The Post-hunter-gatherer Era Microbes Hypothesis for Chronic Inflammatory Diseases

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Abstract

This article proposes an extension of the hygiene hypothesis to explain chronic inflammatory diseases (CIDs) and their increase with westernization. Instead of emphasizing microbes that are missing/reduced due to westernization, a hypothesis is proposed that emphasizes the importance of microbes that are relatively novel. Environmental microbes encountered in association with a pre-agricultural lifestyle would presumably be the most coevolved with the human immune system and thus less likely to promote chronic disease. Post-hunter-gatherer era microbes (PHMs) are microbes that are encountered more frequently and/or at higher levels since humans ceased to live as nomadic hunter-gatherers. It is hypothesized that some PHMs, particularly those increasing with westernization, colonize human tissues and dysregulate/suppress the immune system. This hypothesized colonization of PHMs could cause allergy/hypersensitivity reactions leading to physiological stress, attacks on self-tissue, hypersensitivity reactions to similar cross-reacting environmental microbes and other allergens/antigens, greater vulnerability to diverse infections (e.g., COVID-19) and CIDs. Low-level colonization with diverse PHMs could explain high levels of comorbidities among CIDs, allergic responses to self-tissue (auto allergy), allergies to varied microbial taxa and allergen-initiated stress effects. Allergic reactions and the stress they cause might be adaptive by promoting expulsion and avoidance of potentially dangerous microbes. This is consistent with the observation that selective IgE deficiency leads to increased levels of diseases such as asthma, chronic rhinosinusitis, otitis media and autoimmune disease. PHMs that could be related to CIDs include microbes in tobacco smoke, increased Candida albicans and Aspergillus fumigatus that occurs in some situations, and increased exposure to Pseudomonas fluorescens and Yersinia spp. Additionally, fungi that tolerate multiple extreme environments have been found to be more likely to be opportunistic pathogens. This might suggest that microbes associated with human-created novel and extreme environments (e.g., antibiotics, xenobiotics) would have an increased ability to colonize and persist in humans. The PHM hypothesis could help explain contradictory findings on diet, why many chronic inflammatory diseases resemble chronic infections and why stress and xenobiotics are associated with CID incidence and exacerbations. Four foundations and 11 related hypotheses are discussed. Examples discussed include sarcoidosis, inflammatory bowel disease, asthma, long-term COVID-19 and Kawasaki disease.

Introduction

Chronic inflammatory diseases (CIDs), such as allergic and autoimmune diseases, include a wide array of diseases in which the immune system is thought to cause disease through excessive or dysregulated immune reactions. Since these diseases are only partly genetic[1], many environmental factors have been examined[2,3]. Environmental factors implicated include occupational/environmental chemical exposures[4], diet[3], infections[5–7] and stress[8,9].

Over the last 100 years, many of these CIDs have been increasing in Western countries, and recently have increased in association with westernization in developing countries[3,10,11] The term westernization, as used here, refers to the adoption of practices associated with Western culture that potentially impact health. The

westernized diet typically includes increased consumption of animal products, fat (especially animal-derived fat and vegetable oils), sugar, ultra-processed foods/beverages, salt, and food additives. New exposures from xenobiotics/pollutants and pharmaceuticals are also included.

The hygiene hypothesis is one of the hypotheses proposed to explain the westernization-associated rise in chronic inflammatory disease[12]. The hygiene hypothesis originally attributed the allergic disease increase to decreasing rates of infections. These infections were proposed to "train" the immune system to not react to harmless allergens. Updates to the hygiene hypothesis have been proposed that focus on the reduction of microbes that humans were exposed to throughout evolutionary history[13–15]. These updates to the hygiene hypothesis will be referred to here as the altered microbiota hypothesis. In general, they propose that reduction in likely coevolved, often commensal, microbes lead to microbial and immune system imbalances that can give rise to chronic inflammatory diseases.

The Post-hunter-gatherer Era Microbes (PHM) Hypothesis

Although the reduction of some microbes is likely important, the PHM hypothesis focuses primarily on the increase in certain microbes, the post-hunter-gatherer era microbes, that might contribute to disease processes. In this section, the PHM hypothesis will be outlined, saving more detailed evaluation and supporting information for later sections.

Post-hunter-gatherer era microbes are microbes that are encountered more frequently and/or at higher levels since the advent of agriculture. Some PHMs are novel, such as mutated strains found in association with newer products/substances or relatively novel conditions. Other microbes are PHMs because human exposure to them has increased due to changing lifestyles (e.g., increases in microbes related to food storage or refrigeration). The third category, the "crowd/virulent" PHMs are the causes of infections that arose after agriculture and cause acute diseases in healthy individuals (e.g., smallpox). The last category will not be discussed further. Here the focus is on PHMs that typically have effects via colonization or less obvious infectious processes.

The microbial communities that humans have been exposed to have changed throughout the millennia as human activities have changed. PHMs were likely added with each advance (e.g., agriculture, the mining of metals). There were presumably selective pressures acting on human populations that led to some degree of toleration of the changing microbiotas. However, the PHM hypothesis proposes that in recent years the microbiota changes have occurred so rapidly that the newer PHMs have caused or contributed to the above-mentioned disease increases.

The human genetic makeup largely evolved during the more than 500 million years during which our ancestors lived as hunter-gatherers or gatherers. The microbial exposures associated with those lifestyles would presumably be the most conducive to optimal human functioning. The PHM hypothesis proposes that humans are increasingly exposed to a novel microbial environment[2]. A subset of these PHMs are proposed to colonize or infect human tissues leading to immune system dysregulation, allergy/hypersensitivity reactions, dysbiosis, chronic stress and CIDs.

Colonization and infection are terms that are used differently by different authors[16]. As used here, colonization will refer to a microbial strain's existence in some tissues at a low level that typically would not result in microbial abundances and host reactions that would be recognized as an infection. However, according to the PHM hypothesis, these colonizers can sometimes contribute to symptoms and disease processes.

The PHM hypothesis includes an important role for an extension of the toxin hypothesis of allergy. Rather than allergies being a mistake by the immune system, the toxin hypothesis proposes that allergy is an important defense mechanism that protects the host from harmful environmental substances, e.g., venoms and toxins[17,18]. More recent research continues to support this hypothesis[19,20]. It has also been extended to include allergic reactions serving to promote avoidance of certain microbes[21,22]. The PHM hypothesis proposes that the microbes that produce allergic reactions include numerous PHMs.

In addition to causing allergic symptoms, the PHM hypothesis proposes that PHM-associated allergens would

also produce a stress response. Thus, the observed stress effects that occur in many CIDs could be at least partly due to stress responses resulting from PHMs and other sources of allergens. Chronic allergen-induced physiological stress could create and exacerbate psychological stress and lead to damaging stress-related and inflammation-related effects.

Cross-reactions play an important role in the PHM hypothesis. The effects of allergic reactions to PHMs would be magnified by cross-reactions with multiple allergens from other microbes, self-tissue or environmental substances. Also, one would expect cross-reactions between the PHMs that have colonized the human body and closely-related microbes in the environment.

Similar to what occurs in most infections, the PHM hypothesis proposes that the locations the microbes colonize largely determine the type and location of the symptoms. For instance, low abundance, hard-to-detect PHMs colonizing the skin might lead to atopic dermatitis.

In addition, in many of these CIDs there is a waxing and waning of symptoms. A major contributor to symptom increases could be explained by increases in exposure to antigens in food and the environment that cross-react with the colonizing PHMs and thus increase inflammation.

There are many means by which immune dysregulation and/or suppression might occur as a result of PHM colonization. For instance, some PHMs might produce substances that dysregulate or suppress the immune system. Also, PHMs that colonize the human body could undergo antigenic changes that increase their survival and reproductive potential. These antigenic changes could also reduce the ability of the immune system to eliminate them. This might be partly because exposure to the cross-reacting environmental PHMs bias the immune system toward responding to the environmental PHMs' slightly different antigens. This could reduce the accuracy of the immune system's targeting of the PHMs that have already colonized the tissues. This might be seen as analogous to the situation that can occur in heterologous infections[23] when the immune response to one infecting microbial strain interferes with the response to another microbial strain. However, in this case, one of the strains is found in the environment and is encountered primarily in the mucosa.

Thus, the PHM hypothesis proposes that colonization or infection with a variety of PHMs could lead to various diseases that involve immune hypersensitivity reactions. These reactions may be directed against self-tissues, colonizing PHMs and cross-reacting environmental microbes/antigens that come into contact with the skin and mucosal surfaces. Stress responses and secondary infections often play a role in CID pathogenesis and are proposed to at least partly stem from PHM colonization. Varied genetic susceptibility factors would play a role in determining the type and severity of diseases that develops.

