

Review article

A prescription for clinical immunology: the pills are available and ready for testing. A review

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Abstract

Objective:

Modern immunology has been extremely successful in elucidating many features of the immune system, but not in stemming pandemics of non-infectious, immune-related disease associated with industrialized populations. These pandemics involve a broad range of allergic, autoimmune, and inflammatory diseases, potentially including neuroinflammatory-associated disorders. It is the purpose of this review to outline the literature pointing toward the causes and potential treatments of these problems.

Conclusions:

A wide range of evidence from the fields of clinical medicine, biomedical research, evolutionary biology, anthropology, epidemiology, immunology, and ecology point to the conclusion that pandemics of non-infectious, immune-related conditions arise from consequences of industrialization. Primary among these consequences is the loss of helminths from the ecosystem of the human body, the 'human biome'. In this view, helminths comprise a 'keystone species' of the human biome, and their loss is profoundly felt as pandemics of non-infectious, immune-related disease. Fortunately, evidence indicates that the consequences of industrialization that cause immune disease, such as helminth depletion, can be effectively avoided. Using this approach, it is expected that further pandemics of immune disease may be prevented, although it remains to be established whether prophylaxis rather than treatment of disease is required for some disorders. Thus, it is predicted that those who will succeed in curing and preventing immune-related disease will focus on addressing 'evolutionary mismatches' rather than simply on the molecular and genetic underpinnings of immunological disorders.

The diagnosis: modern immunology as currently practiced cannot overcome current pandemics of immune-related disease

The field of immunology has enjoyed a history of contribution to human health that spans hundreds of years. Pioneers such as Edward Jenner, Louis Pasteur and Robert Koch provided technology that has saved millions of lives during the past few centuries. Over the past 50 years, long after the initial clinical successes centered around vaccine technology, the field of immunology has rapidly expanded, undergoing an information revolution. A basic understanding of histocompatibility has been achieved, a complex understanding of T-cell and B-cell immunology has emerged at a molecular level, and numerous components of innate immunity have been described. This success and the resulting prestige enjoyed by immunologists have only recently been acquired in the academic world, with the first 'stand alone' department of immunology emerging less than 40 years ago, and with most immunologists still in departments that include pathologists, microbiologists, infectious disease experts, or internal medicine practitioners. Still, despite this recent emergence, the knowledge produced by

immunologists has been extensive, with more than 100 journals now devoted either in part or in total to the field of immunology, publishing a total of more than 18,000 articles in 2010 alone.

Paradoxically, while knowledge in the field of immunology has profoundly expanded, diseases related to an over-reactive immune system have also profoundly increased in industrialized society¹. Industrialized populations are faced with a barrage of pandemics related to immunological hypersensitivity. These non-infectious, immune-related conditions are not found in pre-industrial populations and not simply due to an increased surveillance for such conditions^{1,2}, and may be divided roughly into three categories: (1) Allergies, which affect as much as 50% of the industrialized human population. The list of antigens recognized by allergic reactions is extensive, and includes metals, plant pollen, and antigens from numerous foods; (2) Autoimmune diseases, which affect almost 10% of the industrialized human population. The list of autoimmune diseases is extensive and includes lupus, multiple sclerosis, Graves' disease, and type 1 diabetes, among others; (3) 'Inflammatory conditions' that affect millions. These include eczema and various diseases of the digestive tract such as Crohn's colitis and appendicitis. Unfortunately, a wide range of disorders that affect human cognition are also likely manifestations of immune dysregulation and hypersensitivity. For example, chronic fatigue syndrome³ and depression⁴ may be morbidities that result from chronic inflammation, whereas autism may result from inflammation early in development^{5,6}. The potential connection between immune dysregulation and a wide range of other cognitive problems is gaining wider appreciation, being one of the primary foci of the Psychoneuroimmunology Research Society and their journal, *Brain, Behavior, and Immunity*. This may constitute a fourth class of disease that is affected by immune system dysregulation or immune hypersensitivity. These four classes of diseases, taken as a whole, have at their core a pathologically over-reactive immune system, and thus the diseases in these classes can be termed hyperimmune-associated diseases.

