of the study of allergic diseases was that allergenic substances were essentially harmless and allergic reactions were a mistake by the immune system. A new era in the study of allergy began with the hypothesis proposed by Profet[82] that allergic reactions evolved as a defense against toxins. This has been called the toxin hypothesis of allergy. For instance, many host defense proteins in peanuts are known to have damaging effects that target the plant's pathogens/pests, and these damaging effects might be related to the protein's allergenicity in humans[83].

Over the decades since this hypothesis was published, a significant amount of research has been done supporting this possibility. Palm et al[84] reviewed the research, concluding that many arguments as well as experimental and observational studies support the idea that allergy is an important defense mechanism protecting the host from toxic environmental substances, i.e., venoms, toxins, irritants and substances produced by biting insects. More recent research continues to support this hypothesis[85,86].

Palm et al[84] refers to allergic reactions as "allergic host defense responses," and this broader description of the toxin hypothesis will be used in this discussion to refer to this view of allergy. As discussed below, this concept has now become even broader, including responses to microbes.

In recent years, research is pointing to a role for IgE-mediated allergic reactions in providing protection from cancer, viruses, bacteria and other microbes. With regard to cancer, a task force has been formed to study the expanding area of research called AllergoOncology[87], the study of allergies in relation to cancer. Kozlowska[88] found that the incidence of allergies, especially allergic rhinitis, is lower in patients

with some types of cancer. Further support comes from a study showing that patients who have an unusual IgE deficiency have an increased level of cancer that is not due to low levels of other immunoglobulins[89].

Sherman et al[90] reviewed the epidemiological research and found there was support for the idea that allergies are protective against cancer of organs and tissues that interface with the environment. They concluded that the data suggests that what may be occurring with allergic reactions is a rapid expulsion of not only dangerous natural toxins, but microbial pathogens as well. And others have also found evidence of the cancer protective effects of allergic responses[87].

In addition, there is now laboratory evidence that IgE is produced in response to viruses and bacteria and that it is helpful in controlling infectious microbes[91,92]. There are other situations where bacterial allergens are known to be important that will be discussed in later sections.

Thus, IgE-mediated allergic responses may be part of a protective mechanism against toxic or irritating substances and a wide variety of types of microbes. The allergic responses mainly differ from other immune reactions in their ability to produce rapid and sometimes extreme responses that often are related to ejection of the substance (e.g., coughing, sneezing and diarrhea).

The existence of allergic reactions to substances with little, if any, toxic effects could be partly due to limited research on the toxicity of various allergens, however, it is proposed here that much of the proposed negative effects may be related to cross-reactions with microbial antigens, as will be discussed next. Cross-reactions are a key component of the PHMHEC hypothesis.

Cross-reactions

Cross-reactions occur because antibodies, like IgE, are not quite as specific as a key fitting only one lock. It has been found that antibodies generally do bind to multiple similar antigens. If two antigens can both bind to the same antibody, the two antigens are said to cross-react[93,94].

Thus, the immune system might produce antibodies to target an infectious microbe, but the same antibodies might also bind to an allergen, like a pollen, due to a similarity in structure[94]. For instance, it is known that IgE plays a role in fighting parasitic infections. A study found an IgE antibody that targets a protein of a parasite that is apparently similar enough to a common pollen allergen to bind it as well[95]. Thus, this parasitic antigen is said to cross-react with the pollen allergen.

There are many well-known examples of cross-reactions that are important in diverse areas of immunology. It is thought that the most common adult-onset food allergies are the result of certain food proteins cross-reacting with inhaled substances, such as pollens. This is called oral allergy syndrome, and it often occurs in patients with seasonal allergies, resulting in itching and swelling of the mouth as well as more serious reactions[94,96]. Thus, oral allergy syndrome patients have reactions to foods that usually occur more strongly in the season of the year when the cross-reacting pollen is abundant. This is because the effects of the exposures to the food and the pollen are additive.

Another common set of cross-reactions is called latex-fruit syndrome, in which a variety of fruits and some other foods cross-react with latex allergens[97]. Latex is a substance used to make many products, e.g., tires, elastic and adhesives, and is derived from the milky fluid collected from rubber trees. Natural rubber latex has been found to have a rich microbial community[98,99] and thus could be a source of PHM acquired from the air, water and soil. This could contribute to at least some cross-reactions involving latex, according to the PHMHEC hypothesis.

Cross-reactions are likely to be important in many types of hypersensitivity reactions, not just IgE-mediated allergic reactions. Cross-reactions are thought to be important in at least some autoimmune diseases, as will be discussed in a later section.

To illustrate the potential role of cross-reactions in relation to the PHMHEC hypothesis, it is worth discussing Loblay et al's[100] research using double blind placebo-controlled challenge tests to identify food groups

that cause adverse food reactions. A portion of the group of patients being studied met the criteria for chronic fatigue syndrome (aka myalgic encephalomyelitis/chronic fatigue syndrome or ME/CFS), a disease of unknown cause that will be discussed later. Interestingly, around half of the subjects did not have any idea that foods were causing their symptoms. Symptoms often began after a viral infection and resembled symptoms from a chronic viral infection, yet a proportion of the patients responded favorably to elimination diets.

What is notable about this work in the present context is that Loblay et al[100] documented groups of foods that cross-reacted apparently due to a chemical common to all the foods in the group. They noted that this made it difficult to determine what was causing a reaction, because it was not just consuming one food that determined whether the patient reacted, but the cumulative amount of foods containing the chemical. So, on one occasion, a person sensitive to salicylates might react to high salicylate tea and another time they would not, and the difference would be that the time they reacted, they had also recently consumed other foods/beverages with high levels of salicylates. To improve, a period of avoiding all foods with high levels of that substance was important.

Interestingly, Loblay et al[100] also noted apparent cross-reactions involving substances that were not apparently related as well as variability in the symptoms among individuals. The explanation they suggested regarding regulation of the responses of the nervous system might play a role. However, the hypothesis presented here, that the chemicals cross-react with or are associated with antigens from PHM, also provides a plausible explanation. PHM might be associated with certain chemicals due to being able to metabolize them, by producing a substance that cross-reacts with the chemical, or due to their presence as part of the microbiota where that chemical is found (e.g., a plant microbiota).

The PHMHEC hypothesis proposes that these PHM are able to colonize and survive in skin cells, sometimes in areas of rashes, and in various organs where symptoms occur, explaining the individuality of responses. When exposure to a PHM antigen in the diet occurs, the immune system would react with an inflammatory response in the specific areas of the body where that particular PHM had colonized, thus causing the symptoms.

Loblay et al[100] described the food reactions as food intolerance reactions, thus specifying that they did not involve the immune system. However, immunological reactions of some type were not ruled out. So, it may be that immunological reactions were involved, but they were not classical IgE-mediated responses. The type of immune reaction may vary with the person's genetic makeup, microbial exposures and other factors.

Since most of these microbial antigens have not yet been identified, it is hard to make sense of the observed cross-reactions and impossible to detect antibodies to the antigens via blood testing. Limitations in testing would be accompanied by limitations in treatment response.

Microbial cross-reactions could also be part of the explanation for variability among patients as to which foods cause symptoms for those with other conditions involving cross-reactions, like latex-fruit syndrome and oral allergy syndrome, mentioned above.

In sum, it appears that allergic reactions could be defensive responses against noxious and/or potentially dangerous exposures, e.g., toxins and microbes. An even wider range of substances could be producing reactions due to cross-reactions with the toxins' and microbes' antigens.

Psychological and Physiological Aspects of Stress

Difficult circumstances related to family life, work, commuting, interpersonal conflicts, divorce, and tragic life events are all potential sources of stress. Stressor is the term used for something that initiates or contributes to the experience of the stress response. The normal stress response is a common experience and may include increased anxiety, muscle tension, more rapid breathing, increased heart rate, higher blood pressure,

dry mouth and sweaty palms. These responses occur as a result of the release of stress hormones, such as adrenalin, which then triggers the fight or flight response[101].

It is often pointed out that animals evolved to deal with the types of stressors that only happen occasionally, like encounters with predatory animals. Psychological stressors experienced by most people are not as life threatening as being stalked by a lion, but these everyday stressors are considered to be particularly detrimental due to their often chronic nature in modern society, and much research has focused on that[102,103].

However, there is a whole other area of research that needs to be considered when it comes to the stress response: its role in injury and illness and its intricate relationship with the immune system[104]. It is important to think of the stress response in terms of the role it evolved to play in optimizing animals' ability to survive an attack.

First, there are aspects of the stress response that help an animal deal with the immediate crisis, such as increased blood sugar to provide adequate energy, along with increased heart rate and blood pressure[105]. Then, there is an array of responses of the immune system that prepare the body to fight an infection in case of injury[101,106].

A much greater understanding of the changes that occur in immune function as a result of stress has been gained in recent decades[103,104]. Dhabhar et al[107] described immune cells during a stress response as going from the "barracks to the boulevards to battlefields" in order to be prepared to fight infection. The many immune system changes that occur are just as relevant to psychological stress in everyday interpersonal conflicts, since the responses evolved during an era when interpersonal conflict was more likely to lead to injury/infection from a physical attack[105,108].

The stress response is also important during the fight against infectious microbes in general, not just after an attack, and a detailed discussion of this subject is beyond the scope of this paper. Suffice it to say that acute stress lasting for minutes or hours is relatively harmless. Chronic stress, however, is found to be more likely to have significant long-term negative consequences[105].

Stress is found to exacerbate a wide variety of conditions[103], including autoimmune diseases. A recent large study verified previous observations that stress disorders, such as post-traumatic stress disorder, increase the risk of developing autoimmune disease[109]. Stress also can exacerbate or initiate asthma attacks[110,111] and increase the susceptibility to infection[105].

Chronic stress is thought to contribute to high blood pressure, a well-known risk factor for heart disease[112]. An increased resting heart rate, which is also affected by chronic stress, has been found to be a predictor of all-cause mortality in several studies[113–115].

Another measure of stress, heart rate variability, has been increasingly studied[116,117]. Under normal, non-stressful conditions, there is an expected level of fluctuation in the heart rate that generally goes unnoticed but can be studied with special equipment. Heart rate variability typically decreases substantially under conditions of greater stress[117]. Analyzing the changing patterns of heart rate variability under different circumstances has become an important new area of research.

There are other non-psychological sources of stress that are less commonly recognized. It has been shown that air pollution can raise the heart rate and lower heart rate variability in many populations[118–120], even young athletes[121]. Magari et al[122] found that occupational and environmental exposure to inhaled particulate matter negatively affected heart rate variability.

With all of these examples of stress effects and sources of stress as a background, it is now time to return to the PHMHEC hypothesis in the context of the newer view of allergic host defense responses.

Palm et al[84] describes how the extremely high sensitivity of IgE-mediated responses may have evolved to allow anticipation of possibly dangerous exposures and thus cause avoidance of the noxious substances. This avoidance phenomenon was substantiated in experiments in mice[123,124]. It was shown that mice that were

sensitized to an egg allergen showed signs of anxiety when exposed to it and tended to avoid areas with trace amounts of the allergen. These effects on behavior were found to be dependent on classical allergic mechanisms involving IgE and mast cells. Additional experiments in mice and rats have confirmed the ability of allergen exposure to cause increased stress by detecting an elevated level of a stress-related hormone in the brain following the exposure to the allergen[125]. In addition, human studies also have shown the connection between stress-related neuropsychiatric disorders and allergic reactions[126,127].

The PHM-associated allergens/antigens would also potentially produce a stress response. Thus, the observed stress effects (e.g., increased anxiety, sleep problems, elevated heart rate, and lower heart rate variability) that occur in a wide range of diseases discussed throughout this article could be at least partly due to frequent elicitation of the stress response by exposures to PHM along with other sources of allergens/antigens.

The reason the stress response is more intense in some individuals could be partly due to factors that have led to a higher level of PHM colonization/infection, leading to a higher level of response to the PHM and cross-reacting antigens inside and outside of the body. Thus, people with inflammatory conditions would likely be more susceptible to the effects of stressors in the environment as they would be closer to the threshold for having observable negative effects from any additional stress from psychological factors. In other words, according to the PHMHEC hypothesis, those with higher levels of PHM colonization/infection would likely be more affected by stress both from physical and psychological sources and perceive various situations as more stressful.

Thus, it is proposed as part of the PHMHEC hypothesis that important immunological responses that evolved as a defense against potentially harmful toxins and microbes can lead to uneasiness or anxiety and the impulse to avoid certain environments. The avoidance impulse might not be recognized as such, but still the stress would be occurring at a level that may or may not be consciously perceived.

So, even though psychological stressors related to modern life certainly do play a role, their effects may be hard to separate from the effects of physiological stressors. In fact, there is likely a feedback between the two types of stressors. Chronic psychological stressors can suppress the immune system and the mucosal barrier defenses[128], which could allow more microbes to invade. This will cause more physiological stress, which will likely lead to psychological stressors being perceived as even more stressful. In addition, a person's usual coping strategies would likely become harder to use and less effective when the person is burdened by the higher level of stress. And, as will be discussed later in the section on mast cells, there is communication between mast cells and the nervous system that would also likely be involved in exacerbating the effects of stress and increasing allergic responses and the negative effects of PHM.

Another factor likely involved in the above progression involves secretory IgA (SIgA). SIgA is an immunoglobulin that binds microbial antigens and other antigens and is often described as the first line of defense at mucosal barriers. Reduced SIgA has been found to occur as a result of chronic stress[129,130]. Research showed that a condition resembling chronic obstructive pulmonary disease (COPD) spontaneously developed in a mouse model of SIgA deficiency as the mice aged and was associated with an altered lung microbial community and microbial invasion of the lung epithelium[131].

Another line of research worth noting has hypothesized connections of a number of inflammatory conditions, including systemic lupus erythematosus and metabolic syndrome, to elevated norepinephrine and the effects of stress[132]. Norepinephrine (aka noradrenaline) has similarities in its effects to epinephrine (aka adrenalin). Both are released as part of the fight or flight stress response, thus linking this hypothesis to the PHMHEC hypothesis. Elevated norepinephrine could be a response to PHM and cross-reacting allergens, as well as psychological stress.

Some other research related to avoidance of infection supports the idea that evolution would favor the development of mechanisms to avoid a wide range of dangers, which might include PHM. Some species of fungi are known to be able to cause allergic reactions as well as infections and Daschner[133] recently discussed a similar host defense view of disease related to damp environments based on evolutionary considerations. He proposed that some of the symptoms experienced in damp environments could have evolved to promote

avoidance of infection by fungi. There is also a field of research arising from the study of behavioral responses that appear to have evolved to help humans and other animals avoid infecting themselves and others (e.g., avoiding carcasses, sickness behavior, detection and avoidance of individuals consciously or subconsciously perceived to be sick[134]).

Survey of Allergic, Autoimmune and Inflammatory Diseases and Concepts Related to the PHMHEC Hypothesis

This section will give an overview of a variety of allergic, autoimmune, inflammatory and related diseases showing how research in diverse areas has been evolving over the last 10 years in a way that is compatible with the PHMHEC hypothesis.

To summarize many of the main points in this section, increasing evidence is being found in support of the interconnections between many chronic diseases that affect different parts of the body (united holobiont disease hypothesis). The presence of microbes, possibly in all tissues of the body, even in healthy controls, is increasingly being supported. Exposures to post-hunter-gatherer era microbes from a westernized diet, "sick buildings," damp environments, occupational settings and environmental chemicals/pollution are proposed to be involved in the increased rates of many chronic inflammatory diseases. There is increasing evidence that cross-reactivity among antigens from many sources is common. Allergy and other types of immune hypersensitivity to foods and inhalants occur as a result of diverse mechanisms so that no one test can rule them out and they are increasingly found in autoimmune diseases. Recent research is revealing new methods of detecting these reactions.

PHM colonization, sometimes leading to PHM infection, together with hypersensitivity to PHM and cross-reacting antigens can potentially account for diverse symptoms. The PHM effects might include immune suppression/dysregulation that can then increase susceptibility to opportunistic infections that potentially trigger and/or exacerbate many of the diseases being discussed. And the PHMHEC hypothesis could provide a unifying framework for diverse diseases, which could help guide the development of more effective treatment approaches.

Updated form of the hygiene hypothesis to explain the increase in allergic, autoimmune and inflammatory diseases

Before going into more detail about how various diseases and hypotheses are related to the PHMHEC hypothesis, it is important to mention that the hygiene hypothesis, which is often proposed to explain the increase in allergic and autoimmune diseases associated with westernization, has been updated. The hygiene hypothesis[135] postulated that individuals living in modern westernized societies are exposed to fewer infections now, and this means that the human immune system is not trained in the proper way and, therefore, is reacting to antigens that it should not react to, such as harmless allergens.

However, further studies reported observations that contradicted this form of the hygiene hypothesis. For instance, having the usual childhood diseases that were experienced before the era of vaccination did not lead to a reduced level of hypersensitivity-related illness[10,11]. In fact, it has been a matter of concern that some people have interpreted the hygiene hypothesis as meaning that they should not try to avoid infections. This clearly could lead to serious public health consequences[11].

Instead, what makes more sense and is supported by recent studies is that the microbes that appear to be offering some benefit are not the so-called "crowd" infections that affected humans after the beginning of agriculture and large settlements, which includes the aforementioned childhood infections. Instead, the proposed beneficial microbes are mainly from soil, plants and other components of the natural environment that humans were widely exposed to as hunter-gatherers. This also may include some parasitic organisms that humans evolved with. These microbes, with which humans and their ancestors evolved for millions of years,

are reduced or missing, and this is hypothesized to be leading to an increased level of allergic and autoimmune diseases. This revised hygiene hypothesis has been described in several ways, including the altered microbiota or altered microflora hypothesis[10], missing microbes or microbiome depletion hypothesis[12,136], and Old Friends hypothesis[11].