The PHM hypothesis proposes that CIDs might develop in the following way. PHMs from the environment colonize one or more tissues, sometimes after a higher-than-usual environmental exposure (e.g., through a skin or mucosal break and/or disruption). Acute infections, physical/psychological stressors and other factors might serve as additional triggers. Inflammation and barrier breakdown are among the changes that could result. In a proportion of cases, this could be followed by a vicious cycle of increasing PHM colonization, hypersensitivity reactions, increased physiological stress, increasing mucosal barrier breakdowns, secondary infections and tissue damage.

Susceptibility to acute infections that might result from PHM-induced immune dysregulation is part of the PHM hypothesis. The occurrence of repeated acute infections has been reported to be related to the onset or exacerbation of a number of CIDs[2,5,24].

One can postulate alternatives to this hypothesis that might also fit the overall framework presented here. One alternative involves a primary role for hunter-gatherer era microbes (non PHMs alternative). This alternative hypothesis seems less likely since humans would be presumably more adapted to tolerate such microbes and one would not expect the increase in chronic disease rates. However, it might be other factors related to westernization, like the loss of commensal microbes or the increase of xenobiotic exposures that account for a possible increase in susceptibility to non PHMs.

Another alternative is that the implicated microbes do not actually colonize the tissues and instead are just present in the mucus or the gastrointestinal lumen (non colonization alternative). However, most of the other components of the PHM hypothesis might still be applicable to both these alternatives, and thus the overall hypothesis is still relevant. The situation likely varies among diseases and could even involve a mixture of microbes fitting the different alternatives just mentioned.

The idea that PHMs that might contribute to CIDs could be associated with at least some foods/beverages, pollutants and products associated with a westernized lifestyle might appear to be problematic. However, there is increasing recognition of the role of a westernized lifestyle in CIDs[3]. In addition, lifestyle interventions, such as dietary changes that improve disease outcomes and/or symptoms, are gaining support, as will be discussed later. If the PHM hypothesis is validated, a better understanding of the role of PHMs could lead to improvements in interventions, leading to more effective lifestyle and pharmaceutical approaches. Also, the negative effects of PHMs would generally only occur when a trigger occurs that causes the disease process to pass a certain threshold. Lifestyle and pharmaceutical approaches could reduce the PHMs or reduce the consequences of their presence.

Foundations of the PHM hypothesis and comparison with other hypotheses

Four foundational ideas or observations are addressed briefly in this section. They are not novel, but it is proposed that they imply that the PHM hypothesis is a plausible explanation that might have been missed due to methodological limitations.

The first foundation is that a large proportion of species/strains remain uncharacterized. A low level of colonization, particularly in a limited area of the body, could easily be missed by current methods. The situation has been depicted as an iceberg, with the bulk of species/strains hidden from view[25]. This is in accord with ecological research that finds that in most ecosystems, there are many rare species[26,27], usually with patchy distributions[28]. And it is now recognized that differences between strains of species can be of crucial importance[29,30]. Thus, the relevant uncharacterized microbial diversity is likely very large.

The second foundation is that low abundance species or strains could be important. The low abundance oral bacteria Poryphoromonas gingivalis can produce a toxin that affects immune function and has been implicated in many diseases[31,32]. Hypersensitivity and cross-reactions are additional reasons that low abundance species/strains could be important. The additive effects of multiple colonizing species could also increase their effect.

The third foundation is that environmental microbes have the potential to be a significant component of the microbiota of humans[33]. Thus, environmental microbes might comprise a significant subset of the undetected rare species/strains likely present in humans.

The fourth foundation is that changing human activities have led to humans being exposed to many microbial species/strains that they would not have been exposed to at significant levels until recently. The selective pressures from extreme conditions that human activities create for microbes (e.g., cleaning solutions, antimicrobials, toxic chemicals, food processing procedures, industrial pollution) could lead to an increase in novel microbial taxa. These novel microbes would often tolerate diverse and extreme conditions, which might include conditions present in the human body. For instance, it has been found that fungi that tolerate multiple types of extreme environments (polyextremotolerant) are more likely to be opportunistic pathogens[34].

Thus, these foundational ideas and findings in microbiology and ecology suggest that there are far more novel PHMs inhabiting the human body than has been recognized. They support the plausibility of the hypothesis that relatively low virulence, low abundance PHMs might play a significant role in CIDs.

Part of the usefulness of the PHM hypothesis is that it brings together multiple hypotheses and observations

in a way that could explain common features of many CIDs. Some of the similarities and differences between the PHM hypothesis and 11 related categories of hypotheses follow.

1. The hygiene hypothesis[12] and altered microbiota hypothesis[13–15] focus on the absence/reduction of microbes as the cause of microbiota imbalances leading to disease. Although sharing the emphasis on changes in microbial communities, the PHM hypothesis focuses on microbes that are increased in association with a post-hunter-gatherer lifestyle.
2. The molecular mimicry hypothesis posits a cross-reaction between an infectious agent and self-tissue as a cause of autoimmune disease. Root-Bernstein et al[35] discusses this hypothesis and suggests that the need for multiple exposures to pathogens or environmental factors could explain why frequent microbial cross-reactions with self-tissue only occasionally lead to autoimmune disease. The PHM hypothesis also includes a role for molecular mimicry and the likely involvement of multiple disease agents. In the PHM hypothesis, PHMs and opportunistic pathogens that take advantage of an immune system dysregulated by PHMs are implicated.
3. The xenobiotic causation hypothesis[4] focuses on the role of pollution and novel environmental substances in causing CIDs. The PHM hypothesis proposes that xenobiotic-associated PHMs that colonize an affected organ or tissue could be the primary trigger for disease in at least some cases. Alternatively, one or more PHMs may exacerbate the effects of the xenobiotic.
4. The macronutrient emphasis of microbiome research focuses on high sugar, high fat and low fiber diet effects on the microbiome[3]. Changes in levels of these macronutrients leading to changes in immune function, dysbiosis, intestinal permeability and microbial translocation are being observed[36,37]. The PHM hypothesis includes the macronutrient role, but emphasizes how macronutrients might affect the abundance of PHMs. The PHM hypothesis also posits that low abundance PHMs in certain foods/beverages and inhalants contribute to and may initiate inflammation and the resulting dysbiosis and intestinal permeability.
5. The toxin hypothesis of allergy proposes that allergic reactions occur as a defensive response against toxins in the environment[17,18]. The PHM hypothesis includes this view of allergy but also includes PHMs as instigators of defensive allergic reactions and proposes an important role for PHM colonization of human tissues.
6. Psychological stress has been proposed to play an important role in the development and exacerbation of CIDs[9,38], and the PHM hypothesis includes this. However, allergy/hypersensitivity to microbes and other allergens is seen as a crucial and generally overlooked source of physiological stress that can initiate or exacerbate psychological stress.
7. Hypotheses regarding chronic infection as a cause of CIDs, such as asthma, chronic rhinosinusitis, inflammatory bowel disease and some autoimmune diseases have been proposed[2,39,40]. The PHM hypothesis posits that low abundance PHMs are often the cause of immune dysregulation and/or suppression leading to the more overt opportunistic pathogens' increase. The observed opportunistic pathogens may or may not be PHMs as well.
8. Infection by a microbe that also involves hypersensitivity to that microbe is not new (e.g., allergic bronchopulmonary aspergillosis, severe asthma with fungal sensitization). The PHM hypothesis proposes that this concept is applicable to many CIDs, but low levels of the microbes involved are limiting their detection.
9. Focal infection theory proposed that infection in one part of the body is sometimes related to chronic disease processes in another part of the body. The earlier view was that bacterial allergy was often involved in symptom causation[2]. The PHM hypothesis is similar; however, it also proposes that the microbes that are the underlying cause are related to the post-hunter-gatherer lifestyle, and that allergy-related stress, cross-reactions with self-tissues and inhaled/ingested antigens are often involved.
10. Daschner[22] proposed an evolution-based hypothesis for symptoms related to fungi in damp buildings, viewing symptoms as a means of causing avoidance of infection with fungi. The PHM hypothesis is similar but broader, including non-fungal microbes as well as other components, such as a primary role for microbial colonization and relatively novel species/strains.
11. A role for novel microbial exposures has been proposed in some hypotheses. The cold chain hypothesis

links Crohn's disease to microbes that survive well in refrigerated food[6,41]. The PHM hypothesis includes this hypothesis in that consumption of refrigerated food that likely contains PHMs would be a part of a post-hunter-gatherer lifestyle. Other hypotheses that implicate human microbiota effects from novel sources of microbes[42,43], xenobiotics[42] and westernization-related variants of the normal microbiota[44] also have some features in common with the PHM hypothesis.