The concomitant successes in basic immunological science and the apparent lack of progress of clinical immunology to deal with pandemics of hyperimmune-associated disease may seem disheartening. Here we describe a view that considers the evolutionary biology of modern *Homo sapiens*, taking into account the epidemiology of non-infectious disease and the idea that the human body is itself an ecosystem, termed the 'human biome'. This evolutionary and ecological view is not only encouraging, but points toward an approach to rapidly resolve pandemics of immune-related disease that plague industrialized human populations. This perspective is independent of the latest discovery or trend in immune cell signaling, and it even suggests that future discoveries concerning the molecular

details of the immune system (or a lack of such discoveries) will not affect clinical progress. The molecular details of a process need not provide insight toward a clinical solution, but are probably well described as costly and time consuming ventures that do not typically lead to a clinical solution. The first cytokine was discovered less than 50 years ago⁷, at the beginning of the current golden age of expansion of knowledge in immunological science and at a time when allergies and autoimmune diseases were just beginning to attract increased attention. Neither Jenner, Pasteur, nor Koch ever heard the word 'cytokine', yet their contributions were far-reaching. Here we argue that such advances in immunology can be accomplished today. To accomplish such, a radical new approach, one enlightened by evolutionary biology, ecology, and anthropology, is necessary.

Evolutionary mismatches

Today, 'evolutionary mismatches' are the ultimate causes of many of the diseases affecting industrialized countries⁸⁻¹⁴. The basic idea of 'evolutionary mismatch' is that there is an incongruity between our genetics, which evolved in the distant past (our own species, anatomically modern *Homo sapiens*, having likely emerged around 200,000 years ago), and the present environments in which we find ourselves today, particularly in industrialized populations. In the most well-known example, the relatively low demand for exercise and the relatively high abundance of food in many populations are inconsistent with the conditions in which our species evolved. This mismatch has led to pandemics of obesity, cardiovascular disease, type 2 diabetes, and associated morbidities. That is, modern human health is dependent on a certain amount of dietary restraint and exercise, and without these factors, we are susceptible to disease. Similar considerations apply to the immune system; the question can be asked, 'What factors have been lost in modern industrialized populations that may be responsible for contributing to the increasing incidence of immune-related diseases?' Fortunately, just as diet and exercise regimens reliably compensate for evolutionary mismatches affecting the cardiovascular system, available evidence indicates that immune problems resulting from evolutionary mismatches could be readily alleviated. Indeed, studies in human and nonhuman animal models indicate strongly that those evolutionary mismatches that leave the immune system both unstable and over-reactive can be circumvented. The design of such therapy requires only an understanding of the requirements imposed by evolutionary history and ecology of the human biome.

The fundamental building blocks of the immune system found in extant mammals are relatively ancient and conserved, with components of acquired (adaptive, inducible)

immunity likely first evolving more than 400 million years ago with the emergence of jawed vertebrates^{15,16}. As an apparent consequence of this long history of natural selection, the immune system seems to be quite well adapted, with mammals in general experiencing no known widespread pandemics of allergies, autoimmune diseases, or inflammatory related diseases. The only exception to this appears to be industrialized human populations and, to a lesser extent, some of the domesticated animals associated with those populations¹⁷. It is this observation that should drive the key questions in the field of immunology and provide the insight necessary to solve the problem of hyperimmune-associated pandemics.

Evolutionary mismatches affecting the immune system

Evolutionary mismatches that destabilize the immune system are readily identified; any factor that is associated with a wide range of allergic, autoimmune and inflammatory disease is a likely candidate. Although several factors, including chronic stress, deprivation from breastfeeding, and vitamin D deficiency (discussed below) meet these criteria, the most profound loss felt by the immune system in industrialized human populations is probably due to the introduction of sanitary practices aimed at preventing infectious disease. Sewer systems, water treatment facilities, routine use of toilets and hand hygiene have virtually eliminated helminths (intestinal cestode, trematode and nematode worms) from modern industrialized populations by disrupting their reproductive cycle. A large body of evidence indicates that the removal of these species from the human biome over the course of several decades in modern industrialized populations underpins a variety of pandemics of immune-related disease.

The weight of evidence supporting the assertion that a loss of helminths is the primary factor facilitating non-infectious pandemics of immune-related disease comes from both human and nonhuman animal models^{18–20}, and is overwhelming. First, helminths provide a wide range of molecules which directly interact with and down-regulate immune functions¹⁸, and also provide stimulation of regulatory networks or feedback inhibition²¹. Second, at least a 100 million years of coevolution have ensured that the association between helminth and host is necessary for both parties²². Not only are helminths dependent on the host for survival, but the vertebrate host is dependent on the immune regulation provided by these species. Third, direct observations on humans immigrating from pre- to post-industrial countries demonstrates that removing helminths effectively shifts the human immune system to a dramatically altered state consistent with that found in Western populations²³, complete with susceptibility to allergies and autoimmune disease².

Fourth, epidemiologic studies inversely correlate allergic, autoimmune, and inflammatory disease with the presence of helminths and positively correlate those same diseases with the presence of modern sanitation practices which eliminate those helminths²². In this manner, practices of industrialized culture aimed at reducing infectious disease have apparently created the single most potent element destabilizing the immune system in hundreds of millions of humans^{24,25}. We have termed this element 'biome depletion', indicating a state where 'keystone species'²², which play a central role in the ecology of the human biome, have been removed. It is likely that biome depletion in industrialized populations is exacerbated by assaults on the microbiome due to heavy antibiotic use and even changes in parturition and breast feeding^{26–30}. Unfortunately, the elements of a vicious cycle are in place, since immune hypersensitivity due to loss of helminths enhances the tendency of the immune system to interact adversely to a normal microbiome, and alteration of a normal microbiome by aberrant immune activity is likely to further destabilize the immune system.