The PHMHEC hypothesis accepts reduction in some microbes as an important issue, and it proposes that PHM exposure may play an important role as well and may contribute to the reduction or loss of beneficial microbes. This proposal is exemplified by the development of imbalances in the microbiota of the gastrointestinal tract. The PHMHEC hypothesis proposes that an oxygen-rich inflammatory environment often arises to counter a microbial threat that is directly or indirectly related to hypersensitivity reactions to PHM. Then, beneficial species that do not tolerate oxygen from the Bacteroidetes and Firmicutes families have more difficulty surviving[137,138]. This imbalanced state of the microbiota has been given the name dysbiosis. Treatment strategies, such as antioxidant polyphenols, probiotics or manipulating the microbiota or its products may help mitigate the effects of the inflammation-induced changes, but addressing the source of the inflammation is also important. Thus, it is proposed here that increasing exposure to PHM associated with westernization could be a significant part of the explanation for the recent rise in many diseases involving dysbiosis and chronic inflammation.

Three categories of post-hunter-gatherer era microbes

It may be helpful to describe three categories of PHM. The first category are those microbes that are proposed to be PHM due to the fact that exposure tends to be increased in a post-hunter-gatherer environment: the "increased PHM" category, e.g., Legionella pneumophila, halophilic (salt-loving) Archaea[139], fungi in salt-preserved fish[140] and microbes that increase in agricultural products when they are consumed a long time after harvesting.

The second category of microbes are those that are PHM due to their being novel, the "novel PHM" category. This includes many of the low abundance uncharacterized or recently discovered species and strains, like those discovered in cleaning solutions or cleanrooms[141,142] and those that might be adapted to plastics and other relatively novel materials.

The third category, the "crowd/virulent PHM" category, are the causes of crowd infections that arose after agriculture and large settlements and includes microbes that cause acute diseases in healthy individuals, like the bubonic plague and smallpox. It also might include other virulent infectious microbes that might not be related to large settlements but might be more common due to a variety of different activities that have become more common in the post-hunter-gatherer era. This third category will not be discussed further in this article as this hypothesis is based on the first 2 categories of PHM, which are primarily environmental microbes that are much less virulent in healthy hosts. In a few cases, it may not be clear which category a microbe belongs in, but the categories could be helpful for heuristic purposes and might have implications for research.

Variants of the PHMHEC hypothesis; IWAI vs. sterile inflammation; environmental chemical exposure

The PHMHEC hypothesis has several variants. At the most basic level, it proposes that PHM are contributing to inflammation-related diseases through typically slow, chronic colonization/infection. Hypersensitivity-enhanced colonization/infection may be one of the mechanisms for evading the immune system; however, in some cases, some form of hypersensitivity may be present without enhancing colonization/infection, and this might be considered HAC, hypersensitivity-associated colonization/infection. In other cases, colonization/infection might not occur because the microbes might be unable to reproduce in the body, but continual re-exposure or difficulty removing the microbial antigens from the body might lead to constant or intermittent contamination that could lead to a similar disease process. Also, it might be that a primary or

secondary immune deficiency might lead to little or no hypersensitivity. The hypersensitivity or inflammatory response also might decline over time as immune system exhaustion or down-regulation occurs or the colonization/infection produces increasing immune suppression. In these latter cases, the PHM could still be having negative effects.

Another view that is related to the PHMHEC hypothesis is that there is no inherent difference in PHM as opposed to other microbes, yet other aspects of this hypothesis regarding hypersensitivity enhanced colonization/infection might still apply. This variant might be called the microbial hypersensitivity-enhanced colonization/infection or MHEC hypothesis, since it would not require that the microbes be post-hunter-gatherer era microbes. Although this is possible, it seems less likely, since most environmental microbes that humans were exposed to throughout evolution would presumably be coevolved with or at least generally tolerated by humans and unlikely to cause significant chronic disease by themselves. Another possibility is that they could contribute to disease but only in the context of a situation in which PHM or other factors had already caused immune suppression and/or dysregulation.

Another related hypothesis is the post-hunter-gatherer era chemical hypersensitivity hypothesis (PCH), where reactions related to chemical exposures take the place of reactions related to PHM. Research on the role of environmental chemicals or xenobiotics in autoimmunity has pointed to a number of possible mechanisms that include inflammation resulting from chemicals that humans were not exposed to until recently[143–145] and a discussion of these mechanisms is beyond the scope of this article. However, it is worth noting that a recent review of the subject acknowledged that microbial exposure occurring along with xenobiotic exposure could not be ruled out[144]. In the same review, the issue of the long time that it often takes for disease to develop after xenobiotic exposure was also mentioned, and the potential need for another factor, like a second hit, which might include an infection. If the PHMHEC hypothesis is correct, PHM exposure occurring along with the xenobiotic exposure is often significant and the long time needed for disease to develop could be partly related to the time needed for the PHM to multiply.

Interestingly, a recent study indicated that occupational exposure to silica induces a T helper type 2 cell (Th2) immune response that has detrimental effects on the ability of the immune system to control Mycobacterium tuberculosis[146]. This has been described as sterile inflammation, however it would be interesting to investigate whether there might also be low abundance microbes or microbial products in the silica that could also be involved in the effect of silica.

The impossibility, with the limited sensitivity of current techniques, to truly verify sterility is something that should be considered. In light of this, the acronym IWAI, "inflammation without apparent infection," might be used to replace sterile inflammation. Future research on low abundance microbes present in environmental chemicals and the tissues of the body that they affect seems called for.

There is much research to review to do justice to the evidence regarding the PHMHEC hypothesis and not everything can be included here. In order to cover a broad range of research, the following review will take a survey approach, and by emphasizing commonalities in different disease categories, it aims to show how advances in diverse fields are related to the PHMHEC hypothesis. It is beyond the scope of this article to consider all the alternative hypotheses that have been offered for each of the observations discussed, and in many cases, other explanations might still be valid. However, from the perspective of the PHMHEC hypothesis, the role of other hypotheses or mechanistic explanations might be complementary to the role of the PHM or might be part of the processes that arise directly or indirectly from the effects of the PHM.

Noninfectious respiratory diseases

In no area has the impact of advanced microbial sequencing methods had more of an impact than in the study of the respiratory tract, especially the lungs. The lungs were previously thought to be sterile when free of disease but now are known to harbor diverse microbial communities[147].

There are a wide variety of diseases of the respiratory tract that have no known infectious cause; however,

they involve inflammatory processes that resemble chronic low-grade infections[131,148,149]. One category is airway disease, which includes asthma and chronic obstructive pulmonary disease. Both diseases involve difficulty breathing through constricted airways, with asthma being generally more intermittent and often associated with allergic, chemical or other triggers. Allergic rhinitis includes symptoms such as nasal congestion, sneezing and watery eyes. And chronic rhinosinusitis involves inflammation and mucus production in the upper airways.

In recent years, there has been a growing appreciation of the linkages between these conditions, as exemplified by the united airway disease hypothesis[150,151]. For instance, those with allergic rhinitis are more likely to develop asthma[152], and the majority of asthma patients have allergic or non-allergic rhinitis[153]. And there are many other studies documenting the connections between these diseases[152–154].

Another broad category of chronic respiratory diseases, labelled inflammatory lung diseases[155], include many apparently noninfectious conditions including sarcoidosis, hypersensitivity pneumonitis (HP) and idiopathic pulmonary fibrosis. In some cases, inflammation in the lungs has been found to be secondary to autoimmune connective tissue disorders such as rheumatoid arthritis and systemic sclerosis[156].

A type of treatment used in nearly all of these respiratory diseases is immunosuppressive medications, such as corticosteroids, and there are widely varying prognoses, ranging from essentially curable to fatal. Those with the best prognosis are those related to known environmental exposures, like sources of mold or Actinobacteria, often in the occupational setting, where avoidance of the trigger can lead to an apparent cure, e.g., in HP[157].

As will be discussed below, though the origin of these diseases has historically been considered to be noninfectious, there is a growing understanding of the important role of microbes. In at least some of the diseases, there is a greater appreciation of potential interrelationships between microbes and hypersensitivity reactions, including cross-reactions.

Research on the noninfectious respiratory diseases is replete with discussions of triggering or exacerbating effects of well-known infectious agents[158–160]. From the perspective of the PHMHEC hypothesis, a review paper by Earl et al[158] on asthma is pertinent. After discussing established roles for infectious agents as triggers and exacerbating factors in asthma, newer research related to the allergic host defense response is discussed. The authors describe this new view of allergy as an exciting and relatively unexplored area in which potential mechanisms are beginning to be investigated and they discuss some of the new research in murine models. The intriguing role of the gut microbiota and diet in asthma is also highlighted.

The potentially important role of rare microbes is suggested by studies showing that severe asthma with fungal sensitization can be ameliorated by anti-fungal therapy even when the fungi are too low in abundance to be detected[158]. This supports the idea that rare, even undetectable species can be important, in accord with the PHMHEC hypothesis. A recent article made a similar point based on methods that were able to detect fungi, which they stated were clearly part of the rare biosphere[161]. The study found 60 nonpathogenic fungal genera in the oral cavity and noted that this has potential implications for diseases involving hypersensitivity. As has been mentioned for a variety of conditions, such as asthma, hypersensitivity pneumonitis[162] and sarcoidosis[163], it is unlikely that all relevant antigens have been discovered.

Occupational exposure/built environment microbiology

The occupational connection seems to be an important unifying theme across many of these respiratory diseases[164,165] as well as other autoimmune and inflammatory conditions discussed later. Whether the environment is an office building, factory, moldy dwelling or an intensive farming operation, there are exposures, both microbial and chemical, that differ from exposures occurring when humans were exclusively hunter-gatherers. These frequently recognized connections between diseases and occupational/built environment exposures are compatible with the PHMHEC hypothesis.

Farmworkers as well as those who have work or hobbies involving birds, are more susceptible to HP[166].

Besides occupations, activities such as the use of hot tubs and humidifiers, are well-known sources for lung diseases, including disease from mycobacterium avian complex. Occupational asthma and HP occur in a wide range of industries involving chemicals, wood dust, grain, animal dander and fungi.

Even some idiopathic conditions, like idiopathic interstitial pneumonia, are found to have associations with occupational exposures such as metal dust and tetrachloroethylene[167], but the relevant antigens have not been discovered. The PHMHEC hypothesis would suggest that in many cases, microbial antigens and PHM colonization/infection are involved, possibly in addition to the effects of non-microbial antigens. Synergistic effects of combinations of chemicals, inorganic and organic dust and microbes might be key in idiopathic conditions as well as those that are known to be linked to particular substances such as silica, asbestos and beryllium.

In the case of tobacco smoke-associated diseases, like COPD, the many chemicals in smoke are not the only potentially damaging components[168]. Microbes are abundant in cigarette smoke and researchers are beginning to investigate their role[168–170]. Since microbes have the potential to colonize, increase and mutate, they would have a particularly high potential to lead to serious progressive illnesses that could last long after smoking cessation.

Sarcoidosis is an idiopathic lung disease that also may affect other organs, and some authors have proposed that it may be related to chronic infection[149,171] or hypersensitivity to environmental antigens[172]. Newman et al[163] state that sarcoidosis is often "clinically and pathologically inseparable" from HP. They give the examples of chronic beryllium disease and metalworking fluid hypersensitivity pneumonitis as conditions that were originally diagnosed as sarcoidosis until the inciting antigens were discovered. Sarcoidosis has been linked to mold exposure in damp environments[173]. A study[172] found evidence for a greater sensitivity of peripheral blood mononuclear cells to fungal and bacterial cell wall components in sarcoidosis.

In sarcoidosis, there has been research suggesting a causal role for bacteria, such as nontuberculous mycobacterial species[149,174] and Cutibacterium acnes (formerly Propionibacterium acnes)[174]. Antifungal[175] and antibacterial[176,177] approaches have shown some promise, and there is one ongoing antibacterial trial[178] and one that was just completed but results have not been reported yet (see NCT02024555).

The PHMHEC hypothesis proposes a complex interaction arising from the role of the PHM. The PHM antigens in the environment causing hypersensitivity may be identical or cross-reactive with the colonizing/infecting PHM. There could also be secondary opportunistic infections [159], including a polymicrobial infection, e.g., with fungi and bacteria[179]. This complex causal network could explain why so many of these chronic diseases have been so difficult to understand and to successfully treat.

The PHMHEC hypothesis proposes that there is frequently some level of immune suppression/dysregulation occurring as a result of the PHM colonization/infection. This could mean that the typical antimicrobial approach might not be successful, since the immune system would not be very effective in aiding the antimicrobial medication to combat the pathogens.

One or more of the microbes in the polymicrobial infection might be suppressing the immune system by blocking the vitamin D receptor[177,180]. This could be the cause of the high ratio of active vitamin D (1,25-D) to inactive vitamin D (25-D), typically found in sarcoidosis and some other inflammatory diseases[177,181]. A treatment approach that attempts to overcome this hypothesized blockade has shown promise in sarcoidosis and some other autoimmune and inflammation-related diseases[177,182,183]. Further research is needed, including randomized controlled trials.

Interestingly, the average severity of sarcoidosis and mortality from the disease has been reported to be increasing in recent years[184]. In addition, chronic pain conditions, small fiber neuropathy and severe fatigue have been found that may persist after the lung disease is in remission[184]. The PHMHEC hypothesis could explain the systemic development of the disease and these persisting symptoms. PHM from the environment colonize/infect the individual, sometimes after a higher-than-usual environmental exposure. Then, one or more acute infections and/or increased psychological stress might occur, exacerbating the disease process.

At that point, a vicious cycle of hypersensitivity reactions and further colonization and secondary infections occurs, leading to more overt signs of disease. In some cases, the more overt respiratory disease, perhaps largely from secondary infections, might improve, but the PHM might remain and cause systemic symptoms.

It might be that reduction of exposures to potential sources of PHM in the food, in the air or on the skin might help in the recovery and work synergistically with antimicrobial approaches to obtain better results. In depth study of a wide range of microbial exposures is important.

Recently, Horve et al[185] reviewed the groundbreaking research that is being done on the microbial inhabitants of built environments, and much that is being discovered is compatible with the PHMHEC hypothesis. They noted that over 150 fungal and dozens of bacterial allergens have been identified so far.

A study of 15 persons using wearable sampling devices identified over 2500 species of microbes that were encountered, and, remarkably, 43.7% of the DNA information could not be classified[186]. The authors noted that despite their use of advanced methods, their study still greatly underrepresented the diversity of microbial exposures. In addition, Horve et al[185] pointed out how harsh conditions, including exposure to cleaning solutions, could lead to mutant forms, adding to diversity and novelty in the species/strains. The complexity of the microbiology of the built environment is apparent. Microbes that might be beneficial are intermixed with those that could cause disease.

Microbial allergy/hypersensitivity and the role of colonization and infections in chronic respiratory diseases

There are relatively few non-fungal microbial allergens identified so far, but the PHMHEC hypothesis and current trends suggest that this is due to historical factors rather than a scarcity. Recent reviews show that this deficit in identified microbial allergens is beginning to be remedied[187]. One example is research showing that a common bacterial plant pathogen, Pantoea agglomerans is an important cause of human respiratory diseases such as asthma and HP[188]. Lecours et al[189] have shown Archaea to be abundant in some farm environments. They found one of the Archaea provokes immune reactions in the lung and gastrointestinal tract[190]. Viral allergens have been little studied, but IgE-mediated responses to viruses have been found for HIV[191], varicella zoster[192,193], influenza virus[92] and parvovirus[194].

Water-damaged buildings and other damp environments lead to increased fungal and bacterial growth. These damp environments have been associated with the development or exacerbation of a range of noninfectious respiratory diseases, such as asthma, HP, allergic rhinitis and chronic rhinosinusitis[162].

Although dampness was associated with increased disease rates or symptoms in several studies, Mendell et al[162] noted that it was difficult to find clear relationships between disease features and measured microbial exposures. There are a number of theories to explain this[162], but it seems low abundance PHM might play a role, since they too would increase in damp environments and could easily be missed by commonly used microbial detection methods.

Historically, bacteria have not received as much attention in investigations of water-damaged buildings. Researchers have suggested that this is an oversight that should be rectified[195,196], since some bacteria, such as Mycobacteria, can cause greater immune responses and be just as serious a threat as molds[196]. Interestingly, a study of the microbial biofilm on a showerhead found dozens of strains of Mycobacteria, and the authors suggested that some might be a health hazard[197]. And studies of other frequently damp locations in the built environment like drains[198] and kitchen and bathroom surfaces are revealing rich microbial communities[199,200].

In occupational studies, it is easier to find potential disease-provoking antigens because there are groups of employees who have similar, often distinctive, and sometimes extreme levels of exposure. But with the perspective of the PHMHEC hypothesis, and the growing research, there is reason to suspect that occupational exposures are just the tip of the iceberg of environmental microbes' influence on chronic inflammation-related diseases.

Deviating from the focus on chronic disease, it is interesting to consider a type of acute infectious pneumonia known as Legionnaires' disease that was discovered to be caused by the environmental microbe Legionella pneumophila[201]. This bacteria is sometimes an inhabitant of water cooling towers[202], and can be found in other places in the built environment, such as showers, fountains and medical equipment[203], especially in situations without adequate chlorination[204]. Under certain circumstances, our modern practices cause exposure to this microbe in aerosolized form at a much higher level than likely would have occurred among hunter-gatherers, thus it could be considered to be a PHM.