To summarize, the PHM hypothesis builds upon previous observations, ideas and hypotheses. The hypothesis is consistent with much published data, makes predictions that are testable, and could potentially lead to clinical advances.

Evaluation of the PHM hypothesis

This section includes a more in-depth examination of the components of the PHM hypothesis. In addition, supportive findings, illustrative examples, diet, the built environment, xenobiotics and immunosuppressive medications will be discussed. The section ends with an assessment of the potential relevance of PHMs to diseases, such as coronavirus disease 2019 (COVID-19), as well as post-infectious syndromes.

Post-hunter-gatherer era microbes

Ever improving methods in recent decades are allowing increasingly subtle and delayed effects of microbes to be studied. Tissues of the human body that were thought to be sterile in healthy individuals have been reported to contain microbial communities. Examples include microbiotas found in the blood[45–47], lungs[48], synovial fluid[49] and possibly even the brain[50–54]. In addition, there are likely other microbes that are too low in abundance to be detected using current methods[25]. Although some researchers attribute these findings to laboratory contamination, other researchers describe the careful use of controls and the differences founds in microbial communities between controls and patients[55].

Man-made or processed products and toxic chemicals do not seem conducive to significant levels of microbial survival; however, the adaptability of some microbes has now been demonstrated in numerous extreme environments. It may be that the only sterile places on earth are a few laboratory cleanrooms, some hot springs, volcanoes and areas over 150 degrees Centigrade deep in the earth[56]. Scientists at NASA have found new microbial species in their cleanrooms[57]. Some bacterial strains have even been found to use cleaning products as their fuel source[58].

As discussed above, the PHM hypothesis proposes that a subset of low abundance PHMs are important in human disease. The ability of some environmental PHMs to colonize or infect animals could be enhanced by dual use virulence[59]. This occurs when microbes have evolved means to survive inside of their single-celled predators and this allows them to survive inside human cells.

It has been suggested that virulence in animals is of questionable value to many microbes[60]. Thus, low virulence microbes may be common. A number of examples of potentially low virulence environmental PHMs are discussed below.

Some examples of PHMs have been found in high salt conditions. For example, halophilic Archaea[61,62] and bacteria[62] have been found in table salt and in the human digestive tract. Fungi from the genus Wallemia are found in salt-preserved fish[63]. Human exposure to such halophilic microbes was likely low before salt preservation.

The probable PHM, Mycobacterium immunogenum, found in metalworking fluid, caused hypersensitivity pneumonitis in some machinists[64]. The PHM hypothesis suggests that there may be some degree of colonization of this species in the lungs of the affected workers.

Tobacco smoke has been found to be a rich source of microbes, including potential pathogens, and further research is needed to determine their role in diseases like chronic obstructive pulmonary disease (COPD)[65].

Even smoke from wildfires[66,67] has viable microbes, and their effects need more study.

Researchers are beginning to look at the pathogenic potential of air pollution associated microbes. Particulate matter that is 2.5 um or less is a source of microbes that could lead to pathological effects[68,69]. A study found that the proportion of pathogenic species in air samples increased with air pollution levels associated with urbanization[70]. Detection of 142 new microbial genera in the pharynx followed a severe air pollution event[71].

A review of indoor environments associated with water highlights the many relatively novel and extreme conditions that microbes are exposed to in buildings[34]. As mentioned above, recent work has found that fungal taxa that tolerate multiple extreme environments tend to include more opportunistic pathogens[34].

Many extreme conditions, such as high temperatures, dry conditions, and cleaning products found in the built environment would prevent survival of many microbes. However, other microbes that tolerate extremes would likely increase under the high selection pressure of the extreme conditions. The human immune system response to microbes often creates another extreme environment (e.g., production of oxidants). Thus, microbes' evolved toleration of extreme environmental conditions may be advantageous for their survival within humans.

Research shows that dishwashers are inhabited by a polyextremotolerant type of black yeast that is an opportunistic pathogen[34]. In addition, a greater level of allergy in households that use dishwashers compared to those that use traditional hand dishwashing was found[72]. More microbes surviving the hand dishwashing has been suggested to be responsible for the lower rate of allergy. This is in accord with the altered microbiota hypothesis, which proposes that greater microbial diversity is protective.

Alternatively, the PHM hypothesis might suggest that dishwashers typically contain more polyextremotolerant microbes that are capable of colonizing humans, and that could increase allergy. Polyextremotolerant PHMs from the dishwasher might colonize human tissues and lead to allergic reactions. However, it should be noted that the difference in allergic disease was not large, and there are many possible confounding factors, so it would be premature to make conclusions with regard to dishwasher use[73].

In general, a problem with these types of observational studies is that there is confounding between lowering the total microbial levels and increasing overall microbial polyextremotolerance. Cleaning and other factors that reduce total microbial levels create more challenging and extreme conditions for microbes, likely selecting for the more polyextremotolerant taxa.

Thus, other types of studies will be needed to distinguish the effect of the cleaning-related reduction of microbial diversity from the increase in polyextremotolerant PHMs that could occur. In any case, the two explanations are not mutually exclusive. The lower diversity could be a cofactor that increases polyextremotolerant PHMs' ability to survive in the environment and/or colonize humans.

The distribution patterns of PHMs are not likely to be simple. Even without extensive cleaning, including in natural environments, PHMs that could colonize humans and contribute to disease could be present. For instance, PHMs might be in the soil, as a result of factors that introduce or select for PHMs, such as air and water pollution.

Another example of the potential role of PHMs is related to the association between bacterial virulence and antibiotic resistance[74]. Antibiotics are another factor that create an extreme environment that microbes are selected to tolerate. Thus, antibiotics might increase the numbers of pathogenic polyextremotolerant microbes able to colonize/infect the human body. The highly virulent antibiotic resistant microbes are known. However, antibiotic use may also result in other, lower abundance PHMs, with more subtle effects. An example is the cell wall deficient forms that are created under adverse conditions, such as certain antibiotics[40,75–77].

The PHM hypothesis takes the perspective that microbiota changes have been occurring for thousands of years alongside human cultural changes. The most significant changes likely occurred when populations

began forming more permanent settlements and food processing was adopted[2]. In the following centuries, agriculture, large settlements and mining of metals presumably began changing microbial exposures even more. For instance, food storage would lead to increases in some food-associated microbes (e.g., fungi causing ergotism). However, the PHM hypothesis proposes that the known microbes contributing to disease are only the most easily detected, and there are many more awaiting discovery and characterization.

Thus, the PHM hypothesis is able to explain why many of these CIDs were present at a low level before the modern, more hygienic, antibiotic era[78–80]. The earlier presence of these diseases could have resulted from changing PHM exposures in the post-hunter-gatherer era.

Allergy, hypersensitivity and stress

The toxin hypothesis of allergy is related to the PHM hypothesis and the stress response. As mentioned previously, the toxin hypothesis proposes that allergy is an important defense mechanism that protects the host from harmful environmental substances, e.g., toxins, irritants, and venoms[17,18].

Palm et al[18] describe how the high sensitivity of IgE-mediated responses may have evolved to allow anticipation of dangerous exposures and thus cause avoidance of noxious substances. Experiments in mice and rats sensitized to a specific food allergen produced stress/anxiety effects and avoidance behavior associated with trace amounts of that specific allergen in their cages[81–83]. The anxiety-like behavior was shown to be dependent on allergic mechanisms. Corticotropin releasing hormone and Th2 cytokine increases in the prefrontal cortex paralleled the allergen-induced anxiety in the rat experiments[82]. It seems plausible that these allergy-induced effects also occur in humans. Observational studies show stress-related neuropsychiatric disorders are associated with allergic disorders in humans[84,85]. Although the above findings were related to IgE-mediated hypersensitivity, it may be that other types of immune hypersensitivity would have a similar relationship to stress responses.

Stress effects (e.g., increased anxiety, sleep disruption, elevated heart rate, and lower heart rate variability) occur in many CIDs[2,9,86,87]. The PHM hypothesis proposes that this is largely caused by frequent stress responses from exposures to PHM antigens and other cross-reacting antigens/allergens due to PHM colonization. This underlying physiological stress from PHM colonization could lead to greater perceived stress effects from ordinary daily activities and adverse life events.

Chronic stress can have significant effects on immune function through many mechanisms [88,89], including changes in the gut microbiota[90] and reduced secretory IgA[91,92]. A microbe-driven COPD-like disorder spontaneously developed in aging mice with SIgA deficiency[93].

IgE responses may be protective against diverse pathogens. For instance, studies have provided evidence that anti-microbial IgE antibodies may play a protective role in HIV[94] and Borrelia burgdorferi [95] infections. The association of selective IgE deficiency with increased asthma, chronic rhinosinusitis, otitis media, autoimmune disease, cardiovascular disease and cancer may be relevant[96–99]. Although the significance of these associations is uncertain, they are compatible with the view that IgE antibodies help protect humans from harmful colonization/infection.