Interestingly, there was an outbreak of Legionnaires' disease studied in the United Kingdom that was associated with sick building syndrome[205]. Only 1 of the 6 people who developed pneumonia from L. pneumophila was immunocompromised and the average age was 53. Typically, Legionnaires' disease only causes pneumonia in older, more immunocompromised people, so this outbreak was atypical. The attack rate was also higher than usual. As for sick building syndrome, the questionnaires returned by 30 staff members who worked in the affected wing of the building and 69 staff members who did not, revealed a strong association between eye strain and dry cough and working in that wing. For many of the staff, the symptoms were temporally associated with working in that wing. The authors noted that microbes associated with the cooling tower could possibly be involved in the sick building syndrome considering the inadequately maintained cooling tower and air conditioning system.

In relation to the above study, the PHMHEC hypothesis suggests that PHM in the cooling tower water and air conditioner played a causal role in the sick building syndrome symptoms. Dysregulation and/or suppression of the immune system from the sick building syndrome could have been significant enough in some of the workers to allow L. pneumophila to cause acute pneumonia in healthier, younger people than usual. PHM allergy/hypersensitivity and colonization/infection might be hypothesized to be the underlying cause of both the sick building syndrome and the susceptibility to the pneumonia.

In the case of another respiratory disease, chronic rhinosinusitis (CRS), the concept of bacterial allergy has been included by Bachert et al[206] as part of the immune barrier hypothesis. They cite work by Calenoff et al[207] on CRS with nasal polyps and concluded that bacterial colonization is likely exacerbating inflammation through mechanisms involving bacterial allergy. Calenoff et al[207] found that IgE antibodies specific for bacteria were present in 37% of patients with CRS, a percentage significantly greater than in allergic rhinitis. However, this is probably an underestimate, since they were only testing for reactions to known bacterial allergens, and as mentioned previously, characterization of bacterial allergens is far from complete.

If the PHMHEC hypothesis is valid, it would be expected that many microbes that have more virulent features would take advantage of situations in which the immune system is suppressed or dysregulated by PHM. Some examples of such opportunistic species are bacteria such as Haemophilus influenzae, Pseudomonas aeruginosa and Mycoplasma pneumoniae. The fact that many of these species are present frequently and do not cause noticeable symptoms in asymptomatic carriers[208] suggests that other factors, potentially low abundance PHM, are the underlying cause of disease.

An analogy with AIDS might be appropriate. In HIV-AIDS, there is a detrimental effect on the immune system that underlies multiple overt opportunistic infections[209]. The PHM might play an immunosuppressive role analogous to HIV, although in a more subtle, harder-to-detect and more complicated manner.

It is possible that some of the opportunistic microbes would also qualify as PHM and might even take advantage of cross-reactions with closely related microbes in the environment to lead to disease. It is an interesting possibility to consider that the ability of Mycobacterium tuberculosis to cause so much disease in poverty-stricken areas might relate, at least in part, to abundant closely related mycobacteria in the environment. These cross-reacting environmental mycobacteria might reduce the ability of the immune system to control M. tuberculosis. M. tuberculosis is not a PHM since it is found in pre-agricultural human remains[210]. However, perhaps there are PHM in our modern environment that it cross-reacts with, that were not abundant previously, and hypersensitivity to them might affect the ability of M. tuberculosis to

cause overt disease. This is highly speculative but seems worth considering given the toll that tuberculosis is taking globally and the rise of multi-drug-resistant forms. And, interestingly, allergic sensitization has been found to be increased in tuberculosis patients and is reduced after effective antimicrobial treatment[211].

Examples of opportunistic infections found in patients with asthma and various allergic conditions include viruses (e.g., rhinovirus, respiratory syncytial virus) and bacteria (e.g., Mycoplasma spp) as well as fungal and parasitic infections[212]. Even genitourinary infection from E. Coli and reactivation of Herpes viruses appear to be more likely[212].

So, if PHM underlie allergy and generally increase susceptibility to a wide range of infections, the increased susceptibility might also apply to the infections that seem to trigger allergic disease. This would assume that there is some PHM effect occurring prior to development of the more overt allergic disease. This might be observed in the form of susceptibility to severe or frequent infections, which might cause a predisposition in infants and children to the development of allergic diseases[213]. If antibiotics are used in these infections, this would raise issues of confounding with antibiotic use. The focus may be on the antibiotic association in the development of the allergic conditions, as has been the case in some studies[213,214], when actually it may be that the PHM are the underlying cause for an increased susceptibility to infection, leading to the need for antibiotics, which then leads to the allergic diseases. Antibiotic use can have a negative effect on the microbiota, but this type of confounding and the potential effect of the PHM might also be considered.

One likely source of PHM is the fine particulate matter component of air pollution. It has been suggested that particulate matter that is 2.5 um or less is a particularly important source of microbes and could lead to pathological effects[215,216]. A recent study found the proportion of pathogenic species increased with air pollution levels associated with urbanization[217]. A study also found that there were changes in the pharyngeal microbiota following a severe air pollution (haze) event, including detection of 142 new genera in the pharynx[218].

A number of studies have linked fine particulate matter exposure to increased rates of allergic diseases, including asthma[219], respiratory infections[220], emergency room visits[221,222] and overall mortality[223]. A wide variety of other diseases have been associated with air pollution as well, including autism[224–226] and a variety of neurological diseases, including Alzheimer's disease[227,228].

Even smoke from wildfires has been found to contain viable microbes[229]. This is because fires and their smoke are not homogeneous and so not all areas are so hot as to kill all the microbes. The PHMHEC hypothesis proposes that the microbial contribution, including PHM, are likely an important part of the negative effects of smoke and other sources of air pollution.

A microbial cross-reaction example involving 2 fungal species is consistent with the PHMHEC hypothesis

Bacher et al's research[230] related to acute allergic bronchopulmonary aspergillosis, which affects some asthma and cystic fibrosis patients, might be seen as fitting into the PHMHEC framework. The study found that an overgrowth of intestinal Candida albicans causes a T helper type 17 cell (Th17) immune response to be generated against C. albicans. This results in a Th17 hypersensitivity reaction in the lungs to a cross-reactive fungi, Aspergillus fumigatus. What may be particularly problematic for the successful resolution of the disease is that the Th17 response generated by the C. albicans in the gut is apparently not the type of response that is helpful in eliminating the A. fumigatus from the lungs[231]. Bacher et al[230] point out that cross-reactions are very common and not adequately studied. They also suggest that C. albicans may play a similar role in Crohn's disease, a type of inflammatory bowel disease (IBD).

The PHMHEC connection is present because exposure to these two fungal species would not likely have been as high in hunter-gatherer populations. Hunter-gatherers would not likely have been exposed to A. fumigatus to the extent that some individuals are in water damaged buildings[232] or when working near

moldy hay. C. albicans overgrowth has been found to be more common in those with high sugar/starch diets[233] and high sugar and refined grain consumption is a hallmark of the westernized diet.

However, there may be a deeper level at which the PHMHEC hypothesis is involved. It is still not entirely clear what factors allow the C. albicans to overgrow. It might be related to antibiotic use, as is frequently stated[234]. Studies typically show antibiotics are associated with an increased rate of dysbiosis of some type[235], but do not always cause significant negative effects[236]. And the issue of multiple possible explanations for dysbiosis associations with antibiotics has been recognized[234,236]. Interestingly, a recent review found that antibiotic use was only associated with the dysbiosis-related disease, inflammatory bowel disease, in certain ethnic groups, and reviewing IBD studies in many countries, a westernized diet was found to be the most ubiquitous environmental factor associated with disease incidence[237].

The PHMHEC hypothesis proposes that a contributing cause of dysbiosis of many types, including increased C. albicans, could be exposure to PHM that cause host defense responses in the form of allergy/hypersensitivity reactions. Even low grade inflammation has been found to promote C. albicans colonization [238], and that inflammation might be initiated by PHM. Over time, this PHM exposure could contribute to dysbiosis, hypersensitivity reactions, increased physiologic stress and microbial invasion and thus cause increased susceptibility to a number of inflammation-related diseases. Interestingly, C. albicans colonization of the gut in mice was shown to exacerbate several types of allergic reactions[239], and fungal colonization/infection has been suggested to possibly directly influence the tendency to develop allergic diseases in humans[240].

A relevant point was raised in an article discussing the rise of infections with another fungi, Cryptococcus, in recent decades among immunocompetent patients[241]. The authors noted that it is possible that our ability to perceive immunocompetence might be related to difficulties in detecting immunodeficiency. This relates to the above example of a relatively subtle immune imbalance and the discussion throughout this article of PHM colonization/infection causing immune suppression/dysregulation. The type and level of immune suppression/dysregulation might not always be detectable by the usual measures of immune competence, yet might have important implications for susceptibility to infections.

Focal infection and bacterial allergy—history and current research

The part of the PHMHEC hypothesis that is similar to what has been accepted for at least some cases of asthma with fungal sensitization, allergic bronchopulmonary aspergillosis and chronic rhinosinusitis, as discussed above, is the idea that hypersensitivity to microbial antigens combined with the microbe's colonization or infection can contribute to chronic disease. This idea is related to a theory that gained popularity in the first half of the 1900s: the focal infection theory.

The focal infection theory actually traces its roots back long before the 1900s to several ancient accounts, including the observation by Hippocrates of a patient in whom the removal of an infected tooth was followed by the resolution of chronic joint pain[242]. In the early and mid-1900s, the concept of bacterial allergy was often connected to the focal infection theory[243]. One aspect of the theory was that if there was a bacterial infection in one part of the body, for instance, related to a dental infection, it could cause hypersensitivity to that bacteria wherever it occurred, even if there was no obvious infection in that other part of the body. Thus, if the same bacteria were present in another part of the body where symptoms were occurring, for example, a joint, then resolution of the dental issue could decrease bacterial hypersensitivity and help resolve the joint pain.

An updated version of at least some aspects of the focal infection theory has gained increasing acceptance in recent years due to the recognition of the association between oral infections, such as periodontitis, and several other chronic diseases[242]. In this updated version, systemic infection or infection of nearby organs and immune dysregulation or autoimmunity are discussed, rather than bacterial allergy. For instance, P. gingivalis found in periodontitis, has now been found in the brain of Alzheimer's patients and in atherosclerotic plaque[244] and has been associated with a number of other diseases[245].

A combination of factors likely led to the loss of interest in the focal infection theory. It was probably partly due to the lack of current molecular techniques to evaluate the theory. In addition, overzealous practitioners were going too far in removing teeth and organs that were thought to be sources of infections that might be contributing to other diseases. There was no understanding of the PHM related concept that at least some of the infectious agents might be microbes that were being ingested or were continually present in some environments. Thus, simply removing an infected tooth would not be adequate, though it might help a few people to some extent.

Interestingly, desensitization to bacterial allergens was tested in several clinical trials and appeared to be successful in treating several diseases. For example, among the few articles published in English in the last 50 years, Nogaller et al[246] found bacterial immunotherapy to be successful in treating chronic colitis. Bacigaluppi et al[247] concluded that bacterial allergy is more important than bacterial infection as a cause of allergic rhinitis and asthma in many instances. They implicated the bacteria, S. aureus, Klebsiella pneumoniae and Diplococcus pneumoniae. Oehling et al[248] reported a high success rate with bacterial immunotherapy in 80 children with asthma who were considered to have bacterial asthma in contrast to allergic asthma. They were treated with bacterial vaccines, and it was reported that 86.2% had good or very good responses. Another study showed that autologous bacteria induced chemotaxis of peripheral blood mononuclear cells from non-atopic asthmatics but not healthy subjects and cited work on bacterial allergy in this context[249]. A review by Malling[250] concluded that the evidence was strong for the use of bacterial vaccines in at least some proportion of asthma cases.

The use of the term vaccine by researchers of the era is interesting, since it is usually defined as stimulating the immune system to prevent or eliminate infections. In the current era, allergen-specific immunotherapy is typically described as desensitizing the immune system to harmless allergens through small doses of sublingual or injected allergen extracts[251] or via the newer method of inducing oral immune tolerance by gradually increasing allergen ingestion in a carefully controlled manner[252].

The PHMHEC hypothesis would suggest that the earlier researchers using bacterial vaccines may have been increasing the ability of the immune system to reduce bacterial colonization/infection, thus reducing symptoms. Similarly, one might speculate that some forms of current allergen-specific immunotherapy may be stimulating the immune system to eliminate at least some PHM that cross-react with the known inhalant or dietary allergens. It might be hypothesized that a lack of understanding of the extent of microbial colonization might limit the effectiveness of bacterial vaccine and current immunotherapy approaches.

Need for higher-level analysis?

It may be that some PHM are particularly harmful in certain contexts, but it also may be that the effects of many PHM accumulate, and disease might result from the equivalent of damage from "a thousand pinpricks." This might require a different outlook when looking for patterns. Just as some researchers have used microbial diversity for a higher level or higher scale of analysis in the context of hierarchy theory[253,254], researchers might need to examine the diversity of PHM relative to total diversity. This might be more productive than looking for the colonization/infection of only one or a few species/strains. This will be difficult to do adequately until more research is done that identifies relevant PHM. Perhaps biomarkers that are proxies for PHM might be discovered that might be validated for at least some diseases.

Autoimmunity – microbes cross-reacting with self-antigens (aka molecular mimicry)

Only a few of the respiratory conditions discussed here are currently thought to be autoimmune. Sarcoidosis has some connections with autoimmune diseases but known autoantibodies are lacking[255]. There are a number of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis, that often involve the respiratory tract[256]. Epidemiological research shows that inflammatory bowel disease, an inflammatory condition that used to be considered autoimmune and is associated with a

number of autoimmune diseases[257], is often preceded by airway diseases[258]. And as discussed previously, many airway diseases are known to be commonly associated with microbe-rich environments, such as damp buildings or in agriculture. This adds to the evidence supporting a connection between inhaled microbes and non-respiratory diseases. And the above connections between respiratory conditions and autoimmune diseases is compatible with a role for inhaled PHM in at least some autoimmune diseases.

Interestingly, evidence for some degree of autoimmunity has been found in a number of chronic respiratory diseases that are not traditionally considered to be autoimmune, such as asthma[259], chronic rhinosinusitis[260], idiopathic pulmonary fibrosis[261] and COPD[262].

From the perspective of the PHMHEC hypothesis, whether a condition has a strong autoimmune component or not may not be the key issue with respect to underlying factors in disease causation. Autoimmunity has been found to be a natural phenomenon during infections[263] and even in healthy controls as a means of "cleaning up" after damage that occurs for a variety of pathological and non-pathological reasons and possibly serves other functions as well[263,264]. Instead, the key may be to recognize a microbial cause of inflammation that may be leading to a higher level of autoimmunity than usual[264].

It is interesting to consider the title of Trost et al's[265] paper, "No human protein is exempt from bacterial motifs." And they found the high degree of similarity between human proteins and bacterial sequences by looking at only 40 species of bacteria. On further consideration, the high bacterial cross-reactivity with human self-proteins might have been expected considering the fact that all life evolved from the same unicellular ancestors. In addition, mutations to enhance cross-reactivity with host proteins could be adaptive for microbes attempting to survive inside their larger, multicellular hosts, be they plants, animals or protists.

This frequent cross-reactivity has been seen as a reason to downplay the importance of cross-reactions of microbes with self-antigens as a cause of autoimmune disease, or at the very least, to conclude that other factors must be involved as well. The complexities of this and other autoimmune disease causation issues are discussed by Root-Bernstein et al[266,267]. The simultaneous involvement of multiple infectious agents could account for some of the difficulties in explaining autoimmune disease causation[266]. Dysregulation or suppression of the immune system by PHM could increase susceptibility to multiple other infectious agents and thus contribute to autoimmunity.

According to the PHMHEC hypothesis, repeated exposure to microbes and chemicals that humans did not coevolve with, coinciding with the reduction of microbes that humans did coevolve with, occurs in genetically susceptible individuals. These factors, possibly combined with stressful triggering events and triggering infections, lead to a vicious cycle. This vicious cycle is essentially one of increased microbial invasion, microbiota and stress-related barrier breakdown, hypersensitivity, immune suppression/dysregulation, more PHM invasion, secondary infections and increased psychological and physiological stress. This is proposed to eventually lead to chronic allergic, autoimmune or other inflammation-related diseases. Those individuals with fewer triggering/exacerbating factors and/or lower genetic susceptibility usually remain healthy but may have some subclinical signs and symptoms related to PHM.

The PHMHEC hypothesis proposes that in those with diagnosable illnesses, this vicious cycle has such significant pro-inflammatory and stress-related effects that it may eventually overcome the usual methods that the neuro-immune system uses to avoid, eliminate or tolerate PHM and withstand opportunistic infections. Arleevskaya et al [268] describes how repeated infections tend to precede rheumatoid arthritis development, and this has been observed in other conditions, like chronic rhinosinusitis[269], asthma[270] and COPD[270].

PHM are hypothesized to be evading the immune system in multiple ways

According to the PHMHEC hypothesis, IgE-mediated allergic responses are protective at least to some degree. In fact, as mentioned previously, this appears to be supported by research. Selective IgE deficiency may lead to more serious illness than many allergic condition (e.g., more infections, allergic-type symptoms,

cancer and autoimmune disease[89,271–274]). This suggests that the IgE-mediated reactions are not the cause of disease, but a response to the cause.