PHM colonization could signal the immune system that there is a need for an increased protective response, including allergic responses and avoidance behavior. Thus, allergic symptoms and stress responses that would increase avoidance would be appropriate.'

More research is needed, but these findings are compatible with microbial hypersensitivity contributing to the defense against many types of microbes, including PHMs.

Cross-reactions

Cross-reactions play an important role in the PHM hypothesis. Trost et al[100] found that "no human protein is exempt from bacterial motifs." The extensive cross-reactivity they found between only 40 bacterial species

and human self-tissue is significant. It also may have implications for agricultural products. It seems plausible that the plant-associated microbiota would have a similar high level of cross-reactivity with plant proteins. The PHM hypothesis proposes that food hypersensitivity might be at least partly related to plant-associated microbial antigens cross-reacting with known food allergens.

Plant microbes that increase after harvest and reach elevated levels in stored food might be a source of PHMs that colonize humans. PHMs would also likely be present in animal products, due to the animals' microbiotas including PHMs they acquired from their food and other sources. Cooking eliminates most of the microbes but is likely insufficient to eliminate all PHMs.

Cross-reactions are a potentially significant factor in CIDs as suggested by two recent examples. Bacher et al[101] provided evidence that a cross-reaction between two fungi, intestinal C. albicans and lung A. fumigatus, could lead to the inflammatory lung disease, allergic bronchopulmonary aspergillosis. Both fungi might be considered to be PHMs. High A. fumigatus exposures can occur in farming[102] or in damp or water-damaged buildings[103,104]. C. albicans overgrowth might be related to westernization-associated factors, such as diet[105] and medication[106].

Another example is a study[107] that found that Pseudomonas fluorescens cross-reacts with gliadin and might be linked to celiac disease. P. fluorescens can survive in refrigerated food and is found in moldy buildings, on walls and shower fixtures[108] and thus might be a PHM.

Chronic inflammatory disease features

Many characteristics of CIDs are consistent with the PHM hypothesis. Given the diversity of exposures, the PHM hypothesis suggests that PHMs are numerous and each patient has a unique mix of PHMs colonizing varied tissues. Consequently, comorbidities among CIDs would be expected to be common and allergic, autoimmune and other inflammation-related diseases would have significant overlap. And this is increasingly being found.

Allergy is being found in autoimmune and other CIDs. For example, in a large retrospective analysis of a UK population, Krishna et al[109] found a significantly higher rate of at least one of 3 allergic diseases (allergic rhinoconjunctivitis, atopic eczema and asthma) in almost all of the 11 CIDs that they examined. Allergic disorders or sensitization have been found to be associated with Type 1 diabetes[110–112] and with diabetes associated autoantibodies[113]. A recent analysis indicated that celiac disease and HLA-related autoimmune disease susceptibility was associated with IgE sensitization in young children[114].

Autoantibodies are common and occur even in people who are healthy[115,116]. It has been proposed that autoantibodies might only become a problem when there is a source of chronic immune activation, e.g. from chronic infection, causing a higher level of autoimmunity than usual[115].

Autoantibodies have been detected in non-autoimmune diseases such as asthma[117], chronic rhinosinusitis[118], idiopathic pulmonary fibrosis[119] and COPD[120]. IgE antibodies targeting self-antigens (auto allergy) are found in many autoimmune/inflammatory diseases[121], including systemic lupus erythematosus (SLE), Graves' disease, multiple sclerosis and rheumatoid arthritis. According to the PHM hypothesis, auto allergy could be the result of cross-reactions between colonizing PHMs and self-tissue.

The respiratory tract has been found to be involved in a number of autoimmune diseases, including rheumatoid arthritis, SLE and systemic sclerosis[122]. Epidemiological research shows that inflammatory bowel disease (IBD) is often preceded by airway diseases[123]. These findings are consistent with a connection between inhaled microbes and non-respiratory diseases.

Evidence linking stress to autoimmune diseases[8,9,124] and allergic diseases[38,125] has been accumulating. Elevated resting heart rate and low heart rate variability occur with increased stress[126,127] and have been associated with all-cause mortality[128–132]. Sleep disturbances, which may be related to stress, may predispose to the development of autoimmune disease[86].

Other components of the PHM hypothesis are also found commonly in CIDs. Specifically, opportunistic pathogens[5,24,133,134] and/or dysbiosis[24,134,135] have been documented in many CIDs. Dietary alterations that would tend to reduce PHM exposure are showing benefit, as will be discussed in more detail in a later section.

An example of a CID that potentially fits the PHM hypothesis is sarcoidosis, a systemic disease marked by chronic granulomatous lung inflammation. It has been linked to mold exposure in damp buildings, and these damp buildings likely would have elevated PHM levels. A study[136] found evidence for increased sensitivity to fungal and bacterial antigens in sarcoidosis patients. There has also been research suggesting a causal role for bacterial infection[137,138]. Antifungal[139] and antibacterial[140,141] approaches in sarcoidosis have shown promise. Their limited success might result at least partly from some PHMs being less susceptible to most antimicrobials. This could be due to the potentially polyextremotolerant nature of PHMs, polymicrobial infections (e.g., requiring multiple antimicrobials), PHM-induced immune dysregulation and possible chronic PHM exposure. Although non-PHMs might also be involved, the PHM hypothesis predicts that the initiators of the disease process would be PHMs. Secondary opportunistic infections also occur[142].

Many IBD findings also appear to be consistent with the PHM hypothesis. IBD patients tend to have increased oxygen in their intestinal tract, resulting from inflammatory processes[143]. This leads to a greater abundance of oxygen-tolerant Proteobacteria and lower levels of microbial diversity[143,144]. The family Enterobacteriaceae, within the Proteobacteria, includes many pathogenic bacteria[144]. A reduction of species associated with anti-inflammatory effects is also observed[145]. An immune reaction to commensal microbes can occur as well, which might be due to the intestinal permeability and immune activation that develops[146]. Immunosuppressive drugs, an elemental diet and fecal microbiota transplants are approaches that shown some benefit in treating IBD[145].

It is not yet known what initiates the inflammatory processes and the other features of IBD. In one of the IBDs, Crohn's disease, an antibiotic combination targeting Mycobacterium avian subspecies paratuberculosis (MAP) infection has been reported to lead to long-term disease remission[147–151]. Agrawal et al[149] discuss recent promising data and addresses several common objections regarding MAP's role, making a compelling case for the involvement of MAP or similar species. It has also been suggested that other CIDs might be caused by MAP[152].

How MAP is acquired is still uncertain[153]. If its acquisition is related to a westernized diet or lifestyle it might itself be considered to be a PHM.

There has also been increasing evidence for the cold chain hypothesis for Crohn's disease, which postulates an inflammation-provoking role for Yersinia spp ingested from refrigerated food[41]. Substantiation of the MAP and cold chain hypotheses is hampered by the difficulty of detecting the implicated microbes and their relatively low pathogenicity.

Diverse IBD hypotheses could be seen as unified and explained by the PHM hypothesis. Both MAP and Yersinia spp could be viewed as opportunistic pathogens that take advantage of PHM-induced immune system dysregulation. Other microbes could contribute to disease as well (e.g., fungi[154]), and the particular species/strains involved could vary among individuals.

The anti-mycobacterial antibiotic approach targeting MAP shows signs of working best early in disease[151]. Perhaps this is because fewer PHMs and opportunistic infections that dysregulate/suppress the immune system have colonized and increased.

PHM-induced immune dysregulation or suppression postulated by the PHM hypothesis might be thought of as analogous to HIV weakening the immune system and leading to secondary infections. But in this case, the PHMs' effects on the immune system are proposed to be typically more subtle and the opportunistic infections may be harder to detect.

The PHM hypothesis can also explain the connection of IBD with a westernized diet[11], food reactions[155,156], allergic diseases[109,157–159] stress[160,161] and microbe-rich environment associated lung

diseases[123,162]. The periodic exacerbations in IBD may often be due to variations in exposure to inhaled/ingested PHMs and/or stress from PHM reactions, sometimes combined with psychological stress[2]. Seasonal variation in IBD disease activity that appears to be linked to inhalant allergies has been found[158]. The implicated foods and inhalants may be associated with PHMs or might cross-react with PHMs. The PHM hypothesis can also potentially explain the reported effectiveness of varied dietary interventions in IBD (see diet section below).

Thus, looking at diverse types of observations, it appears that many CIDs are compatible with the PHM hypothesis. The evidence supporting the PHM hypothesis for a number of other CIDs is discussed in more detail elsewhere[2].