If the allergy/hypersensitivity responses are protective, as the PHMHEC hypothesis proposes, then why are these diseases more prevalent in recent decades? The PHMHEC hypothesis suggests an answer: that humans did not evolve the ability to optimally respond to and control the post-hunter-gather era microbes in the current context of rapidly increasing exposures associated with westernization. Thus, protection afforded by IgE-mediated and other immune hypersensitivity responses can be helpful, but in certain contexts, is inadequate and can become pathogenic.

The immune system has many lines of defense, and a single microbial strain often has multiple adaptations that counter host defenses. "Dual use" virulence factors allowing survival within cells, as described previously, are one set of adaptations; and a few of the other ways by which microbes, and, in particular, some PHM, might suppress/dysregulate the immune system are discussed below.

Camouflage –antigenic variation and immunodominance

Colonizing/infecting PHM might be viewed as being camouflaged by the closely related microbes encountered in the environment. It would be expected that antigenic variation would occur as environmental microbes adapt to the diverse habitats within the human body. This antigenic variation, by itself, can enhance the ability of the microbes to evade the immune system[275].

With so many different areas to colonize in the human body, there would be potential for a large adaptive radiation, a term used in evolutionary biology to describe a diversification of microbes to fill a large variety of ecological niches or roles. In this situation, diverse environmental microbial antigens encountered at mucosal surfaces would be similar, but not identical, to those already adapted to living in one or more tissues/organs. Thus, the environmental microbes could provide a type of camouflage that could make it more difficult to target those that have already colonized. One method of removing the camouflaging, according to the PHMHEC hypothesis, would be to reduce the exposure to the reaction-provoking environmental microbes so that the immune system can more effectively target the different antigens of the PHM inside the body.

This is similar to the situation where the immune system responds to certain antigens that are considered immunodominant, while other subdominant ones result in a much lower and essentially ineffective immune response. For instance, the immunodominant component (epitope) of the influenza virus keeps the immune system from focusing on more widespread conserved subdominant components. This has led to an approach to developing a universal influenza vaccine where the immunodominant component is bound to a substance so that it won't be recognized and this will allow the immune system to target the subdominant component[276]. Other related research has discussed how one virus may influence the ability of the immune system to target another virus[277].

Faucet analogy – outer-directed Th2 immune response reduces inner-directed Th1 and Th17 immune response

A simple way of viewing how some PHM might avoid elimination might be illustrated by the analogy of the sink overflowing due to a faucet being left on. The faucet being left on might be seen as environmental microbes being encountered at surfaces of the human body that have interfaces with the external world. The immune system can sense that external microbes are a continued threat and are continuing to enter the body. In the context of the analogy, the immune system senses the faucet has been left on. To address the faucet being on, the immune system uses the Th2 responses involving IgE and other antibodies, mast cells and eosinophils. These rapid responses are important for countering incoming threats. The immune system prioritizes the faucet being on instead of the water already in the sink (the microbes already colonizing the body). This might be seen as the tendency for Th2 responses to downregulate T helper type 1 cell (Th1) and Th17 responses. Whether or not one of these three T helper cell responses dominate is determined by many

factors, including levels of a number of cytokines. But a recognized feature of Th cells is their production of cytokines that can promote their own differentiation and decrease that of other Th cells.

Once the external microbial antigen threat is reduced or eliminated, for instance, through antigen avoidance, the immune system can presumably increase the non-Th2 mechanisms that may be needed to help reduce or eliminate many of the microbes already colonizing the body. Once the external focus is no longer needed, the Th2-mediated hypersensitivity is likely to decline. If exposures are kept within a more moderate range and mucosal barrier defenses are maintained, exposures below a certain threshold potentially could be tolerated without noticeable symptoms.

The exact mechanisms involved in what determines Th1 vs Th2 reactions is still not fully elucidated[278] and is clearly complex. Interestingly, a review of the topic by Bretscher[278], discusses research showing that adding a component to an antigen that makes it more foreign increases the tendency toward a Th2 response. It would seem that at least some of the PHM antigens would be likely to be perceived by the immune system as more foreign, and this might lead to stronger Th2 allergy/hypersensitivity reactions.

Recent research also supports the idea that stress biases the response toward a Th2 response[279]. And obesity also appears to potentiate a Th2 response according to a recent study using a mouse model of the skin disease, atopic dermatitis[280]. Th2 responses include IgE-mediated rapid responses that would help protect against invading microbes according to the PHMHEC hypothesis.

Misdirection of immune response related to cross-reactions

Microbes that have antigens that cross-react with one another might misdirect the immune response. An example of this was discussed previously, where a C. albicans induced Th17 response in the intestinal tract combined with a cross-reaction with A. fumigatus in the lungs, apparently contributed to lung pathology[230]. This example also reinforces the systemic nature of the inflammation, since the C. albicans overgrowth in the gut appears to negatively affect the immune response in the lung.

Toxins that manipulate the immune system

P. gingivalis, interacting with several other oral pathogens, apparently leads to periodontitis by manipulating the immune system[281]. Periodontal disease has been associated with many other diseases (cardiovascular disease, Alzheimer's disease, rheumatoid arthritis[78]), including a number of respiratory diseases (e.g., asthma, COPD[282–284]).

P. gingivalis is typically present at low levels and is able to have an effect disproportionate to its low abundance due to its immune manipulation. It might be considered to be a PHM because it has been found at increased levels from ancient DNA in oral plaque since the beginning of agriculture[285]. However, the recent rise in its ability to cause disease might be secondary to other factors, possibly including other PHM exposures.

Another possible example of a toxic effect is the proposed Vitamin D receptor blockade in autoimmune disease[177,181]. As mentioned previously, it has been hypothesized that a microbial product blocks this important immune pathway. One might speculate that in some cases, the immune system might produce an immune response to the VDR-binding toxin, and there would be a cross-reaction with other substances with a similar structure that also bind the VDR, like vitamin D. And in fact, antibodies against vitamin D have been found at a higher level in certain autoimmune diseases[286].

The potential for medication allergy/hypersensitivity reactions being related to medication cross-reactions with microbial antigens seems worth investigating. It might lead to the discovery of microbes that produce toxins that have similarity in structure to various drugs, which might have implications for treatment.

Systemic nature of allergic, autoimmune and inflammatory diseases – the united holobiont disease hypothesis

The more allergic, autoimmune and inflammatory diseases are studied, the more connections among different diseases are being found. The subject of these connections is too extensive to cover completely here, but published research indicates that if one studies virtually any inflammation-related disease, one finds increased risk for comorbidities as well as medical conditions that precede disease onset. Many of these are mentioned throughout this article. For instance, people with certain autoimmune diseases have a higher chance of developing another autoimmune disease[287]. Having three or more autoimmune diseases has even acquired the name multiple autoimmune syndrome and is increasing [288].

The allergic march is frequently discussed in which children develop one allergic condition after the other, e.g., atopic dermatitis, allergic rhinitis, asthma and food allergy, not always in the same order[289]. Marple[290] noted links between allergic rhinitis and disorders such as asthma, otitis media, nasal polyposis, and chronic rhinosinusitis. Genetic factors are likely involved, however the increasing disease rates indicate environmental factors are involved as well.

There are also interesting connections between conditions involving many systems of the body, including the brain, autonomic nervous system and the gastrointestinal system. For instance, chronic rhinosinusitis patients are reported to experience more premorbid anxiety, headaches, gastroesophageal reflux disease and sleep apnea[291]. An interesting study has implicated microbes from the sinuses in chronic rhinosinusitis patients as an etiologic factor in ulcerative colitis[292].

The interconnectedness of allergic, autoimmune and inflammatory diseases is what would be expected if there was an important role of many widespread PHM. The disease that appears first in an individual, the progression of that disease and the addition of comorbid diagnoses would depend on multiple genetic and environmental factors, including the pattern of PHM exposures.

Analogous to the united airway disease hypothesis, one might envision a united holobiont disease hypothesis. Over the years of research on airway diseases, it was found that there was overlap between upper and lower airway diseases, leading to the united airway disease hypothesis, as discussed in an earlier section. It is worth considering whether a similar unity might be supported on the scale of the entire holobiont (the organism and its microbiota).

Once milder manifestations that typically do not lead to a diagnosis are included, the connections that would support a united holobiont disease hypothesis might become more extensive and clearer. Examples of milder manifestations include occasional bowel symptoms, rhinitis after meals, mild premenstrual or menstrual symptoms (e.g., pain, diarrhea, and mood fluctuations), occasional rashes or itching, increased levels of itching after insect bites, occasional mild to moderate headaches, mood changes and insomnia. Many of the milder manifestations likely would precede diagnosis of a clear allergic, autoimmune or inflammatory condition, but sometimes might develop later. The changing pattern of immune responses and additional PHM exposures/invasion and opportunistic infections, along with other factors like stress and environmental chemical/pollutant exposures would be predicted to influence the evolving disease processes throughout a lifetime.

This interconnectedness not only would be expected to arise from the tendency for microbes to spread throughout the body, e.g., cell to cell, and via the lymphatic system and the blood supply, but also would be expected due to immune system and nervous system effects that occur throughout the body (i.e., neuro-immune cross-talk), including effects at distal locations. A recent review describes this phenomenon of multiple factors potentially leading to systemic effects in the case of oral inflammation[78].

The increasingly recognized relationship between gut microbiota imbalances and allergic, autoimmune and inflammation-related diseases also tends to support the systemic nature of these diseases [293–295]. Thus, a discussion of some diseases affecting the gastrointestinal tract is an appropriate preliminary to a survey of some additional autoimmune and inflammation-related diseases.

Gastrointestinal diseases: irritable bowel syndrome and inflammatory bowel disease

Irritable bowel syndrome: pathogenesis, treatments, tests for food reactions

Studies have varied in their estimates of the incidence of irritable bowel syndrome (IBS), with some studies showing it to be as high as 22% of the population studied[296]. In addition, a recent study showed self-reports of at least some degree of bowel symptoms in a European population at 68.6%, with 56.3% of these individuals reporting symptoms at least 3 days per month[297].

IBS incidence has been reported to be increasing in many countries in recent decades in association with westernization[298]. It typically includes symptoms such as abdominal pain, diarrhea and/or constipation, gas and bloating. IBS commonly occurs in conjunction with other conditions, such as allergic diseases[299], ME/CFS[300] and fibromyalgia syndrome[301]. Although its underlying cause is unknown, advances have been made in understanding the mechanisms involved and in developing new treatment approaches.

Some interesting advances include the finding of increased mast cells, which are important in allergic reactions, in the gastrointestinal tract in IBS patients[302]. In subsets of patients with IBS, associations with food allergies[303], food hypersensitivities[304] and food intolerances[305] have been found.

Non-IgE-mediated food hypersensitivity tests are a controversial area in IBS research[306,307] as well as other conditions[308]. Historically, the term food intolerance has been used to include virtually all reactions that are not IgE-mediated immediate reactions as shown by skin prick tests or IgE specific blood tests. However, there is now recognition of several non-IgE-food hypersensitivity conditions, including an often severe condition mainly affecting infants and small children called food protein-induced enterocolitis syndrome[309].

There are other types of adverse food reactions that have often been assumed to be non-immunological even though tests have not typically been done to verify that assumption. Proving that a reaction does not involve the immune system could be extremely difficult in many cases, since one would need to test for all possible immune reactions to show that they were not involved, and new tests are revealing new types of reactions, as discussed below. One example of a non-IgE-mediated adverse food reaction is the type that has been investigated as possibly being related to elevated immunoglobulin G (IgG) levels specific for particular foods.

IgG4 is a subtype of the B cell produced IgG antibody. Tests based on high IgG4 antibodies specific to particular foods have been criticized at least partly because increases in specific IgG4 antibodies have been correlated with the success of immunotherapy conducted to desensitize patients who have IgE-mediated allergic disorders. As a result, they have been called "blocking" antibodies, and it has been proposed that they are associated with tolerance and should not be used as a means to assess food reactions[306].

However, increasing evidence in a variety of areas suggests that this view needs to be reassessed, at least in certain diseases[304,308]. This is especially true given the lack of a thorough understanding of the role of IgG4 antibodies in the immune system and the increasing incidence of a class of diseases called IgG4-related diseases. In IgG4-related diseases, chronic inflammation is associated with IgG4 antibodies[310], some of which can bind food antigens[311]. In addition, a recent study showed that IgG4 levels appeared to correlate with IgE levels and hypersensitivity to inhalants in asthma and upper airway disorders, but not in atopic dermatitis[312]. And there is evidence for the role of IgG4-mediated food reactions in inflammatory bowel disease[308,313] and eosinophilic esophagitis[314,315].

In the light of the above evidence, it would appear preferable to base assessment of tests based on specific IgG4 and other immunological markers on the results of well-conducted randomized controlled trials rather than theories about mechanisms. Some studies have shown that food hypersensitivity tests involving IgG, including IgG4 specific tests, led to successful treatment of IBS[304], and there is support for this type of approach in other conditions[313,316,317]. However, more studies are needed.

Another type of non-IgE-mediated food hypersensitivity test has shown a statistically significant benefit in a double blind randomized controlled trial of a diet intervention in 58 adults with irritable bowel syndrome[318].

The antigen leukocyte cellular activation test (ALCAT) results were used to determine the diet intervention. A reduction in neutrophil elastase concentrations was found to be associated with symptom reduction. A later study attempted to elucidate the mechanism of the reactions and implicated eosinophil DNA release associated with protein kinase C signaling pathways[319].

The use of ALCAT results to shape a dietary intervention was also tested in a 4-week double blind randomized controlled trial that assessed body mass index, inflammation and medical symptoms[320]. The trial included 87 adults in the treatment group and compared them to a placebo group of 46 adults. The treatment group had foods removed from their diet that they were sensitive to according to the ALCAT test and the placebo group had foods removed from their diet that they were not sensitive to according to the test. The diet based on the ALCAT test results was associated with significantly improved body mass index, serum amyloid A and medical symptom questionnaire scores.

A test that focuses on non-IgE-mediated hypersensitivity reactions to foods and chemicals is called the LRA (lymphocyte response assay). The results of testing led to individualized diets, and when combined with a nutrient repletion program, was found to improve pain and several other symptoms in fibromyalgia syndrome patients compared to controls, although the results did not reach statistical significance[321]. A similar approach in both type I and type 2 diabetes mellitus (T1D and T2D) showed promising levels of blood sugar reduction, which reached statistical significance for T2D[322]. Cow dairy was the most frequently identified food reaction in patients with T2D according to the LRA. Healthy controls do not typically show any food reactions with LRA testing[322]. Interestingly, in T1D, the number of individuals with immune hypersensitivities to toxic minerals, environmental chemicals and food additives was particularly high according to the LRA results. When immune reactions to chemicals occur, they are typically due to the chemicals being haptens, with their antigenicity resulting from their ability to bind to a larger molecule.

A study using confocal laser endoscopy (CLE), showed that reactions to foods in many IBS patients did not involve the typical mast cell-mediated reactions, but apparently did involve eosinophil degranulation[323]. After 6 months on an elimination diet based on the test results, 68% of the patients showed at least 80% improvement. Patients that showed reactions using this test were typically atopic (allergic), having a 4-fold increase in prevalence of atopic disorders. The authors of a recent study called this type of reaction an "atypical allergic reaction not involving IgE[324]."

Other variations of typical allergic reaction mechanisms are being found, thus showing that diverse types of tests may be needed to find all the relevant reactions. A study by Savage et al[325] found that one type of IgE-mediated reaction to peanuts involved basophils rather than mast cells. The basophil activation test has also been shown to be useful[326]. Interestingly, local allergic reaction assessment based on measurements of local IgE levels and nasal allergen challenges shows promise in elucidating mechanisms in some cases previously thought to be nonallergic rhinitis[327].

Specialized testing methods are now being used in eosinophilic esophagitis, showing the importance of food-specific IgG4 levels in the esophagus[314,315]. IgE does not appear to be involved in this disease[328]. And it has also been found that skin mast cells do not respond in the same way as esophageal mast cells. It might be hypothesized that the difference in mast cell response in the esophagus might be related to PHM colonizing/infecting the esophagus.

Further insights might arise from recent research in eosinophilic esophagitis. Wright et al[314] noted that eosinophilic esophagitis has been known to develop during oral immunotherapy and speculated that IgG4 might initially be produced to reduce IgE-mediated disease, but eventually might lead to a pro-inflammatory state in some allergic individuals. If this is true, then it might be that this progression might also apply to the development of IgG4-related diseases and perhaps other diseases.

These studies implicating different hypersensitivity mechanisms and showing benefits from diets based on the results of different types of tests are related to the PHMHEC hypothesis in that many types of hypersensitivity reactions would be expected in association with diverse microbial exposures and genetic contexts. And it is further evidence that reliance on any one type of test, like IgE specific blood tests or skin prick tests, is

inadequate to rule out food allergy/hypersensitivity reactions. Multiple hypersensitivity mechanisms may even be involved in the same patient.

An underappreciation of the role of allergy/hypersensitivity reactions has probably resulted from reliance on the more limited types of tests previously available. The availability of multiple novel testing methods and increasing understanding of the diversity of mechanisms and antigens shows promise in elucidating disease mechanisms, not only in IBS, but in many other diseases. However, further studies evaluating the newer types of tests in a variety of diseases are needed.

It is interesting that current IBS dietary recommendations[329] include avoiding or limiting carbonated beverages, alcohol, tea and coffee as well as fatty and spicy foods, all items that would be expected to be high in PHM. Carbonated beverages contain a number of novel ingredients that might contain PHM and spices are often consumed long after harvest, so at least some PHM might increase in abundance. Fermentation used to make beverages, like alcohol, coffee and tea, would give more opportunity for at least some PHM to increase. In a later section on diet, fat as a potential source of PHM is discussed. Some IBS patients also have more symptoms when consuming gluten, which may be a result of gluten itself or other characteristics of gluten-containing foods[305], as will be discussed later.

Another interesting topic is that of small intestinal bacterial overgrowth (SIBO), which occurs in 4 to 78% of IBS patients[330]. Dietary approaches that reduce the foods that fuel bacterial growth, like the low fermentable carbohydrate or low FODMAP (low Fermentable Oligo-, Di-, Mono-saccharides and Polyols) diet and an elemental diet, have support[329,331,332]. Certain antibiotics also appear to be helpful[333].

Antibodies produced against self-tissue as a result of certain types of acute gastroenteritis is a mechanism for SIBO that is gaining support[334]. These autoantibodies are thought to affect the migrating motor complex that causes normal intestinal motility and helps keep the small intestinal bacterial levels low. Whether or not the autoantibodies are involved, the true underlying cause of SIBO is still unknown[333,335].

The PHMHEC hypothesis has the potential to explain many features of IBS and SIBO. It could explain, for instance, why some patients have higher levels of the autoantibodies mentioned above. The higher autoantibodies in the more treatment-resistant patients could result from a higher level of PHM colonization/infection and/or a greater exposure to PHM and their cross-reacting antigens in food and inhalants. The continued presence of a proportion of the PHM that might be antibiotic-resistant and/or repeated reinfection with PHM could also explain why some patients with SIBO need repeated antibiotic treatments. At least some PHM might cause an upregulated Th2 immune response and perhaps even be a necessary precursor to the autoantibody production thought to underlie the abnormal intestinal motility. A recent study showed functional gastrointestinal disorders, which include IBS, are associated with a pro-inflammatory state in the central nervous system, and the authors concluded that this immune activation could be mediated by the gut microbiota[336].

At least some PHM in the intestinal tract would likely be reduced in patients who are on a low FODMAP diet or who are taking antibiotics, and this could help to reduce symptoms. Reduction of antigens based on allergy/hypersensitivity testing methods might be helpful partly because it could reduce at least some of the antigens that cross-react with the PHM-produced antigens and may directly reduce PHM as well.

Just as in other diseases discussed here, stress and infections have also been found to be related to IBS. A study of IBS in military personnel found significant interactions between infectious gastroenteritis, depression, anxiety and subsequent risk of IBS[337]. Post-infectious IBS is found to occur in a significant number of individuals who have acute infectious gastroenteritis from bacteria such as Campylobacter, Salmonella and Shigella. It was found that persons who developed post-infectious IBS were more likely to have greater anxiety scores before the acute gastroenteritis episode, and they also showed a Th2 skewed immune response[338]. These study results could be explained by the PHMHEC hypothesis since prior PHM colonization/infection and hypersensitivity could potentially account for both the stress-related symptom of anxiety and the Th2 skewing occurring before the gastroenteritis. Thus, the reactions to PHM-associated antigens are hypothesized to lead to the anxiety, which often occurs with depression, and the increased susceptibility to the

gastroenteritis and IBS.

Another infectious agent linked to IBS is the bacteria, Chlamydia trachomatis, which has been detected at low levels in the small intestines of some IBS patients[339,340]. From the perspective of the PHMHEC hypothesis, this could be a secondary opportunistic infection contributing to disease symptoms in some patients.

Some authors have emphasized the role of infectious agents[341] and multiple treatable causes, with one author even questioning the existence of IBS as a clinical entity[304]. Helpful interventions might well be overlooked if these treatable causes are neglected. This view of IBS as heterogeneous is compatible with the PHMHEC hypothesis, since the multiple treatable causes are seen as potentially stemming from the three PHM-related components of PHM colonization/infection, stress and hypersensitivity.

Inflammatory bowel disease: Crohn's disease and ulcerative colitis

Crohn's disease and ulcerative colitis are the most common types of IBD, and both involve inflammation of the gastrointestinal tract. They differ in a number of respects, however, both are increasing worldwide in association with the adoption of a westernized diet[237,342]. They were previously considered to be autoimmune, but now they are hypothesized to result from abnormal immune responses to intestinal microbiota[343].

Dysbiosis is thought to play a role in IBD and it has been observed in both patients and their non-affected family members[344]. So, dysbiosis may precede the illness. In what at first would appear to be conflicting data, another study focusing on detecting the onset of Crohn's disease found that just prior to the development of Crohn's disease, the gut microbiota was close to that of healthy controls[345]. This would indicate that the dysbiosis began after the onset of the disease.

This apparent conflict regarding dysbiosis is likely largely due to different types or degrees of dysbiosis being discussed. The use of the term dysbiosis has been criticized of late due to its being used to mean different things in different situations[346]. A wide variety of types and degrees of dysbiosis as well as dysbiosis present in seemingly healthy controls would be consistent with the PHMHEC hypothesis; many relatively asymptomatic individuals might still have some level of effect from the PHM, which would often be reflected in some degree of dysbiosis.

In any case, a greater abundance of oxygen-tolerant Proteobacteria and lower levels of microbial diversity are typically observed in IBD, and that is one common type of dysbiosis. The Proteobacteria, in particular, the family Enterobacteriaceae, include many pathogenic bacteria. An increased level of Enterobacteriaceae has also been noted in the intestinal tract in asthma and a number of other inflammatory diseases[137,347].

Microbes such as adherent invasive E. Coli are thought to play a role in IBD, and bacteria, such as Mycobacterium avian subspecies paratuberculosis, Yersinia spp and Listeria spp, have been implicated in Crohn's disease. A reduction of species associated with anti-inflammatory effects is also observed[343].

A type of dysbiosis involving low abundance PHM might be what leads to the disease according to the PHMHEC hypothesis. This might then be followed by the usually observed increases of the Enterobacteriaceae, including known opportunistic pathogens that overgrow during chronic inflammation.

Roberts-Thomson et al[348], when discussing the cause of ulcerative colitis, included in a list of potential pathogenic responses "impaired tolerance to new microbiota," without explicitly discussing what constitutes the new microbiota. The PHMHEC hypothesis proposes that the new microbiota could be PHM. And the idea of impaired tolerance might be replaced by the concept of a strong host defense response occurring due to PHM colonization/infection when combined with environmental and dietary exposures to cross-reacting antigens.

In a recent article by Rani et al[349], it has been proposed that IBD lies on a continuum with IBS, even mentioning an "overlap syndrome." Although this is not a generally accepted idea, a discussion of this concept is interesting because it highlights many similarities between the diseases. Both diseases appear to

involve many of the same factors, such as stress, infections, a westernized diet and dysbiosis as discussed in Rani et al[349]. And in IBS and IBD, positive responses to elimination diets and antibiotics have been observed, as discussed elsewhere in this article.

From the perspective of the PHMHEC hypothesis, it seems plausible that IBD can develop from IBS or subclinical dysbiosis. Increases in PHM, with their translocation/invasion across mucosal barriers, and subsequent increase of opportunistic pathogens, might occur in genetically susceptible individuals. The observed immune response to known commensal microbes could be the result of an upregulated immune response due to the increased abundance of PHM. The inflammatory response from hypersensitivity to PHM could also cause greater intestinal permeability. Thus, many microbes, including commensal microbes, would likely cross the intestinal mucosal barrier more frequently, contributing to increasing immune reactions against them.

Although there appears to be some modest benefit from antibiotics in IBD, the evidence is conflicting[350,351]. And this might be partly because at least some of the PHM may not be affected significantly by the antibiotics. Archaea, fungi, viruses and protozoa could potentially be involved, and antibiotics would be ineffective against them. In addition, according to this hypothesis, some of the microbes involved may be present in the environment or food, and thus, reinfection may occur. And as mentioned earlier, immune suppression/dysregulation from the PHM might lead to lower antibiotic effectiveness as well.

A hypothesis proposed to explain Crohn's disease is relevant to this discussion of the PHMHEC hypothesis. The cold chain hypothesis was proposed to explain Crohn's diseases in 2003[352]. It was noted that the use of refrigeration (the cold chain) paralleled the outbreak of Crohn's disease in the 20^{th} century. Bacteria that survive in refrigerated environments, such as Yersinia spp and Listeria spp, are often found in Crohn's disease lesions. A study by Forbes et al[353] made observations on the timing of the beginning of the use of refrigeration and found it coincided with increasing Crohn's disease incidence, thus supporting the cold chain hypothesis.

The PHMHEC hypothesis suggests that other unknown species may also be part of the cause of this suggested link to refrigeration. In addition, other changes were occurring in the food system and in lifestyles during the era when refrigeration was becoming widespread, so the causation may be more complex and involve PHM from diverse sources, not just refrigerated products and not just Yersinia spp and Listeria spp.

An interesting approach currently being studied is fecal microbiota transplantation (FMT). It is generally found to be effective in Clostridioides dificile infection (formerly Clostridium dificile)[354]; however, more research is needed. FMT also appears to be helpful in ulcerative colitis but generally has to be repeated regularly for improvement to be maintained[355]. From the point of view of the PHMHEC hypothesis, this might be expected since changing the fecal microbiota would likely lower the exacerbating antigens and potentially increase more anti-inflammatory microbes, leading to remission. However, it would not likely affect PHM and opportunistic infections that may have invaded the mucosal lining. In addition, it would not change PHM exposure in the environment and diet. Perhaps if FMT were combined with reduction in the latter two sources of PHM it would be more effective. FMT is being studied in many different conditions (e.g., Crohn's disease[356], IBS[357], and autism[358]) and is showing promise; however, there is concern that some people are trying to do it themselves, without medical supervision. Long-term safety and efficacy of FMT has not been established for these conditions, and, recently, a death due to an infection from FMT has been reported[359].

Other autoimmune, inflammatory and related diseases

Multiple sclerosis, amyotrophic lateral sclerosis, rheumatic heart disease, celiac disease, spondyloarthritis

Discussion of all the many diverse autoimmune and inflammation-related diseases is beyond the scope of this article. However, as will be summarized below, for many of the most thoroughly studied diseases

the findings appear to be generally compatible with the PHMHEC hypothesis in all the relevant areas. Allergy/hypersensitivity to foods and inhalants is increasingly being found in autoimmune diseases as discussed further in a later section on mast cells. Stress has been found to be associated with the initiation and exacerbation of autoimmune diseases[109,349,360]. Sleep disturbance, which often accompanies stress responses, is found to predispose to the development of autoimmune disease[361]. Microbes have been implicated in multiple ways[362,363], including changes in the gut microbiota[293].

Differences in microbial communities in the affected tissues in autoimmune/inflammatory diseases is increasingly being found. Branton et al[23] and Alonso et al[77] detected significant differences between microbial communities in multiple sclerosis patients relative to controls in brain autopsy tissue. Kriesel et al[25] found evidence suggesting that multiple sclerosis is triggered by a diverse set of microbes found in brain lesions. They analyzed brain biopsy specimens of living multiple sclerosis patients and found significant differences as compared to similar samples from epilepsy patients. In amyotrophic lateral sclerosis, brain autopsy evidence implicating both fungi and bacteria has been reported, and it has been suggested that the effectiveness of anti-microbial therapy should be assessed[76]. Hammad et al[20] found differences in the fungi and bacteria in the synovial fluid of rheumatoid arthritis patients compared to controls and found a borderline significant increase in Aspergillus in the patients. Although more studies are needed, this appears to be a promising line of research.

Regarding cross-reactions, several autoimmune diseases have been proposed to involve cross-reactions. In rheumatic heart disease, it is believed that streptococcal bacterial antigens cross-react with heart tissue leading to heart damage[364]. And in celiac disease, cross-reactions between microbial antigens and gluten have some support (see below), however, the pathogenesis is complex and only partially understood[365].

Root-Bernstein et al[266] has discussed how at least one additional infecting microbe, in addition to Streptococcus pyogenes, may be needed to explain rheumatic heart disease. The PHMHEC hypothesis would suggest that there are likely multiple colonizing or infecting PHM involved, which could predispose to infections with a number of opportunistic pathogens.

In celiac disease, asymptomatic infection with reovirus[366], Epstein-Barr virus[367] and enterovirus[368] have been suggested as possible triggering factors. Also, certain rod-shaped bacteria have been implicated in a Swedish outbreak of celiac disease[369]. Small intestinal bacterial overgrowth has been suggested to be involved in some celiac disease patients[370]. Other autoimmune and allergic disorders have been found to be more common in celiac disease patients in the United States[371]. The role of intestinal dysbiosis and environmental factors, along with the requisite genetic predisposition, are discussed in a recent review[372].

The frequent systemic nature of celiac disease and the fact that not all celiac patients recover when they strictly eliminate gluten also point to the existence of one or more missing factors. The PHMHEC hypothesis would suggest that PHM immune suppression/dysregulation and/or PHM cross-reactions are potential missing factors leading to immunological responses to one or more infectious agents and the reaction to gluten/gliadin.

Interestingly, a recent study[373] found a cross-reaction between gliadin epitopes and antigenic peptides from Pseudomonas fluorescens. P. fluorescens is an environmental bacteria that can be found in the human gastrointestinal tract, lungs and other areas of the body without causing symptoms, but can also be an opportunistic pathogen[374]. P. fluorescens has been found in moldy buildings and on plant surfaces, stainless steel surfaces, showerheads and walls and can survive in refrigerated food[374]. If this cross-reaction is confirmed to be causally involved in celiac disease, it might be seen as consistent with the PHMHEC hypothesis. P. fluorescens could be a PHM and/or an opportunistic pathogen that increases as a result of a PHM-induced suppressed/dysregulated immune system.

Air pollution and microbe-rich environments have been implicated in incidence or exacerbations of many diseases, including autoimmune diseases[162,375,376]. The increased incidence of allergic and autoimmune disease in the last 50 years has been proposed to be related to increased air pollution[375–378] and/or environmental chemical exposures[379,380]. For example, type 1 diabetes, in which the insulin-producing

cells of the pancreas are destroyed by autoantibodies, has been linked to air pollution[381–383].

One of the most well-known of the autoimmune diseases is multiple sclerosis, and there have been recent advances supporting the role of chronic infections. Although much more research is needed, multiple sclerosis patients on 6 months of a combined antibiotic protocol (minocycline, roxithromycin and tinidazole) have shown promising improvement in extracranial venous circulation[384]. The antibiotic approach was attempting to treat Chlamydia pneumoniae infection, but it was also effective in patients who did not show evidence of C. pneumoniae infection. Some suggestive evidence of antibiotic effectiveness in multiple sclerosis was also found in another study[385]. These studies, combined with research implicating other microbes[23,25,386,387], suggest that there may be multiple infectious agents involved. The antibiotics might have resulted in benefit due to reducing multiple PHM and opportunistic pathogens. These results are compatible with a causal role of westernization-related PHM suppressing/dysregulating the immune system, leading to susceptibility to multiple opportunistic infections.

A possible fungal role in multiple sclerosis and other diseases is discussed by Benito-León et al[388]. They discuss multiple lines of evidence, including a report of the successful use of anti-fungal medication to treat several multiple sclerosis patients[389].

It is interesting to consider the role of global warming, which has been implicated in the emergence of a new drug-resistant fungal pathogen simultaneously and separately on three continents[390]. It is hypothesized to be, at least partly, the result of warming temperatures driving evolution of the fungi toward toleration of a higher temperature, which is closer to the temperature of the human body, thus facilitating infection.

This appears to be the first case of a fungal pathogen emergence that appears to be related to global warming. However, there could be other undetected instances of greater fungal colonization/infection leading to disease that might be related to warming temperatures. The increased atmospheric carbon dioxide from burning fossil fuels is yet another effect of westernization occurring on a global scale. Increasing fungal involvement in chronic disease that might result from warmer temperatures could significantly add to the serious and increasing effects climate change is having on health and many other aspects of life[391].

Another hypothesis related to fungal infection is an updated version of the Catterall-King hypothesis for spondyloarthritis and related diseases[392]. It proposes a causal role for a chronic infection with an unknown fungi that is primarily sexually transmitted. Exposures to varied inflammatory stimuli, such as bacteria, viruses and other fungi, result in periodic disease exacerbations that are hypothesized to be due to increased immune reactions to the proposed causal fungi. The PHMHEC hypothesis would suggest that the proposed fungi may be part of a polymicrobial infection. The underlying chronic infection, along with periodic acute exacerbating infections might result from immune suppression/dysregulation and hypersensitivity reactions from the effects of the PHM. Limited data supports an association of spondyloarthritis with a westernized diet[393], allergy/hypersensitivity[317,394] and stress[395], which is consistent with the PHMHEC hypothesis.

Autism spectrum disorder

Autism spectrum disorder (ASD) is an increasingly common neurodevelopmental disorder that leads to a variety of symptoms, including difficulty with social interaction. Although there is a genetic contribution, there is also a significant environmental component[396,397].

In recent years, ASD research is revealing ASD features that are compatible with the PHMHEC hypothesis. Peripheral and brain inflammation are involved[398], and associations have been found with autoimmune diseases/autoantibodies[399], maternal inflammation[399], allergic conditions[400] and obesity[398]. Mast cells have been connected with some of the symptoms of ASD, such as anxiety/fear[401]. It has been reported that the rate of ASD is 10-fold higher in patients with mastocytosis[402], a condition in which there are increased numbers of hypersensitive mast cells in multiple organs.

Affected ASD individuals were shown to have lower heart rate variability than members of control groups[403], and this variability is potentially related to the role of stress as discussed earlier. In some studies, exposure

to air pollution has been associated with ASD incidence[396,404].