Microbial allergy/hypersensitivity

Fungal allergens have long been known. However, in recent years, non-fungal microbial allergens are increasingly being found[163,164]. A common bacterial plant pathogen, Pantoea agglomerans causes human respiratory diseases such as asthma and HP[165]. Farm environments have Archaea[166] that are capable of causing immune reactions[167]. IgE-mediated responses to viruses (i.e., HIV[94], varicella zoster[168,169], influenza virus[170] and parvovirus[171]) are also being found.

In Bachert et al's[172] review of chronic rhinosinusitis (CRS), the concept of bacterial allergy and colonization was one component of their proposed immune barrier hypothesis. Calenoff et al[173] found an elevated level of bacterial allergy in CRS.

Microbial allergies are potentially increased by exposure to damp environments due to increased fungi and bacteria. Damp environments have been associated with the development or exacerbation of a range of respiratory diseases, such as asthma, hypersensitivity pneumonitis, allergic rhinitis and chronic rhinosinusitis[174].

Although dampness has been associated with increased disease rates, Mendell et al[174] found no clear relationships between disease features and measured microbial exposures. The PHM hypothesis suggests that low abundance PHMs would increase in damp environments and might be an important missing factor.

Researchers have noted inadequate research on bacteria in damp buildings[175,176]. Mycobacteria can cause greater immune responses and be just as serious a threat as molds[176]. A study of showerhead microbial biofilms found high levels of non tuberculous mycobacteria and other potential pathogens[177].

Focal infection theory and bacterial allergy

As mentioned previously, the PHM hypothesis has some similarity to the early version of the focal infection theory, which also included the concept of bacterial allergy[2]. Desensitization to bacterial allergens was tested in several clinical trials and appeared to be successful in treating several CIDs, including chronic colitis[178], allergic rhinitis[179] and asthma[180,181]. Research found that autologous bacteria induced chemotaxis of peripheral blood mononuclear cells in non-atopic asthmatics but not controls[182], suggesting a role for hypersensitivity to colonizing bacteria. A review[181] concluded that bacterial vaccines (immunotherapy) were useful in at least a proportion of asthma cases.

However, a later review concluded that the evidence did not sufficiently support immunotherapy for bacterial allergens in asthma[183]. The discrepancy might be explained by an increasing effect of diverse, low abundance microbes, leading to decreasing effectiveness of approaches that focus on only a few bacterial species.

The PHM hypothesis suggests that earlier researchers using bacterial vaccines may have been increasing the ability of the immune system to reduce bacterial colonization, 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 PHMs that cross-react with the known inhalant or food allergens. The

elimination of the colonizing microbes by the immune system might be what leads to desensitization and reduction or elimination of symptoms in a proportion of patients.

The variation in severity of allergic reactions might reflect the levels of colonizing PHMs. Asymptomatic sensitization to allergens might be due to PHM colonization levels that are below the threshold needed for a detectable reaction.

Immunosuppressive therapies and disease persistence

Immunosuppression is a frequently effective method for controlling symptoms in many CIDs. It might be argued that if microbial colonization is the underlying cause, as proposed by the PHM hypothesis, then immunosuppressive therapies should be harmful. However, if the PHMs are relatively low virulence microbes and/or the immune responses against the PHMs are minimally effective or counterproductive, immunosuppression may have more benefit than harm.

According to the PHM hypothesis, the ineffectiveness of the immune response against the PHMs in CIDs is supported by the usual persistence of CIDs. This ineffectiveness could be due to varied factors, including microbial toxins, the microbes' antigenic changes and the effects of heterologous immunity as discussed previously. Chronic PHM exposure or repeated reinfection could also play a role. The IgE and other immune responses may be generally protective but perhaps not effective in the context of colonization by multiple novel PHMs in a westernized environment.

Occupational/built environment and xenobiotic exposures

The role of the occupational environment seems to be important in many CIDs[184,185]. For example, farmworkers and those who have close contact with birds are more susceptible to hypersensitivity pneumonitis (HP)[186]. Occupational asthma and HP may be related to exposures to diverse substances, including chemicals, animal dander, plastic residue and fungi[187].

The PHM hypothesis proposes that occupational and xenobiotic related CIDs could at least sometimes be due to low level, often undetected PHM colonization. In some cases, microbial antigens and PHM colonization might be involved, in addition to the potentially synergistic effects of non-microbial antigens and xenobiotics.

New research is revealing high levels of unknown microbes in built environments[2,188,189]. A study using wearable sampling devices found over 2500 species, and nearly half of the DNA information could not be classified[190]. Gilbert et al[189] discussed how new materials and diverse chemicals used in buildings could provide unique selective pressures, potentially shaping microbial evolution. The new species/strains that could result would fit the category of novel PHMs and might be polyextremotolerant and more able to colonize humans.

Regarding experiments that evaluate the effect of xenobiotic exposures, it is worth considering microbes and/or their antigens that are probably present in the tested xenobiotics. So, it would be desirable for toxicological studies to take this into account.

This need to address microbial contamination has become apparent in an analogous situation in which microbial DNA is found in test kits used for microbiological assays[191]. Research using the test kits use controls and other methods so that reagent microbes do not bias the study results.

Thus, xenobiotic's effects could potentially result from a combination of the xenobiotic itself and xenobiotic-associated microbes. Autoimmune diseases may develop years after xenobiotic exposure[4]. This could be partly explained, according to the PHM hypothesis, by the length of time needed for colonizing xenobiotic-associated microbes to increase. Also, with long-term colonization, microbial mutations could occur that might aid microbial adaptation to the human tissue environment and pathogenicity.

Diet, the Intestinal Microbiota and the PHM Hypothesis

There is an increasing appreciation of the role of diet in shaping the gut microbiota. Many dietary factors have been implicated in inflammation-related diseases[3]. However, it is proposed here that PHMs could be an important factor contributing to the effects of different diets. PHMs in food/beverages might explain the benefits achieved from apparently contradictory dietary approaches (e.g., low fat vs low carbohydrate approaches), as will be discussed below.

Evidence supporting the connection between the adoption of a more westernized diet and CIDs have come from studies in developing countries[10,192–195]. The asthma rate in a study in India, for example, was associated with greater consumption of sodas and sweets[196].

In inflammatory bowel disease research, some promising interventions involve avoidance of many components of a typical westernized diet. A recent review found that most environmental factors were only associated with IBD in certain ethnic groups or countries; however, a westernized diet was found to be the most ubiquitous environmental factor associated with IBD incidence[11]. The same group proposed a plant-based diet approach [197], finding patients that used this approach had a much lower rate of recurrence after remission.

A Crohn's disease exclusion diet has been developed that essentially eliminates gluten, dairy, soy, animal fats, processed meats, emulsifiers, canned and packaged products, coffee, chocolate and alcohol[198]. A recent randomized controlled trial[199] found that this diet combined with partial enteral nutrition was significantly more effective than exclusive enteral nutrition in Crohn's disease.

The PHM hypothesis predicts that foods that are consumed a long time after harvest, food additives, animal products, ultra-processed foods and fatty foods contain more PHMs. The fermentation of foods and beverages like alcohol, chocolate, coffee and tea, would give more opportunity for at least some PHMs to increase, which could be a problem for some individuals. Food additives and ultra-processed foods provide conditions for microbes during their processing that are different from less processed foods. The resulting differences in selective pressures could lead to increases in PHMs.

Animal agriculture could promote PHM colonization of animals in a manner analogous to how humans are proposed to be colonized. And since animals provide an environment similar to human tissue, animals potentially could contain more PHMs that could colonize humans. Conventionally-raised farm animals, living an animal version of a westernized lifestyle, would potentially be even more colonized with polyextremotolerant PHMs that could affect humans. This has been studied most extensively in the case of antibiotic resistant microbes that humans acquire from animal products due to the use of antibiotics in agriculture[200]. This research supports the idea that modern agricultural practices are shaping animal microbiotas in a way that impacts human health.

Vegan or vegetarian diets have been observed to be beneficial in asthma[201] and rheumatic disease[202,203]. Reduced levels of animal products are found in the Mediterranean diet, which appears to have beneficial effects in many diseases[204]. A healthy and long life span in particular societies consuming low levels of animal products has also been described[205].

Another food component that might contain more PHMs is fat from animals and plants. Fats might provide a particularly favorable environment for microbes adapted to petroleum products. The utilization of hydrocarbons associated with fossil fuels has been suggested to be linked to lipophilic and neurotropic tendencies in some polyextremotolerant black yeast[206]. Bacteria have recently been found in human adipose tissue, with bacterial abundance associated with inflammatory parameters[207–209]. It would be interesting to determine if some of these bacteria are associated with petroleum products or ingested sources of fats.