Regarding microbial involvement, gut dysbiosis, with or without gastrointestinal symptoms, is present in many individuals with ASD[397]. A westernized high saturated fat diet led to autistic-like behaviors in a mouse model in one study[405]. Interestingly, a recent study detected dysbiotic patterns of bacteria and fungi, including the fungus, A. fumigatus, in the blood of ASD patients and their mothers[406].

Of course, more research is needed. However, studies in ASD are beginning to show that at least a proportion of individuals with ASD may have a low grade polymicrobial infection and an underlying etiology that potentially fits the framework of the PHMHEC hypothesis.

Myalgic encephalomyelitis/chronic fatigue syndrome

ME/CFS is a complex disease of unknown cause that can apparently be triggered by infections, stressful events and/or toxins[300] and involves inflammation of the brain[407,408], abnormalities in cellular energy production[409,410], nitrosative and oxidative stress[411] and unrefreshing sleep[412,413]. Oxidative and nitrosative stress occurs when oxidants are increased relative to anti-oxidants.

Virtually all of the previously discussed factors related to the PHMHEC hypothesis are found in ME/CFS. For instance, studies have shown an association between preexisting allergies and the development of ME/CFS[414,415]. And one of the approaches that has been found to be helpful is the elimination of exacerbating foods[416–418]. A recent study showed that patients with psoriasis, an autoimmune skin disease, were significantly more likely to develop ME/CFS[419]. Autoimmunity has been implicated in ME/CFS since there is an increased frequency of autoantibodies and family history of autoimmune disease[420].

A study showed a reduction in gut microbial diversity, an increase of species associated with inflammation, and signs of increased incidence of microbial translocation across an inflamed and more permeable gut wall[421]. This would be compatible with the postulated increased invasion of low abundance PHM along with other microbes that is part of the PHMHEC hypothesis. A study showed an elimination diet and nutrient intervention aimed at helping repair the gut wall was successful in improving symptoms in a subset of ME/CFS patients[422].

Morris et al[411] comprehensively reviewed many aspects of ME/CFS. They highlighted the development of a downregulation of the immune system that has been called a hypometabolic, hibernation-like state, perhaps similar to dauer (a hibernation state allowing survival in adverse conditions found in some nematodes[409]).The development of this hypometabolic or downregulated state is an important aspect that has been recognized over the last 5 years. It has been found that to successfully investigate ME/CFS, studies often need to stratify based on severity of illness or length of illness. Otherwise the milder or shorter-term cases will dilute or even negate the patterns.

A recent example of the importance of stratification is the case of low heart rate variability during sleep, which is an indicator of activation of the sympathetic nervous system associated with the stress response. Evidence for greater sympathetic nervous system activation during sleep has been found in ME/CFS[423], but not in all studies. A recent study indicated that the association of lower heart rate variability with ME/CFS is most consistent and clear if severity of fatigue is included in the analysis[424].

Another example of the importance of stratification is the finding that the pro-inflammatory state in early ME/CFS would not have been found if they had not stratified by the number of years of illness[425]. Without the stratification, the immune activation in early disease would have been averaged out by the immune exhaustion or downregulation they detected in those who had been ill for more than 3 years.

On the whole, sympathetic nervous system predominance is supported in studies using a variety of analysis methods, not only for ME/CFS, but for fibromyalgia syndrome, IBS and interstitial cystitis, and it has been proposed that this may be related to an underlying common pathogenesis[426]. The PHMHEC hypothesis suggests that it is part of a common PHM-related stress response.

A vicious cycle involving oxidative and nitrosative stress[411,427,428] is hypothesized to occur in ME/CFS. However, from an evolutionary perspective, it seems probable that humans and other animals have the ability to avoid such vicious cycles persisting indefinitely since any genes leading to this type of damaging cycle would be eliminated by natural selection and thus be rare.

An exception to this is when there is an evolutionary mismatch, i.e., when current conditions differ from conditions under which the organisms evolved. Evolutionary mismatch is an important concept from the field of evolutionary medicine and is, in fact, the underlying principle behind the PHMHEC, altered microbiota, environmental chemical/pollution exposure and hygiene hypotheses[429].

The novel conditions are proposed here to be related to PHM, sometimes with environmental chemical exposures contributing. Thus, the apparent vicious cycle involving oxidative and nitrosative stress and apparent immune imbalances is hypothesized to be primarily a result of ongoing colonization/infection with PHM and possible secondary infections that the immune system is attempting to control. The observed oxidative and nitrosative compounds are an important part of the immune system's mechanisms to fight infection and thus would be expected.

Sick building syndrome has been proposed to result from chemical contaminants and microbial sources and has symptoms that can be similar to ME/CFS[430–432]. Perhaps some cases of ME/CFS might be seen as involving an extension of the concept of sick building syndrome to one where all buildings and even many outdoor environments allow microbial exposures that contribute to symptoms. In at least some of the more severe cases, it might be that the level of PHM colonization/infection, possible secondary opportunistic infections and immune and metabolic changes acquired in one or more sick buildings may not adequately normalize even when in an optimal environment.

Chu et al [300] found that 20% of the ME/CFS patients they surveyed thought a particular toxic substance exposure might have been an initiating factor in their illness and they discuss several other studies with similar results. Although chemical contaminants or toxins could be a contributing factor, the PHMHEC hypothesis suggests that microbes associated with the chemicals could be at least as important.

Although there may be one or more triggering infections and/or genetic variants involved in ME/CFS causation, it also might be that an invasion of many relatively low virulence PHM is the primary underlying cause of ME/CFS. The constant battle with the internal and external threats perceived by the immune system might eventually lead to the immune and metabolic systems shifting toward a downregulated or hibernation-like state. This might be considered a reasonable shift from an evolutionary standpoint. If the invading PHM and other microbes have not killed the individual in the first few years and the immune response itself has increasingly debilitating effects, the alternative approach of downregulating the effort expended in combating the microbes might be advantageous.

This downregulation differs from many well-known autoimmune illnesses where the immune system stays vigorously activated and perhaps in these autoimmune diseases the microbial strains involved might be fewer in number, but perhaps more virulent and/or more immunogenic. Cross-reaction with self-tissue would contribute a significant additional inflammatory component and genetic factors would certainly contribute as well. Of course, significant variation is expected, and in some individuals with an autoimmune disease, the PHM invasion/colonization might also be extensive, perhaps leading to cases of autoimmune disease that are more fatiguing and debilitating.

It is interesting to consider the idea that a high level of virulence is not necessarily a trait that benefits the microbe, recently discussed by Casadevall et al[433]. So, it would not be surprising if low virulence, low abundance microbes, typical of the PHM in the current hypothesis, would be common and would have largely escaped the attention of researchers. This lower level of virulence, together with an immune response that is not very effective in targeting the PHM and opportunistic infections, could explain why immunosuppressive medications are apparently at least moderately effective in many of the diseases discussed here. In other words, the immune system's response is causing tissue damage, with little, if any, benefit as far as combating the infections. Thus, suppressing the immune response turns out to be helpful in many cases, at least for a

period of time.

It is also worth noting a prior hypothesis regarding ME/CFS that resembles the PHMHEC hypothesis in some respects. Bellanti et al[434] presented a model of ME/CFS involving allergy, chronic infection and stress. They also discussed the inconsistent results from research on reactions to food dyes in attention deficit hyperactivity disorder (ADHD). ADHD has been found to be more common in ME/CFS and ADHD adults experience fatigue more often than healthy controls[435]. In light of the PHMHEC hypothesis, the conflicting results regarding reactions to food dyes studied in ADHD patients could be due to individuals differing as to which particular items they react to, with possibilities including a very wide range of microbes, foods, additives and inhalants. These types of individual differences might be expected in ME/CFS as well.

Fibromyalgia Syndrome

Fibromyalgia syndrome, although not apparently an autoimmune condition, is found at a significant rate in a number of autoimmune diseases[436–439]. Fibromyalgia syndrome is characterized by widespread pain, fatigue and sleep disturbances[436]. It commonly accompanies conditions like migraines[440] and IBS[301]. Fibromyalgia pains often vary in location and intensity[441]. This could be a result of variations in PHM and other microbe levels in the affected areas. The variation in pain in a particular area could also result from variations in the level of exposure to PHM in the environment and food/inhalants that cross-react with the PHM in the painful areas, thus affecting local inflammation.

The presence of low abundance PHM in one or several areas, like the area of a rash or a painful muscle or joint, may provide a reservoir of microbes so that, even if they are very rare or absent in some other tissue compartment (e.g., the blood), they may still maintain a presence in the body. This is analogous to how ecological systems maintain stability through spatial extent[254,442]. A microbe could maintain itself indefinitely in a human despite varying in abundance in particular areas.

Skin Diseases Involving Inflammation

Skin diseases involving inflammation (psoriasis, atopic dermatitis, pemphigus vulgaris, urticaria) are only discussed briefly in this article, however, they also may fit into the PHMHEC framework. In addition, it is important to recognize that any microbes colonizing the skin are easily spread to surfaces in the environment and inhaled. And anything that is inhaled also likely enters the mouth and digestive tract, thus providing further potential linkages among inflammatory diseases.

Disease-defining infections

In many of these diseases, there may be infectious agents that take advantage of the hypothesized PHM-induced suppressing/dysregulating of the immune system to trigger the development of a particular disease. These infectious agents, together with genetic factors, might be found to determine which disease might develop and thus be disease-defining. An example might be the proposed role of Yersinia spp in Crohn's disease[352]. There also may be multiple infectious agents that are disease-defining for a given disease.

However, the PHMHEC hypothesis would suggest that these possible disease-defining infectious microbes may be secondary opportunists and would probably not have caused disease in persons less affected by PHM. Treatment of these opportunists with antimicrobials may be difficult in a patient with immunosuppression stemming from PHM and may not lead to full recovery. Reprising the analogy with AIDS, it is addressing the underlying immunosuppressive cause that is key; in the case of AIDS it is HIV, and in the case of the current hypothesis, it is one or more PHM.

However, unlike HIV infection, addressing the PHM issue may not be necessary in all cases. In some cases, the secondary infections might be treatable with current anti-microbials. But the PHMHEC hypothesis proposes that the greater the level of remaining PHM, the more prone the patient may be to disease recurrence and other health problems.

Mast cells are involved in allergic, autoimmune and related diseases

Although mast cells were discovered in the 19thcentury, they have only recently begun to be appreciated for their involvement in a wide array of immune functions[443–447]. They have long been known to be involved in allergy, along with other cells, such as basophils and eosinophils. Mast cells are thought to be one of the oldest components of the immune system and evolved to take on a wide range of roles[448]. Mast cells degranulate to cause an immediate release of preformed molecules, like histamine, as occurs in the life-threatening allergic reaction known as anaphylaxis. They also secrete numerous mediators and they are activated by many signaling molecules, such as cytokines and neuropeptides[449].

The list of roles played by mast cells continues to grow. A recent study indicated that mast cells create an immune synapse with gamma delta T cells to protect against infection with dengue virus[450]. Another study showed that mast cells could help protect against bacterial dissemination but did not prevent colitis[451]. Mast cells appear to be helpful for proper wound healing[452,453] and can help fight bacterial infections on a short-term basis but can have a negative effect in a chronic infection[454]. There are also many other studies showing that mast cells likely play an important role in a broad range of diseases[455,456].

There is a well-documented interaction between mast cells and glial cells in the production of neuroinflammation[457,458]. The hypothalamic pituitary adrenal (HPA) axis, which is involved in the stress response, is in bidirectional communication with mast cells; allergic reactions involving mast cell activation can produce a stress response[125], and a sufficiently high level of stress can cause mast cell activation[459]. And, as discussed earlier, the stress response is proposed to contribute to avoidance of allergens, and potentially PHM.

There is also a connection between severe, disabling postural orthostatic hypotension (POTS) and elevation in the stress-related hormone, adrenalin, in some patients. And it has been proposed that mast cell activation may underlie this hyperadrenergic POTS[460]. Rowe et al[417] found that nonallergic milk reactions were related to POTS in young adults and adolescents who had ME/CFS. A variety of other food reactions have also been implicated in ME/CFS, with the patients typically being unaware that they were reacting to the food since the reactions are often delayed for hours after ingesting the food[418]. Food reactions have been found in other patients with POTS as well[461]. Although the mechanism behind these reactions has not been determined, in many cases, mast cells are likely involved.

Mast cell activation syndrome (MCAS) is increasingly being recognized and is characterized by allergic-type reactions that are thought to be related to an increased tendency for mast cells to degranulate and release histamine and other substances[462]. It is interesting to consider whether MCAS might be due to widespread reactions to unrecognized PHM and cross-reacting antigens in the body and in the environment due to PHM colonization/infection.

In autoimmune disease, the role of mast cells has been increasingly appreciated in recent years[463,464]. Mast cells are of particular interest to the PHMHEC hypothesis because, if the hypothesis is valid, it seems likely that they are often playing an important role in the attempt of the immune system to control PHM in the body and protect against further invasion. And this protective mechanism is proposed to often be related to allergy/hypersensitivity, as discussed above.

Evidence of food allergy/hypersensitivity typically involving mast cells is increasingly being found in autoimmune diseases, such as type 1 diabetes[465,466], multiple sclerosis[467], rheumatoid arthritis[468,469], systemic lupus erythematosus[470,471], pemphigus vulgaris[472], psoriasis[473], ulcerative colitis[474], Crohn's disease[308,475,476], ankylosing spondylitis[317,394] and Hashimoto's thyroiditis[477]. Some studies have shown benefits from IgE-targeting omalizumab[478–480], which reduces mast cell activation, and some have suggested that elimination diets may be an important approach in at least some autoimmune diseases[472,481].

Many of the studies only test for IgE-mediated reactions, so if one considers that non-IgE-mediated reactions are also thought to be common (e.g., nonallergic rhinitis has similar symptoms and prevalence as allergic

rhinitis[482]), then the role of allergies/hypersensitivities to food/inhalants in autoimmune, inflammatory and related diseases is likely much larger. As mentioned previously, bacterial allergens are increasingly being discovered. Thus, there is a great potential for uncovering a larger role for allergy/hypersensitivity reactions in autoimmune diseases as well as cross-reactions between microbial, food, inhalant and self-antigens, as proposed by the PHMHEC hypothesis.

Although mast cells have been linked to many autoimmune and inflammatory diseases, at least some of the research has used animal models. Animal models clearly have their limitations as illustrated by issues raised regarding mast cell involvement in autoimmune and other diseases related to the particular mutations in the animal models used[483].

Fortunately, in at least some cases, studies of human samples show promise of clarifying some of the issues. For instance, in type I diabetes, high levels of mast cells have been found near the insulin-producing pancreatic islet cells, along with evidence of mast cell degranulation in human pancreatic tissue[484]. The extent of mast cell infiltration was also correlated with damage to the pancreatic beta cells. Other studies also linked T1D and allergy/hypersensitivity[322,465,466]. A review by Rivellese et al[485] discussed multiple studies by different research groups showing mast cells to be markers of disease severity in rheumatoid arthritis patients, supporting their role in the pathogenesis of the disease. Allergy, histamine and mast cells have been implicated in multiple sclerosis patients[486–488]. Other research has also linked mast cells to inflammatory diseases[489–491].

A study that linked functional gastrointestinal disorders (IBS, gastroparesis, gastroesophageal reflux disease) to several allergic and autoimmune conditions is also relevant here[492]. The aforementioned success in IBS of elimination diets, antimicrobials and diets that limit microbial small intestinal overgrowth is compatible with hypersensitivity to foods and cross-reacting PHM being involved in the comorbid conditions as well.

This discussion is not meant to imply that the important allergic and hypersensitivity reactions are limited to those involving mast cells. Eosinophils and basophils are other types of white blood cells involved in allergic reactions. Increased levels of eosinophils are common in asthma[493]. As discussed previously, tests related to basophils and eosinophils are showing promise.

So, from the previous discussion of the varied types of reactions revealed by new methodologies and the increased evidence of mast cell involvement, it appears that food and inhalant allergy/hypersensitivity is likely more extensive than previously thought.

Diet, the Intestinal Microbiota and the PHMHEC Hypothesis

There is an increasing understanding of the importance of diet in shaping the gut microbiota. This has important implications for the many studies of dietary approaches conducted over the last 50 years.

A wide range of diets have been studied in inflammation-related diseases. Many dietary factors have been implicated; however, it is proposed here that PHM could be a particularly important factor contributing to the effects of different diets. The effects of PHM in food/beverages might offer a unifying explanation for benefits achieved by diverse, sometimes apparently contradictory, dietary approaches. The literature on diet is vast, so to simplify, a few types of diets and their relationship to the PHMHEC hypothesis will be discussed.

Plant-based diets vs. high consumption of meat and animal products

A vegan diet was found to reduce symptoms and the need for medication in 92% of long-term asthma patients after a year on the diet[494]. Studies assessing the effects of diet on patients with rheumatic diseases have reported benefits from vegan or vegetarian diets[495,496]. Rheumatoid arthritis has been reported to be improved by fasting followed by a vegetarian or vegan diet[497].

The longer life span and reduced incidence of inflammation-related diseases in certain populations around the world that follow near vegan, vegetarian or reduced animal-consumption diets has been described[498]. In fact, a reduced level of animal products is one of the features of the Mediterranean diet, which has shown benefits in many diseases[499].

The PHMHEC hypothesis would predict that conventionally raised animals would potentially harbor a wider range of PHM that could colonize/infect humans. This is because there would be more opportunity for the PHM to acquire adaptations for living in animals/humans. It would seem likely that PHM would likely be able to colonize/infect animals to a greater extent in the crowded conditions in industrialized agriculture, where the animals consume diets that are not typically natural for them (e.g., soy, corn and potatoes fed to cattle).