There is evidence that a low fat diet is beneficial in heart disease[210,211] and possibly multiple sclerosis[212,213]. It is possible that ingested fat and especially animal fat, could contain PHMs that contribute to disease in humans.

Benefits from avoiding gluten, as recommended by diets like the above-mentioned diet for Crohn's disease, could be related to hypersensitivity to gluten. However, gluten has the potential to increase intestinal permeability, even in those without celiac disease[214,215], and may be a problem for that reason as well. This, and other factors that increase intestinal permeability[215,216], could facilitate PHM colonization.

Obesity has been linked to a westernized diet[217]. Obesity is also associated with inflammation and CIDs, such as asthma[218], allergic rhinitis[219], chronic rhinosinusitis[220] and several autoimmune diseases[221,222].

Low-fat diets and low-carbohydrate diets have demonstrated essentially equal success in reversing obesity[223]. A randomized controlled study comparing low-fat to low-carbohydrate diets found each diet was successful in a subset of study participants[224]. Analysis of genetic markers and baseline insulin secretion levels revealed no predictive relationships. The PHM hypothesis suggests that success in weight loss on a particular diet might stem from individual differences in colonizing PHMs.

Individuality was also evident in a study using continuous blood sugar monitoring since participants differed in the foods that caused the highest blood sugar increases [225]. The differences in blood sugar responses appeared to be at least partly related to features of the intestinal microbiota. According to the PHM hypothesis, the observed microbiota patterns could be related, directly or indirectly, to PHM colonization related effects.

Stress is known to increase blood sugar[226]. Thus, a blood sugar increase in response to a food might result from a stress response to PHM-related allergens in the food. It should also be noted that air pollution has also been linked to blood sugar elevation[227] and type 2 diabetes mellitus incidence[228,229]. According to the PHM hypothesis, air pollution likely contains PHM.

A recent study by Hall et al[230] showed that inpatient adults given a diet of ultra-processed food gained more weight than those given relatively unprocessed food with the same levels of fiber and macronutrients. The PHM hypothesis proposes that this might be at least partly due to a higher level of PHMs present in ultra-processed food.

Food cravings can be an important issue in weight loss. It has been speculated that some intestinal microbes might have an evolutionary advantage if they cause a craving for foods they use for fuel[231]. The PHM hypothesis suggests that this phenomenon might include 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 PHMs. This could cause a temporary lift in mood that could contribute to food craving and overconsumption. Interestingly, consumption of ultra-processed foods has been linked to food addiction[232].

Diets that have garnered recent interest include so-called Paleolithic diets. These diets typically eliminate dairy, grains and legumes and encourage consumption of fruits, vegetables, nuts, meat and fish[233].

The autoimmune Paleolithic diet also involves avoidance of certain proposed inflammatory foods. The foods avoided include gluten, dairy, legumes, refined sugar, industrial seed oils and nightshade vegetables. An observational study found an improvement in endoscopic inflammation and symptoms in patients with IBD who were on this diet[233]. An approach that included a Paleolithic diet also led to improved health-related quality-of-life and symptom scores in Hashimoto's thyroiditis[234]. A modified Paleolithic diet was associated with significant improvements in a randomized controlled trial in relapsing remitting multiple sclerosis[235].

From the PHM hypothesis perspective, the various Paleolithic diet approaches‘ apparent success in these small initial studies might be due to reduction of PHMs partly via avoidance of ultra-processed foods. Encouragement of consumption of fresh fruits and vegetables is also common in these diets. Presumably, the sooner the food is consumed after harvesting, the less opportunity for PHMs to increase.

Plant-based or vegan versions of a Paleolithic diet have been proposed[236]. The previously mentioned findings supporting vegan, vegetarian, low fat and lower animal product diets would suggest that these alternative versions of a Paleolithic diet are worth studying.

The role of past PHM colonization should also be considered. If the PHM hypothesis is correct, the foods/beverages consumed during the majority of the time prior to illness might contain PHMs that contribute to the disease. Thus, a diet that differs significantly from the patient's previous diet might be most helpful.

Food Allergies and Hypersensitivities

Traditional food allergy tests have revealed connections between food allergies and some CIDs. For instance, a study showed that multiple sclerosis patients with food allergy had greater disease severity than those without food allergy[237], however, conflicting results indicate the need for more research[238]. In a subset of rheumatoid arthritis patients, a study using skin prick testing for food allergy detection [239] found a number of foods that affected symptoms and inflammatory markers.

Some studies have shown CID benefits from the IgE-blocking drug, omalizumab[240–242]. And some authors have suggested that elimination diets may be an important approach in at least some CIDs[243,244]. A recent review of several types of diets used in inflammatory arthritis research suggested significant benefit from dietary approaches, but noted that more research is needed[245].

In 14 rheumatoid arthritis patients, intestinal fluid samples contained significantly increased food specific antibody levels (IgM, IgG, IgA)[244]. The immune system attack on joints was suggested to be driven by multiple modest food hypersensitivity reactions. Immune complex formation and cross-reactivity with self-antigen were proposed to result from the reactions. The authors noted that these modest reactions would have been missed by studies using brief tests of small amounts of foods. The PHM hypothesis suggests that colonizing PHMs that cross-react with the food antigens initiate the disease process.

Other variations on allergy testing methods have been evaluated. Examples include the basophil activation test[246] and local allergic reaction assessment based on measurements of local IgE levels[247]. Nasal allergen challenge tests reveal local IgE increases and may clarify mechanisms in some cases regarded as non-allergic rhinitis[247].

Another condition that has been studied in the context of diverse types of food reactions is irritable bowel syndrome (IBS)[248]. Although not traditionally considered to be an inflammatory disease, IBS has now been shown to be associated with CIDs[249–251]. A recent study showed functional gastrointestinal disorders, which include IBS, are associated with a pro-inflammatory state in the central nervous system, possibly mediated by the gut microbiota[252]. Mast cells have been found to be increased in the intestinal tract in IBS[253]. Food allergy and non-celiac gluten hypersensitivity have been found in subsets of IBS patients[254].

In IBS, an intervention based on the antigen leukocyte cellular activation test (ALCAT) test led to significant benefit in a double-blind randomized controlled trial[255]. A reduction in neutrophil elastase concentration was associated with symptom reduction in the intervention group. Eosinophil DNA release associated with protein kinase C signaling pathways was implicated in the reactions[256]. An ALCAT-based dietary intervention resulted in beneficial effects on body mass index, serum amyloid A and medical symptom questionnaire scores in a 4-week double-blind randomized controlled trial[257].

IBS research using confocal laser endoscopy found that reactions to foods involved eosinophil degranulation rather than the typical mast cell-mediated reactions[258]. After 6 months on an elimination diet based on the results, 68% of the patients showed at least 80% improvement.

It is interesting that current IBS dietary recommendations[248] include avoiding or limiting carbonated beverages, alcohol, tea and coffee as well as fatty and spicy foods. These are all items that would be expected to be higher in PHMs, as discussed above.

A controversial type of approach for determining foods that cause inflammation uses serum IgG4 levels. Elevated IgG4 antibodies specific for foods have been observed in some CIDs[259–261]. And dietary interventions based on these IgG4 levels have shown promise[156,260]. Thus, it appears possible that IgG4 specific

to particular foods indicates chronic antigen-driven inflammation associated with those foods in some cases.

However, the dominant view is that IgG4 serves as an anti-inflammatory blocking antibody and may be a marker of tolerance. This view arises partly from the finding that IgG4 specific antibodies increase during allergen immunotherapy for IgE-mediated allergies[262]. The PHM hypothesis combined with recent research may help shed light on these apparently contradictory views.

Chronically elevated IgG4 is thought to be a sign of chronic antigenic stimulation[263]. Selective IgG4 deficiency is associated with frequent respiratory infections [264,265], which might suggest IgG4's importance in protection against infections.

When IgG4 is high in the serum, it can also be associated with repeated infections[266]. From the perspective of the PHM hypothesis, when the IgG4 is high, it could be reflecting the presence of chronic colonization with PHMs. This might dysregulate the immune system and lead to increased infections.

If a PHM is colonizing human tissues, there might be an elevation in IgG4 against the PHM's antigens. IgG4 specific food antigens or self-antigens might be detected, but they might be cross-reacting with the unrecognized PHMs, which could be the true causal factor, according to the PHM hypothesis.

Total serum IgG4 has been found to be elevated in a number of chronic inflammatory conditions (e.g., pemphigous vulgaris, myasthenia gravis, rheumatoid arthritis)[267]. The traditional view is that IgG4 is anti-inflammatory and not able to activate complement. However, recent research indicates that IgG4 can be proinflammatory and even bind complement under certain circumstances[268,269]. It may be generally relatively anti-inflammatory when compared to IgE, IgG1 or IgG3; however, in certain situations, IgG4 could still cause inflammation.

A study found that total serum IgE and IgG4 levels were correlated in atopic patients[270]. This finding is compatible with the PHM hypothesis perspective that both isotypes are part of the response to PHMs.

In IgG4-related disease, a recently recognized group of CIDs, the role of IgG4 is not yet clear[268]. A polyclonal IgG4 response to multiple environmental antigens, including food antigens, has been found[271]. The authors note that this is consistent with a lack of immune regulation, but does not exclude it being antigen-driven.

IgG4-related disease has been associated with occupations with higher exposures to xenobiotics, such as solvents and metal dusts[272]. According to the PHM hypothesis, xenobiotic-associated, low abundance colonizing PHMs could be a causal factor. Disease often develops late in life, possibly due to colonizing PHMs increasing over time and potentially mutating to become more pathogenic.

Thus, the research discussed above suggests that the significance of IgG4 elevation resulting from chronic antigenic stimulation depends on the circumstances, and may or may not lead to detectable symptoms. It would appear that food specific IgG4 tests need to be evaluated separately for each disease in well-controlled trials to adequately assess their utility.

Whether or not IgG4 elevation leads to symptoms in the short-term, they potentially could lead to long-term negative consequences due to immune suppression[263] in some cases, or inflammation[268] in others. The PHM hypothesis suggests that the long-term outcome would depend on the pathogenicity of the PHMs that the IgG4 are produced in response to, combined with host factors.

Overall, the PHM hypothesis proposes that apparent immune dysregulation in various CIDs often begins with the inadequate attempts of the neuroimmune system to induce avoidance or elimination of PHMs. And food hypersensitivity reactions are proposed to arise from food cross-reactions with PHMs that have colonized human tissues.

Acute infections and post-infectious syndromes

As has been mentioned previously, according to the PHM hypothesis, PHM colonization and associated hypersensitivity and stress often lead to immune dysregulation and/or suppression. This could increase susceptibility to infections.

Cardiovascular disease, diabetes and chronic lung diseases have been associated with greater mortality from COVID-19[273]. These comorbid diseases have all been associated with low grade inflammation, air pollution, a westernized diet and increased levels of pathogenic or dysbiotic microbes[133,274–276]. It is interesting to consider whether the severe inflammatory component of COVID-19 could be related to an intensified immune reaction to some of these colonizing microbes. These microbes might be PHMs or opportunistic pathogens acquired secondary to PHM colonization.

The PHM hypothesis proposes that before the viral infection, the immune system was reacting to these colonizing/infecting microbes with low-grade inflammation. Changes in the cytokine milieu occurring due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection might result in the low-grade inflammatory response to the PHMs being transformed into a more intense inflammatory response (e.g., via isotype switching). This could potentially contribute to or cause the excessive inflammation in severe COVID-19. Elevated autoantibodies have recently been found in a proportion of severe COVID-19[277]. This might reflect increased reactions to PHMs that cross-react with self-tissue

Mast cells, traditionally known for their role in allergies, have been proposed to be a potential target in COVID-19 to address excessive immune reactions[278,279]. In fact, some early trials that targeted the mast-cell product histamine generated positive results[280–282]. These findings require validation in large, randomized controlled trials.

Mast cells are being implicated in chronic inflammatory conditions as well[283–285]. Beyond their role in allergy, mast cells have been recognized as having a protective role against a broad range of infectious agents[285]. The same may be true of IgE-mediated responses, which are also being implicated in protection against infections, as discussed above.

It may be relevant to consider the linkages that have been found between COPD and asthma and/or allergic conditions[286–289]. A study showed that 37% of adults between 65 and 86 years of age who had asthma or COPD had asthma-COPD overlap syndrome[290], which was associated with worse outcomes. The progression of asthma to asthma-COPD overlap syndrome increased with higher exposure to fine particulate matter[288] and workplace mold odor[291]. This is consistent with the PHM hypothesis in that these environments likely contain elevated PHM levels that could contribute to disease progression.

COPD's underdiagnosis[292] and frequent connections with allergy and/or asthma might be reason to investigate IgE levels in COVID-19. The potential for local IgE elevations without elevated IgE levels in the blood should also be considered[293].

Although patterns may differ with different viruses, IgE levels were found to be higher at the beginning of a viral respiratory infection, declining over the following 3 months[294]. However, perhaps the IgE levels would stay high or be even more elevated in at least some of the more severely ill COVID-19 patients and might contribute to the severity of the inflammation. IgE elevation was observed to persist longer after a viral infection if the patient was atopic[294]. Interestingly, there is some evidence that IgE-targeting omalizumab is protective in viral infections[295,296]. A patient with asthma who was taking omalizumab was reported to recover from COVID-19 without undergoing any severe effects[295]. This topic requires further investigation.

Liu et al[133] found that disease occurrence, exacerbation frequency and inflammatory markers, such as IL-6 and IL-8, were associated with an increase in pathogenic fungi in COPD patients' lungs. The PHM hypothesis suggests that these pathogenic species could be PHMs or occur secondary to PHMs' effects and might contribute to the greater susceptibility of COPD patients to severe COVID-19.

It is still unclear how often bacterial and fungal co-infections are involved in COVID-19[297,298]. A study[299]

showed that bacterial DNA and LPS in the plasma was significantly higher in patients with the most severe disease. Bacterial DNA or LPS were also significantly correlated with inflammatory mediators, such as IL-6[299]. It is possible that this might be related, in some cases, to PHMs in various tissues that might be influencing the course of the disease. Of course, these are only speculative ideas to stimulate research, and the latest recommendations are that antibiotics and antifungals should be used judiciously in COVID-19[300].

Another possibility involving a bacterial or fungal strain as a factor in excessive inflammation in COVID-19 was suggested recently[274]. It might be that another microbe that cross-reacts with SARS-CoV-2 is present in the alveoli or other tissues in some individuals with severe disease (L. Carrasco, UAM, personal communication). This cross-reacting microbe could be a PHM and might exhibit antimicrobial resistance, making recovery more difficult.

Relevant to the previous discussion of IgG4, Chen et al[301] suggested that IgG4-RD patients may be more susceptible to severe COVID-19. Also, elevated IgG4 was found in the fibrotic tissue of a surgically resected tracheal ring in a patient with severe COVID-19[302]. It might be that elevated IgG4 is a sign of chronic antigenic stimulation by PHMs, as discussed above. Thus, these findings might be supportive of a role for PHMs in COVID-19 severity.

Excessive inflammation can occur in connection with other infections, such as influenza and sepsis[303]. Perhaps an intensified reaction to PHMs might also contribute to the excessive inflammation in conditions such as these.

PHMs might also be considered in post-infectious syndromes or other diseases linked to infections, like multisystem inflammatory syndrome in children and adolescents resulting from COVID-19 (MIS-C). Afrin et al[304] proposed that MIS-C might be a form of mast cell activation syndrome. Mast cell stabilization was proposed as a treatment to relieve prolonged symptoms following acute infection with SARS-CoV-2[305]. It seems plausible, based on the PHM hypothesis, that mast cell activation syndrome could be occurring as a response to antigens from PHM colonizers[2].

Prolonged symptoms, often involving fatigue, following COVID-19 have been compared to other post-infectious entities[306]. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been reported to often begin following an infection, stressful event and/or toxin exposure[307]. A study of ME/CFS patients found elevated blood Proteobacteria was part of a composite score associated with symptom severity[308]. One might speculate that this reflects increased blood PHM levels, since the phylum Proteobacteria includes diverse environmental microbes. Some ME/CFS patients have reported that diet changes have been helpful in symptom reduction[309–311], and a trial of a diet and nutrient intervention led to patient improvements[312].

It also is worth considering the relevance of recent insights into Kawasaki disease (KD), a disease that closely resembles the multisystem inflammatory response syndrome in children and adolescents associated with SARS-CoV-2 infection. KD has been suggested to be linked to gut dysbiosis[44,313], a westernized lifestyle/hygiene[44,313], westernization-associated variants of normal flora[44], autoimmune disease[314] and allergic disorders[315,316]. Some recent KD research has implicated a microbe or its toxin transported by tropospheric air currents, along with a triggering infection in genetically susceptible individuals[317,318].

Increasing cedar pollen has been associated with increasing KD and other diseases in Japan[319]. The role of pollen-associated PHMs might be worth investigating. Pollen-associated microbial communities have been found to be affected by urbanization-related pollution[320]. The potential for detrimental effects from hypothesized pollen-associated PHMs warrants investigation, especially given a recent study that found an association between pollen levels and cancer incidence[321].