If a proportion of the PHM are well-adapted to an environment rich in fat, as might be the case in petroleum-adapted microbes, the fatty tissue that animals provide might be a favorable habitat for them. An interesting possibility is that part of the problem with consuming saturated fats from animals is due to the PHM that might be present in fat at low levels, perhaps even at levels undetectable with the usual methods. Fats from plants might also be prone to have more PHM from petroleum from a variety of sources, including air pollution. Thus, reduction in PHM might be a factor in the success of low-fat diets reported by some researchers[500,501]. The low-fat Swank diet (20-25% calories from fat), with particularly low saturated fat intake, has shown promise in multiple sclerosis[502,503]

A study of processed meat has found elevated levels of microbial components that can cause inflammation (pathogen associated molecular patterns or PAMPs)[504]. This might partly explain why highly processed meats are more strongly linked with negative health effects than less processed meats[505]. Thus, PHM and microbial PAMPs might be added to the list of possibly harmful components of animal products[506–509].

Plant diversity and processed foods

A greater diversity of plants in the diet (more than 30 types per week) has been linked to greater human gut microbiota diversity, more so than a particular dietary pattern, such as omnivore or vegan[510]. Greater microbiota diversity has generally been considered to be a positive attribute[41,45,421]. In addition, each serving of fruit and/or vegetables, up to 5 servings per day, reduced all-cause mortality by 5-6% according to a meta-analysis of 14 studies with follow-up periods of 4.6 to 26 years[511]. A study with a 6-year follow-up period found a 27% decrease in all-cause mortality in older adults who had 2 medical conditions and consumed 5 or more servings of fruits and/or vegetables per day compared to those who consumed less than or equal to 3 servings per day[512]. And they noted that increased fruit and vegetable consumption has been linked to a Mediterranean-style diet involving less ultra-processed foods, sugar and animal products. Although the greater intake and diversity of plant foods is probably beneficial in and of itself, it would likely be accompanied by reduced consumption of processed foods and animal products. Thus, it might also be lower in PHM and this might be part of the reason for the benefits seen.

Processed foods would be expected to be higher in PHM for multiple reasons. They are often consumed much longer after harvest than vegetables and fruits, allowing time for any animal/plant-associated microbes to increase. Of course, refrigeration and preservatives would reduce the presence of microbes related to overt spoilage. However, with the adaptability and diversity of microbes, other microbes would likely survive, and an adaptive radiation might occur to fill the available niches. This could lead to an environment conducive to an increase in species and strains that humans have not been exposed to at significant levels until recently. In addition, processed foods may contain additives and high amounts of salt, which might contain unique microbial communities that include PHM[140,513]. Sugar is also added to many processed foods and would likely fuel growth of PHM. And sugar may have its own PHM as well.

Some of the clearest connections between diet and inflammatory diseases have come from studies in developing countries. These studies show links between the adoption of the westernized diet and their newly acquired

increase in allergic and autoimmune diseases[9,514–517]. A study in India linked greater asthma rates with consumption of processed foods, like sodas and sweets[518].

In inflammatory bowel disease research, some promising interventions involve avoidance of many components of a typical westernized diet. A plant-based approach has been proposed by Chiba et al[519]. And a Crohn's disease exclusion diet (CDED) has been developed that essentially eliminates gluten, dairy, soy, animal fats, processed meats, emulsifiers, canned and packaged products, coffee, chocolate and alcohol[520]. This CDED combined with partial enteral nutrition appeared to be significantly more effective than exclusive enteral nutrition, with a sustained steroid-free remission rate of 75.6%[521]. Several diets used in IBD and other conditions are summarized in a recent review that also points out nutrients that might need to be supplemented in each diet[520].

Obesity and diets for weight loss

Obesity has been associated with a wide range of inflammatory conditions, including allergic and autoimmune diseases, and has been linked to a westernized diet[522]. Obesity itself has been linked to inflammation as well as metabolic syndrome. Metabolic syndrome includes conditions such as high blood pressure, insulin resistance and increased abdominal fat and is associated with an increased risk of diabetes (T2D) and cardiovascular disease. Metabolic syndrome and/or obesity have been linked to asthma[523], allergic rhinitis[524], chronic rhinosinusitis[525] and several autoimmune diseases[526,527]

Among weight loss studies, there has been equal success using low-fat diets and low-carbohydrate diets[528]. A recent study comparing low-fat to low-carbohydrate diets found each diet was successful in a subset of study participants, with neither one being superior overall[529]. They analyzed data on several genetic markers and baseline insulin secretion levels to try to determine which study participants would lose weight on a particular diet and found no predictive relationships. Apparently, there are other factors involved.

The PHMHEC hypothesis would predict that success in weight loss could partly stem from individual differences in the food and microbial hypersensitivities arising from the PHM that a person happens to react to. The resulting food reactions could affect blood sugar, food cravings and subsequent overeating. This individuality appears to concur with observations by a research group doing constant blood sugar monitoring[530]. They found that the foods that caused the highest blood sugar increases were highly individualized, and they were able to correlate the blood sugar patterns with changes in the intestinal microbiota. According to the PHMHEC hypothesis, the observed microbiota changes could be influenced by the food-associated PHM.

A blood sugar increase in response to a food might reflect a stress response to PHM in the food and food antigens that cross-react with PHM. Blood sugar typically increases as part of the stress response and the need for fight or flight, which requires adequate blood sugar for anticipated intense activity[531]. Thus, the magnitude of the blood sugar increase after the consumption of certain foods might be partly influenced by the human body's adaptive response to stress.

Increases in blood sugar may reflect inhalant exposures as well and this should be considered. For example, studies have linked blood sugar elevation[532] and T2D incidence to air pollution[381,533].

Although more studies are needed, the significant improvements in body mass index[320] and blood sugar[322] shown by diets based on food hypersensitivity test results discussed previously supports the potential PHM connection. According to the PHMHEC hypothesis, the stress response related to PHM colonization/infection and continual exposure to PHM and cross-reacting antigens in the diet may be shaping blood sugar responses and the propensity to gain weight.

A recent study by Hall et al[534] showed that inpatient adults given a diet of ultra-processed food consumed more calories and gained more weight than those given a relatively unprocessed food diet with the same amounts of sugar, fat, fiber and macronutrients. Those on the minimally processed food diet actually lost weight. So, this study suggests that there is something about ultra-processed food that tends to cause overconsumption and weight gain. The PHM might be a contributing factor to investigate.

Another issue related to obesity is the role of cravings. It has been speculated that some gut microbes may have an effect on cravings, since the microbes would "benefit" if humans had a craving for foods that the microbes use for fuel[535]. This might be extended to a craving for foods that contain the microbes. In addition, for some people, a mild stress effect might occur in response to consuming food containing higher levels of PHM and this could cause a stimulated feeling that might cause a temporary lift in energy or mood. This could be a contributing factor in food addiction and associated obesity. In fact, calorie dense processed foods are closely linked to food addiction[536].

There are some encouraging results from certain dietary plans that completely change eating patterns and eliminate ultra-processed foods[537,538]. It appears that with some training and support from a patient's physician and/or nutritionist, new eating patterns can be successfully maintained by a significant proportion of patients when attempting to combat a chronic disease.

Food elimination diets

In asthma[539] and atopic dermatitis[540], food allergies tend to make the other allergy-related conditions worse and avoidance of allergenic foods can be helpful. Food sensitization is common in allergic rhinitis and chronic rhinosinusitis[541,542]. However, only avoiding foods associated with IgE-mediated reactions might not be enough, since other hypersensitivity mechanisms may be involved, as discussed previously.

Gluten-free diets are being discussed in many different contexts in recent decades. Celiac disease, where gluten avoidance is mandatory, was mentioned previously. Non-celiac gluten sensitivity is now recognized as well[543]. Another factor with regard to gluten consumption that should be considered is its ability to cause a more permeable intestinal wall, which is true in everyone, not just in those with the above two conditions[543]. The question arises as to whether the reason some people report benefits from avoiding gluten may be partly due to its effect on permeability. The increased intestinal permeability from gluten would allow an increase in translocation of microbes and allergens/antigens into the blood stream. Thus, the problem with gluten consumption might sometimes be related to a greater absorption of these non-gluten components, including PHM.

Hvatum et al[481] tested intestinal fluid samples and found significantly increased food specific antibody levels (IgM, IgG, IgA) when comparing 14 rheumatoid arthritis patients to healthy controls. They suggested that the immune system attack on joints in this disease might be driven by multiple modest food hypersensitivity reactions involving immune complexes and cross-reactivity with self-antigens. They noted that these modest reactions would likely not be evident with brief tests of small amounts of foods, as done in previous studies. Studies that focus on one type of food, such as red meat or animal products, may fail to detect differences on a large population scale because of the individuality of patient reactions.

Paleolithic diets have been increasingly investigated in recent years. These diets attempt to mimic the type of diet that our Paleolithic ancestors would have eaten. These diets typically eliminate dairy, grains and legumes and encourage consumption of fruits, vegetables, nuts, meat and fish[538].

A Paleolithic diet that also involves avoidance of certain foods that have been proposed to promote inflammation has been called an autoimmune Paleolithic diet. The foods avoided include gluten, dairy, legumes, refined sugars, industrial seed oil and nightshade vegetables. A study evaluating this diet found significant improvement of symptoms and endoscopic inflammation in patients with inflammatory bowel disease[538]. A lifestyle approach that included a Paleolithic diet also led to significantly improved health-related quality-of-life and symptom burden scores in Hashimoto's thyroiditis[544]. A modified Paleolithic diet has also been associated with significant reductions in fatigue and quality-of-life measures in a randomized controlled trial in relapsing remitting multiple sclerosis patients[537].

From the PHMHEC hypothesis perspective, the Paleolithic diet likely has some benefits as far as reducing PHM because of avoidance of ultra-processed foods, gluten, dairy and some common allergens. Paleolithic

diets at least sometimes emphasize the consumption of animal products from more naturally raised animals, which would be expected to help reduce PHM.

A vegan or near vegan diet that also attends to food allergies/hypersensitivities and adequate nutrient intake might be especially helpful in some conditions. It also might be interesting to consider that whatever diet a person was eating when they developed their disease might contain more of the microbes that are contributing to their disease progression. This might partly explain individual differences in responses to diets that patients might be assigned to as part of a study.

Jethwa et al[545] recently reviewed several of the diets discussed here (e.g., vegan, Mediterranean diet, elimination diets) in the context of inflammatory arthritis and concluded that several of the small trials demonstrated significant benefit. However, they concluded that larger clinical trials are needed.

Microbes in food/beverages

Although salivary enzymes, stomach acid and bile acids reduce levels of microbes, it was found that foodborne microbes were able to survive passage through the stomach and intestines and could transiently be detected in fecal samples[546]. This shows it is not just spore-forming microbes and foodborne pathogens that can reach the large intestines. Some research groups have begun looking at microbes in food to begin to investigate how they affect the gut microbiota.

For example, Zivkovic et al[547] presented data from a small pilot study and could not detect significant differences in the microbes in the foods from three different eating patterns, probably due to low sample size. The largest numbers of microbes were from meals that included uncooked fermented foods such as cheese and yogurt. They noted that more research needs to be done, including looking at the effects of transport and provenance. These two issues are often related to the length of time since harvest, which would likely affect PHM abundance. Plus, transport and provenance might themselves affect the types of PHM present. The authors also mentioned that future research should look at the effects of packaging. Research shows packaging contamination is an important issue to be considered[548,549]. The low abundance PHM that may originate from the packaging materials themselves also needs more research. And, in general, more research on microbes in food/beverages is needed, including low abundance microbes.

A recent study by Johnson et al[550] found that the composition of a person's fecal microbiota did reflect dietary choices, but not conventional nutrients, from the previous several days. These microbiota patterns were not generalizable to other individuals in the study. A possible explanation for the lack of generalizability might be that an individual's undetected low abundance PHM affect the abundances of the detected microbes.

It is interesting to consider some research that has been conducted in marine environments. The plastic pollution of the ocean has led to study of the microbes that survive and thrive on plastic, and the term plastisphere is used to describe these communities[551,552].

Studies have found that some of the microbes that survive on plastic can become so integrated into the plastic that even extreme measures cannot remove all of them[551]. Different plastics have different microbial communities and the use of soy-based ingredients in plastics[553] is another factor that might affect the communities. It is interesting to consider, with the current pervasive exposure to plastics of many types, including those in close contact with our food and beverages, what effect microbes associated with plastic may have when inhaled and ingested. The adaptive radiation that might occur due to all the diverse plastics in our modern world could lead to many novel species and strains.

One might hypothesize that the presence of legume-related microbes in certain types of plastics that include soy-derived components might be related to the development of an increased level of of allergies to peanuts, another legume, in the last 50 years. Plastic-related microbial allergens originally from soy, that might be found on the skin, in the air and in food, might cross-react with other microbial allergens from peanuts. And combined with the peanut's non-microbial allergens, could potentially underlie the severe reactions to peanuts that have been increasing in prevalence. An analogous problem may exist when it comes to vegetables

oils, which are being used in some plastic items and adhesives[553]. These are highly speculative ideas, but seem worth investigating.

There are certain foods/beverages with a higher microbial content and higher histamine levels that can cause adverse reactions for some histamine intolerant people[554,555]. Examples are sauerkraut, yogurt, alcoholic beverages, coffee, tea and chocolate. Histamine is produced by many types of bacteria and some yeast. Low histamine diets, which include reduction of fermented foods/beverages have been reported to be useful in some conditions, including chronic urticaria[554–558]. Supplementation of the enzyme that breaks down histamine (diamine oxidase) has shown some benefit[559].

However, there is still controversy regarding the diagnosis of histamine intolerance[556]. It is interesting to consider that high histamine foods, with their higher microbial content, might also tend to have more PHM and this might partly explain the pattern of reactions. Histamine increases in patients after ingesting certain foods could be partly due to basophils and/or mast cells degranulating and releasing histamine and other substances in response to allergens produced by PHM. This would add to the effect of the histamine in the food. Since not everyone likely reacts to the same PHM, individuals might tolerate some high histamine foods and not others due to the PHM they contain. Specifying a more limited set of fermented foods that cause adverse reactions for an individual would be useful, since fermented foods are thought to be potentially beneficial[560].

Some additional connections with histamine are worth noting. A hypothesis to explain ME/CFS was proposed by Dechene[561] that included the role of histamine and hypersensitivity reactions to pathogens and thus has some similarities to the PHMHEC hypothesis[561]. The effectiveness of very low dose tricyclic antidepressants for sleep in ME/CFS and insomnia appears to be due to their ability to block the H1 histamine receptor[562]. And of course, histamine release by mast cells links the histamine-related hypotheses to allergies/hypersensitivities and mast cell activation syndrome discussed above.

Aging, diet and stress: why do young people increasingly get diseases of aging?

Research on the aging process[563–565] has examined several biochemical pathways that can promote aging that appear to be responsive to dietary alteration. The pathways are growth hormone-insulin-like growth hormone-1 (GH-IGF-1), target of rapamycin (TOR) and protein kinase A-RAS (PKA-RAS). As a result of research on these pathways, a low protein/low sugar diet and/or a periodic fasting-mimicking diet have been studied to evaluate their ability to combat diseases that increase with age, including autoimmune diseases, cancer and cardiovascular disease[565–567]. Although much of the original work was done with yeast, many aspects are being corroborated in humans. For instance, lower protein intake (i.e., .31 to .36 g per pound of body weight) is thought to be beneficial to reduce the GH-IGF-1 pathway activation; however, that only applies to those under age 65[568]. Lower GH-IGF-1 appeared to have a beneficial effect on aging-related signaling/diseases in a population with a mutation leading to severe growth hormone receptor and IGF-1 deficiency[569].

The question as to why children and relatively young adults sometimes get diseases of aging, such as diabetes, cancer and autoimmune diseases, is of great interest. The PHMHEC hypothesis may be relevant to the above theory of aging and cases of early disease onset.

New research on 2 of the 3 aging-related pathways mentioned above appears to demonstrate a relationship with physiologic stress that might be related to PHM and the PHMHEC hypothesis. Although more research is needed, it is interesting that the GH-IGF-1 pathway appears to also be activated in response to chronic stress[570]. Increasing activation of the PKA-RAS pathway can lead to high blood sugar and insulin resistance[567]. As discussed previously, the PHMHEC hypothesis suggests that allergy/hypersensitivity to PHM in food/beverages or inhalants may constitute a stressor that contributes to increases in blood sugar and this would add to the aging-related effect. Interestingly, lower heart rate variability indicative of chronic stress has been found to precede the development of type 2 diabetes mellitus, a disease associated with chronically high blood sugar levels[571].

Thus, PHM-related physiologic stress responses may have aging-related effects that could add to the known effects of the PKA-RAS and GH-IGF-1 pathways and contribute to both early and late onset diseases. This would be in addition to the other effects of PHM discussed previously.

Combination approaches

Combinations of different dietary approaches that have a focus on the PHM issue are worth considering in future research. For instance, an emphasis on foods that have been recently harvested, like from a home garden or farmer's market, could be evaluated. This would likely help minimize PHM. Likewise, use of glass containers instead of plastic containers for cooking and storage could be tried, in addition to reducing ultra-processed foods and animal products in the diet.

Also, evaluation of a person's food allergies/hypersensitivities could be included when planning the diet. This would likely minimize the exposure to PHM-related antigens that cause reactions for a given individual. Evaluation to detect IgE and non-IgE-mediated food reactions through various means, such as blood tests, elimination diets and blood sugar monitoring, as discussed previously, might increase the benefit of the diet by tailoring it to the individual.

Lowering histamine consumption in food/beverages could be tested as well. High FODMAP foods that provide more fuel for small intestinal microbes might be reduced and this might tend to reduce PHM, as discussed previously in the context of irritable bowel syndrome.

Combining the above PHM reduction approaches with other anti-PHM approaches, like antimicrobial therapies, might result in the highest success rate. It also might be helpful to extend the avoidance strategy to investigate whether more explicit temporary avoidance of a broader range of PHM exposures (e.g., inhalant and skin exposures) might be helpful. The PHMHEC hypothesis suggests that there would be a variety of types and degrees of PHM involvement in various diseases and patient subgroups.

If the PHMHEC hypothesis is correct, at least some diet changes in certain situations might alter microbial and immune system status in ways that might potentially lead to significant adverse events. For instance, immunopathology reactions from a reduction in immunosuppressive effects of PHM could possibly occur. Also, if multiple PHM are a problem, then reduction of some PHM might cause the immune system to react more to one or more other PHM in foods that were not suspected to be a problem, leading to exacerbations. These issues are likely to be more significant in more severely affected and/or elderly patients.

Immunopathology also occurs in a subset of AIDS patients during initiation of antiretroviral therapy and is called immune reconstitution inflammatory syndrome[572]. It occurs due to a restored immune system attacking opportunistic infections or as a result of autoimmune conditions that develop[573]. From the perspective of the PHMHEC hypothesis, these autoimmune conditions may be the result of the restored immune system reacting to and attempting to eliminate colonizing/infecting PHM.

The aforementioned potential immunopathology reactions are probably not a contraindication in most cases, just reason for caution, and perhaps reason to make changes gradually under some circumstances. In any case, randomized controlled trials are needed to test these interventions in a variety of diseases.

PHMHEC Hypothesis: Implications for Future Research

A wide variety of types of studies might be used to test the PHMHEC hypothesis. Research in the areas of microbiology, immunology, stress-related effects and epidemiology will be discussed. And implications for research on treatment approaches will be addressed.

Microbiology

Studying the microbiological aspects of this hypothesis may prove somewhat challenging initially, since some of the microbes may be very low in abundance, but as improved methods[574–577] become widely adopted and new methods are developed, the ability to test the hypothesis will improve. New microbial species are continually being detected, so the potential for progress is great.

As discussed previously, most studies tend to focus on the most abundant species, so just shifting that focus may start to yield interesting results. That is probably particularly true regarding the microbiotas of man-made products, chemicals, and agricultural products. Because most research focuses on preventing spoilage[578], or on the microbes involved in fermented foods and beverages[579] the focus is on the more abundant microbes or a few that are known to cause disease[580,581].

Studies of the built environment must compensate for particularly low levels of microbes (the low biomass problem). Often microbes are only identified as being within a higher-level taxonomic group instead of being identified to the species level[582]. However, many of these taxonomic groups contain diverse species. For example, crude oil, which contains diverse, abundant microbial communities, contains at least some genera that are the same as those found in humans[37,583]. One of these genera is Pseudomonas. Pseudomonas is a genus of bacteria that is very common in the environment and in humans. If it is found in a home, it may be assumed that the Pseudomonas is a species/strain that has always been present in humans. However, there are other Pseudomonas species that might have a completely different source, such as petroleum and thus might be PHM[37]. The genus Mycobacterium is similar in that it includes species that live in humans as well as diverse environments, such as petroleum and petroleum-contaminated soils[584,585] and there are other genera with similar distributions[585].

An analysis done at the genus level and higher taxonomic levels might fail to detect important patterns. Species level identification is likely not even adequate, since there are sub-species and strains within a species that may have important differences[4,586].

A sequencing study of a community of microbes on a prosthetic hip found a species that was reportedly found in deep sea hydrothermal vents[587]. In most microbiota analyses, there are many microbes that fall into the category of unclassified and unknown[588]. Identification/sequencing of the species/strains in the wide array of chemicals and man-made products and their addition to the genetic sequence libraries will facilitate evaluation of some aspects of the PHMHEC hypothesis.

A historical or archaeological approach investigating the microbiotas of ancient humans or humans from different historical periods could yield interesting results[39]. Research might need to be limited to more common microbes, since the rarer microbes would likely be even harder to detect in older samples, however there may be some exceptions in the case of particularly well-preserved animal and human samples.

Many interesting questions could be addressed. For instance, would there be changes in the human microbiota that accompanied the beginnings of the Bronze Age or the Iron Age and would the changes be associated with the different microbes in the metals? Would there be different microbes associated with agricultural products from the Americas that were not present before those foods were introduced into Europe? And, of course, it would be interesting to look for associations between changes in PHM and disease patterns inferred from archaeological remains and historical accounts.

Investigations of PHM from air, water, soil, plants and petroleum, along with other extracted or mined substances from beneath the earth's crust, would be useful. Studying the microbes found in humans and the environment and determining their sources would be helpful in evaluating the PHMHEC hypothesis. These types of studies might be seen as part of an effort to develop a "field guide to microbes," as called for by the UC Davis microbiologist, Jonathan Eisen[589].

Comparing ancient soils to modern soils might be of interest, and the changes in the soil microbes could be correlated to changes in the human microbiota. Soils lacking exposure to air and water from industrial activities might have to be sought in deeper layers to use for these comparisons[590]. Presumably, PHM

associated with air and water pollution are in surface level soils all around the world, but there are likely differences in the degree to which microbes from industrial activities would reach the soil and food supply in places far from industrial activity[591,592].

Further improvements in analyzing microbial communities with greater resolution in various organs and tissues of humans and animals will likely eventually allow testing of this hypothesis in the most complete manner.

While it would take some time to accomplish the above research goals, there are other lines of research that could be used to evaluate the PHMHEC hypothesis. These other lines of research would also be important for understanding the role of PHM and how they might contribute to disease.

Immunology: allergic, autoimmune and related diseases

Laboratory studies of mice have utility in many contexts. Of course, mice used in studies that model diseases are also affected by PHM, since they are fed processed lab chow and housed in the built environment. It would be virtually impossible to give them the same food and environment that they coevolved with, but one could vary the degree of exposure to PHM. For example, one could use soil and food derived from traditional farms and compare their effects with urban soil and conventionally grown foods. Some studies looking at the effects of different types of dust on mice have been done[593,594], but studies looking at the microbial content of the soil, food and air and the effect on the animal's microbiota and immunological responses could also be conducted. Perhaps even ancient soil could be used in some cases for the sake of comparison. Fresh food vs food stored for varying periods of time could be compared and the effect of food packaging could be tested.

Human subjects could be tested for food allergies or hypersensitivities, looking specifically for microbes that may be cross-reacting with known allergens. Even without knowing what microbes are involved, certain procedures could be carried out to test whether it appears that microbes might be involved in the allergic reactions.

For instance, one could test whether there might be a food-related microbe contributing to a given reaction. For instance, a comparison could be made between food that is kept warmer for a few hours, to foster microbial growth, and food that is kept colder, and the differences in reactions could be assessed.

One could evaluate the ability to cause reactions of food just harvested compared to refrigerated food harvested weeks before. One would expect that in most cases, the living plant's immune system would keep the microbial level lower, so recently harvested food would likely have fewer microbes than food picked weeks before. The recently harvested food might be less prone to cause allergic reactions.

It would be interesting to determine if plant microbial antigens cross-react with plant antigens to the same extent that human-associated microbes cross-react with human tissue antigens[265]. This would seem to have significant implications for the PHMHEC hypothesis if this also occurred for plant allergens/antigens that contribute to allergic and autoimmune diseases.

Cross-reactions between food and inhalants are another area of interest. One reason that studies often do not corroborate patients' reported food reactions[595,596] could be because the inhalant exposures in the laboratory or hospital where testing is done are different than those usually experienced by the patient in their daily life. It is interesting to consider whether, just as in oral allergy syndrome, the reactions are as much to the inhalants that cross-react with a food as they are to the food. If that is the case, it might be important to include consideration of the inhalants and not just the usual ones, like pollen and dust mites. The level of recent consumption of the tested food and any cross-reacting foods might also affect the ability of double-blind placebo-controlled challenge tests to accurately reflect the reactions of the patient in their usual environment with their usual eating pattern. The fact that gluten increases intestinal permeability and many people eat gluten-containing foods at nearly every meal might also need to be considered. Not consuming gluten during the test might lead to a failure to detect some reactions because the intestinal permeability allowing antigens to be absorbed would be less.

Despite the progress being made, the great complexity of the immune responses will be difficult to unravel and interpret. The types of studies that would be particularly useful for evaluating the PHMHEC hypothesis would be studies of how immunologic features of different diseases are affected by diet changes or other attempts at PHM reduction. Biomarkers could be measured before, during and after the interventions. This would help elucidate the significance of the immunological mechanisms and the PHM sources in these conditions. Similarly, trials of antimicrobial therapies could incorporate measurements of immune responses to better understand the role of various microbes. This would help determine what factors are driving the inflammatory responses. A study by Karatay et al[469] showed that skin prick testing for food allergy revealed foods that had significant effects on symptoms and inflammatory markers for some rheumatoid arthritis patients. Further work that is even more extensive, including various treatment approaches, multiple types of allergy/hypersensitivity tests and in-depth immunological analyses would be especially instructive.

It will be important to be aware of individual differences among patients in what microbes and allergens/antigens are involved, since otherwise the heterogeneity within diseases may obscure important patterns. Importantly, the complex immune system activation patterns found in allergic, autoimmune and inflammation-related diseases could be due to the response to multiple secondary opportunistic infections intermingled with the response to a wide variety of PHM. These considerations are in accord with the current trend toward the recognition of the need for more personalized medicine.

Stress-related research

There is already significant research being done on the relationship between stress and allergic[111] and autoimmune diseases[109]. However, targeted research approaches could be undertaken that take into account what has been learned about the hypersensitivity responses and their interactions with the HPA axis and the stress response, as discussed in previous sections. In addition, the knowledge gained in studies regarding PHM using approaches discussed in the above sections could aid in the investigation of the effects of stress.

Epidemiology

Historical studies investigating the increase in incidence of various diseases in relation to cultural practices or occupations could be carried out. An example of that type of study has already been mentioned, i.e., the attempt to test the cold chain hypothesis[353].

In addition, the changes in cultural practices, products used and food/beverage intakes could be examined in various countries to help pinpoint what types of exposures might be worth examining further. Examples of studies that have already been undertaken include ones that linked certain cultural changes associated with urbanization to increased incidence of multiple sclerosis[597,598] and studies investigating the effects of heavy metal exposure[599] and silica dust on autoimmune disease incidence[143]. Rather than assuming the effects are solely due to chemical exposures, analyses of the PHM associated with the exposure and microbe-derived substances that might cross-react with the chemical could be included. Many dietary studies have been done on immigrants[517,600], and if questionnaires about exposures were included, they would likely be even more useful, especially if they led to microbiological and immunological investigations.

Treatment approaches

A wide range of treatment approaches are worth examining in relation to the PHMHEC hypothesis, including antibiotics, antifungals, immune modulating medications, allergen specific immunotherapy, probiotics, diet, lifestyle, stress reduction techniques and altering environmental exposures. Some combinations of approaches were discussed above in the section on diet.

In general, the PHMHEC hypothesis would predict that treatment approaches that incorporate diet and lifestyle changes that decrease PHM exposure, decrease stress and use antimicrobial therapies would have

the potential to be the most broadly effective. In some cases, antimicrobial therapies might not be necessary, but might be important in more severe cases. What is required specifically in each disease might vary widely.

What is learned in the other types of studies could be applied to evaluating treatments. For instance, it would be important to determine whether current or newly developed treatment approaches lead to elimination of the PHM or just the elimination of the reactions to them.

Avoidance measures are, of course, an important component of the treatment of conditions involving allergy/hypersensitivity, but when it comes to PHM, much has yet to be learned about how much avoidance is needed and what needs to be avoided. Clearly, there are some cases where the agents are known, for instance, in many cases of hypersensitivity pneumonitis.

However, for some diseases that might involve hypersensitivity to microbes that are abundant in an office building or home, the issues can become more difficult. It may be useful to do detailed research on the sources of microbes in these situations rather than just the chemicals present in buildings that are associated with symptoms. In some situations, improvements could be made, like the ones mentioned previously related to better maintenance of air conditioning systems, along with eliminating sources of microbes associated with dampness. In addition, other sources of microbes could be sought, for instance, areas that are typically overlooked when cleaning, i.e., small cracks and crevices. Even small crevices, if not accessible to cleaning, could foster growth of a broad range of microbial taxa, and eliminating those sources of microbes might reduce symptoms.

Conclusions and Perspectives

This article explores the hypothesis that microbes that are more abundant in a post-hunter-gatherer environment cause or contribute to disease through colonizing/infecting humans, typically causing allergy/hypersensitivity responses and physiological stress. Although many of these PHM may be quite rare and difficult to detect, there are some that are more easily detectable, such as L. pneumophila, P gingivalis, C. albicans and A. fumigatus. And in some cases, research is beginning to show that they might cause disease in a manner that fits the PHMHEC hypothesis.

There are few, if any, other hypotheses that can account for as many disease characteristics and provide a unifying explanation for the three main features of microbial, hypersensitivity and stress involvement. This hypothesis also has the ability to explain the presence of at least some of these diseases going back to the earliest historical accounts, the connection of these diseases with westernization and the increase in these diseases in recent decades. Variability in PHM and cross-reacting antigen exposures combined with subsequent increased susceptibility to secondary infections provides a plausible explanation for the heterogeneity common in these disorders, the frequent comorbidities, the effects of diet, relationship with environmental chemical/pollution exposures, the periodic exacerbations and varied target organs/tissues. In addition, this hypothesis essentially unites most of the main hypotheses attempting to explain autoimmune and allergic disease.

This hypothesis can also explain why, despite decades of study, the causes of these diseases have been so difficult to elucidate. The role of a few, or in some cases, numerous PHM that are difficult or sometimes impossible to detect with current methods are suggested to be a large part of the problem. The hypothesized ability of low abundance or even very rare microbes to cause chronic diseases can be explained by several mechanisms involving hypersensitivity and/or toxic effects that alter the immune response. Hypersensitivity and cross-reactions with other microbes and antigens in the air, on the skin and in food would magnify the effect of low abundance microbes. And of course, the additive effect of several or perhaps numerous PHM is potentially an important issue.

The large number of microbes that diverge greatly from known species, which was recently found via cell free DNA analysis of blood, suggests that unknown species play a greater role than previously expected[601].

This finding is consistent with the PHMHEC hypothesis.

The PHMHEC hypothesis suggests a focus for research that is close, in many respects, to the current direction research is taking. It is hoped that presenting this hypothesis and the research related to it will prove helpful as an organizing framework and a stimulus for future research and the generation of additional hypotheses.

There are many important questions regarding the possible role of PHM. For perhaps the majority of PHM, we do not know to what extent any potential colonization/infection by PHM is harmful in and of itself, or whether the main harm is related to the immune reactions to the PHM. It may be that the hypersensitivity reactions evolved as a precaution to handle the unknown, as the immune system can not necessarily anticipate which new microbe will prove dangerous.

If the PHMHEC hypothesis is valid, eliminating most PHM colonization/infection might be preferable, but not always attainable. It could be that approaches that modulate chronic inflammatory responses, such as immunosuppressive medications, may be effective approaches for controlling or adapting to the PHM in some situations, at least in the near term. In any case, a better understanding of the PHM could be helpful in optimizing treatment safety and effectiveness and developing new treatments, especially for treatment-resistant and severe cases.

Although laudable and important attempts are being made to reduce air pollution and improve dietary choices, it seems unlikely that there will be a significant change in the increasing global industrialization and westernization process. The viewpoint proposed here, arising from the PHMHEC hypothesis, is that although we live in an increasingly urban, industrialized, westernized world, it should be possible to substantially reduce most, if not all, of any negative effects through adequate knowledge of the PHM and neurological/immunological/hormonal mechanisms associated with our responses to them.

Opinions differ regarding processed foods in the westernized diet. There has been a recent trend, driven by both research and consumers, toward more "natural" foods and those with fewer artificial ingredients. This has led to changes in processed foods, for instance the banning of artificial trans fats in the U.S. and the replacing of petrochemical based food dyes with natural food dyes in many products, especially in Europe. Further research on the PHMHEC hypothesis and other hypotheses may lead to additional ways of improving processed foods. Increased knowledge of the PHM, should this hypothesis be validated, could help in optimizing restrictive diets that may prove useful, at least temporarily and, it is hoped, reduce the level of restriction needed.

Until then, it is notable that the PHMHEC hypothesis is in accord with current recommendations for increasing intake of whole plant foods, such as fruits and vegetables and other aspects of a healthy lifestyle (e.g., adequate nutrient intake, maintenance of a healthy weight, avoiding foods and other substances that cause adverse reactions, stress reduction methods, adequate sleep, smoking cessation) that are already showing a benefit in a wide range of diseases. If the PHM are important factors in the manner hypothesized here, it seems likely that the above recommendations are probably also helping to reduce the PHM's ability to contribute to disease.

Given the ubiquity, adaptability and abundance of microbes, the rapid changes in sources of microbial exposures accompanying westernization, the widespread nature of cross-reactions and the "dual use" virulence factors of some environmental microbes, it could be argued that the phenomenon described by the PHMHEC hypothesis has likely played at least some role in the increasing rates of inflammation-related chronic diseases discussed here. How much of a role is still to be determined.

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Competing interests

JCW has plans to file one or more patents that are related to this hypothesis and plans to donate all proceeds from her share of any profits from them to charity, including charities that fund medical research.

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