Thus, the possible involvement of westernization-associated gut microbes, environmental microbes/antigens and triggering infections suggest that the PHM hypothesis is potentially applicable to KD. And the evidence for the involvement of an airborne component in KD causation is reminiscent of the apparent association between severe COVID-19 and air pollution[322–324].

Taken together, these findings are consistent with the hypothesis that PHM colonization could be the underlying cause or a factor in susceptibility or severity of a number of acute infections and their sequelae.

Testing the PHM Hypothesis

Fully validating the PHM hypothesis may prove challenging initially, since some of the microbes may be very low in abundance. In-depth analyses of the microbiotas of man-made products, xenobiotics, air pollution and agricultural products is needed. A more thorough assessment of colonizing microbes is an important goal. This would allow validation of this hypothesis through determining the sources of colonizing microbes and their associations with symptoms and pathogenesis.

Regarding COVID-19, studying the virus-induced effects on immune reactions to the tissue microbiota would be of interest. The microbiotas and immune reactions of COVID-19 patients could be compared to healthy controls and patients with the comorbid conditions who do not have COVID-19. One might find that those who recovered from COVID-19 more easily had fewer potential PHMs and/or a lower or more transient immune reaction to them.

According to the PHM hypothesis, allergies are often due to PHM colonization. Thus, allergy-suppressing modes of treatment might be evaluated, as discussed above, to help control excessive inflammation in COVID-19. Both PHMs and secondary opportunistic pathogens that might be contributing to the inflammation could be sought and potentially targeted by antimicrobials or other approaches designed to affect the microbiota balance. Immune modulation designed to reduce reactions to PHMs might be appropriate. These approaches also might be investigated in those who are symptomatic months after COVID-19.

Laboratory studies in animal models have utility in many contexts and could help evaluate the PHM hypothesis. Animals used in studies that model diseases would also be affected by PHMs. It would be impossible to give them the same environmental conditions that they evolved to tolerate. However, one could vary the degree of exposure to PHMs using different types of food, water, soil and other exposures.

The effects of dietary interventions on health outcomes in CIDs could be assessed. The effects of length of time since harvest and other factors potentially affecting PHMs' abundances could be analyzed. Ideally, high resolution assessments of the food and human microbiomes would be included. Antimicrobial, immune modulatory and microbiota modulatory approaches could be assessed, alone or in combination with dietary approaches.

It would be useful 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[100]. If they do, it would lend support to the PHM hypothesis proposal that microbes in food are involved in allergic diseases and other CIDs. Microbes that cross-react with particular allergens could then be sought and their relevance in disease processes investigated.

Many other types of studies could be done to evaluate various aspects of the PHM hypothesis[2]. For instance, epidemiological studies could look for associations of disease with PHMs. Experiments could investigate stress effects of PHM allergen exposure in humans or assess effects of microbes present in xenobiotics.

With regard to stress, the ability of PHM exposure to affect the perception and physiological effects of stress could be studied. Research has shown that food allergic individuals have greater histamine and tryptase release under cold pain stress[325] and this research could be expanded to look specifically at PHM colonization effects.

If the PHM hypothesis is correct, then reducing or eliminating PHM colonization would likely allow toleration of previously reaction-provoking foods and environmental exposures. This could be tested if antimicrobials, immunotherapy, probiotics, medications, diet change or other approaches could be shown to eliminate or reduce symptoms and the relevant PHMs. However, to be most useful, all relevant PHMs and opportunistic

infections would need to be considered. This perspective is in accord with the increasing recognition of the importance of polymicrobial infections[24,54,326,327].

Discussion

To briefly summarize, the PHM hypothesis proposes that a subset of microbes that have increased in our environment due to a post-hunter-gatherer era lifestyle are able to colonize human tissues under certain circumstances. This could lead to immune reactions to the colonizing microbes inside the body and the cross-reacting microbes and other antigens in the environment and food. PHMs' cross-reactions with self-tissue could lead to autoimmunity, especially in genetically predisposed individuals. Subsequent hypersensitivity reactions, stress responses and immune dysregulation could promote barrier breakdown and susceptibility to opportunistic pathogens, exacerbating inflammation further.

Although much of the research supporting this hypothesis could be explained by other hypotheses, this is not seen as a drawback. In fact, the diversity and complexity of the microbial and immune system interactions means that many other explanations and mechanisms are likely to be important. These other explanations may often be complementary to the PHM hypothesis. Many observed mechanistic explanations might be describing downstream or late-stage consequences of the effects of PHMs on aspects of microbial communities and human physiology.

The broad scope, unifying power and consistency with diverse observations makes this hypothesis worth consideration. This is especially important because, in many cases, lower abundance PHMs with patchy distributions will not be detected unless research uses methods that focus on improving resolution. Examples of attempts to improve resolution are the focused approach used to assess Yersinia spp abundance[41], culturomics approaches[25,328] and approaches arising from methodological advances[329–331].

It is interesting to reflect on mast cells, which are best known for two types of activities. The historically recognized role of mast cells is in hypersensitivity reactions. Their more recently understood role is their part in the defense against numerous pathogens, including bacteria[332]. IgE, basophils and eosinophils are also involved in allergy and increasingly being recognized for their roles in fighting infection by many pathogens, not just parasites[95,333–335]. The dual role of the other 3 traditionally recognized non-IgE types of immune hypersensitivity reactions is also known, as they all can be involved in infections and hypersensitivity[336].

The PHM hypothesis is consistent with the idea that in many cases, these two roles (anti-infection and hypersensitivity) are really the same. The main difference, according to the PHM hypothesis, is that in diseases attributed primarily to hypersensitivity reactions or chronic inflammation, the causal microbes have not yet been identified and/or recognized.

Low level colonization may have a disproportionately large effect via cross-reactions with self-tissue, environmental microbes/substances and food components. In addition, there may be many PHMs involved, with additive effects. These features, which could allow low abundance microbes to have substantial effects, are proposed to be a large part of the reason that the effects of PHMs have been previously underestimated.

In the case of autoimmune disease, the potential role for cross-reacting microbes has long been appreciated. This is mainly due to the well-known example of Streptococcus pyogenes cross-reacting with heart tissue, which has been associated with tissue destruction in rheumatic heart disease[35].

In the case of allergy, cross-reactions between inhalants and foods are widely recognized in the form of oral allergy syndromes[337]. And there has been a growing appreciation of microbial allergy, as discussed in previous sections.

The PHM hypothesis posits that many, or possibly most CIDs could stem from PHM colonization that develops and increases over the years. The frequency of cross-reactions and diversity of microbial species/strains

suggests that there may be foods, inhalants, self-tissues, colonizing and environmental microbes involved in a single reaction in some cases.

Although there is much evidence that is consistent with the PHM hypothesis, there is not enough evidence to validate it. The point of this article is to bring awareness to the plausibility and explanatory potential of the PHM hypothesis so that it can be evaluated.

Diverse treatment approaches are worth examining in relation to the PHM hypothesis, including antimicrobials, immune modulating medications, allergen specific immunotherapy, probiotics, diet, lifestyle, stress reduction techniques and altering environmental exposures. Approaches that have several components might be the most broadly effective, like combining antimicrobial approaches with diet and lifestyle approaches. The best approach in each disease would probably vary.

It would be important to distinguish between approaches that eliminate PHM colonization and those that just reduce reactions to PHMs. If elimination of PHM colonization is not feasible, other approaches that mitigate damaging effects might be emphasized.

If the PHM hypothesis is validated, the challenges that would ensue might not be as difficult as they might seem initially. If the identities and characteristics of the important PHMs and the immune responses to them are better understood, then more effective treatment approaches can be crafted. If the health problems associated with westernization are microbial in origin, there is likely a wide array of approaches available due to the power of the immune system, microbiotas and the treatments that affect them.

In conclusion, the PHM hypothesis proposes that colonization by microbes associated with a post-hunter-gatherer lifestyle, and especially a westernized lifestyle, underlie many CIDs. Additionally, immune hypersensitivities, cross-reactions, stress effects and opportunistic infections would typically result from PHM colonization and exacerbate the disease processes.

The PHM hypothesis arguably accounts for more of the basic research and clinical trial results in varied chronic inflammatory diseases than any other hypothesis. Given the adaptability of microbes, the changes in microbial exposures, the selection pressures for more polyextremotolerant microbes, and the frequency of cross-reactions, it seems reasonable to test the PHM hypothesis. If validated, it could lead to reduced morbidity and mortality through treatment approaches that could also minimize the need for permanent diet/lifestyle changes.

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Competing interests

JCW will be involved with a company that will conduct and/or promote research related to this hypothesis and may file for patents related to the concepts presented here.

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