Perhaps the most compelling evidence that the loss of helminths lead to allergic and autoimmune disease is the fact that some such diseases can be averted with the reintroduction of helminths, with the vast majority of experiments being conducted in nonhuman animal models^{25,31–33}. One of the most widely appreciated examples is colonization with *Heligmosomoides polygyrus*, a roundworm commonly found in the small intestine of a variety of rodent species. This helminth effectively averts or treats experimentally induced colitis, experimentally induced allergy, and type I diabetes in rodent hosts^{34–36}. Similarly, colonization with another roundworm *Nippostrongylus brasiliensis*, alleviates experimentally induced allergy in rodents³⁷. In addition, accidental helminth colonization of humans apparently halts the progression of multiple sclerosis²⁰. Further, two clinical trials have demonstrated that exposure to a porcine helminth, *Trichuris suis*, effectively treats some patients with inflammatory bowel disease previously untreatable with modern pharmaceuticals³⁸.

Reduced production of vitamin D represents a second evolutionary mismatch as a result of our predominantly indoor working environment. Decreased exposure to ultraviolet radiation reduces production of vitamin D, and it has become clear that a wide range of immune-related diseases, including allergies and a variety of autoimmune diseases, are associated with low vitamin D levels. Vitamin D deficiency has become epidemic in many modern industrialized societies, with about a quarter of the population being deficient³⁹. Vitamin D not only serves as a critical cytokine and is required for proper function of the immune system, but plays a strong role in metabolism⁴⁰. Given the close connection between immunity and metabolism⁴¹, it seems highly likely that destabilization of one system will

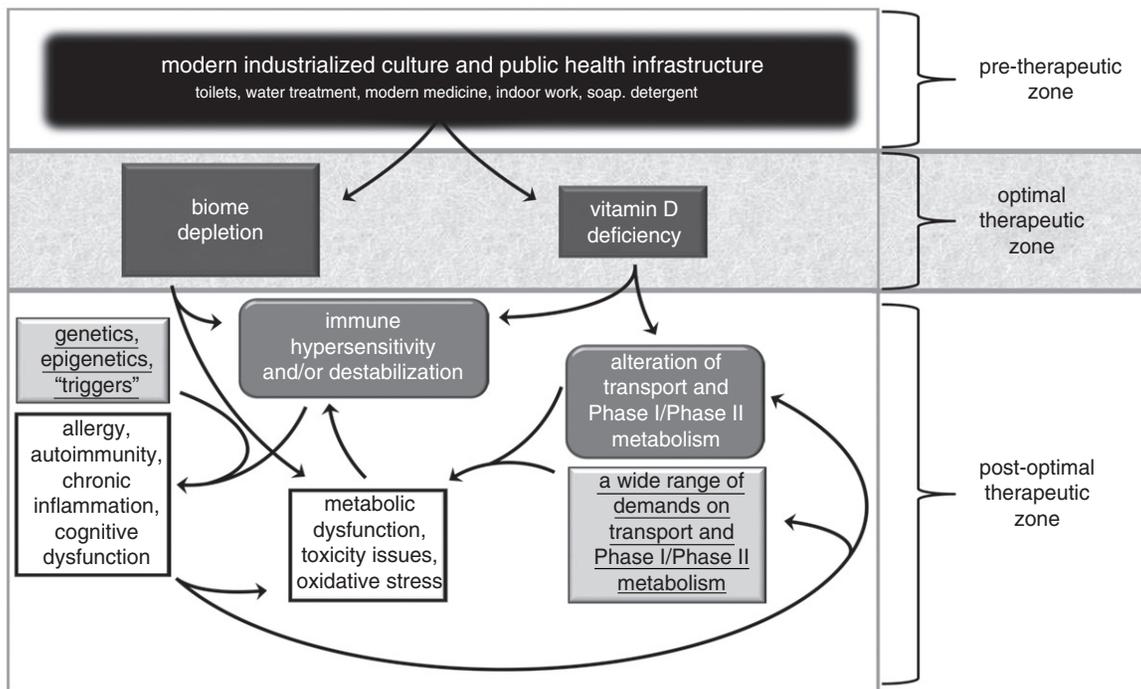


Figure 1. The etiology of biome depletion associated pandemics, stratified according to therapeutic potential. The cultural factors which initially lead to disease are considered necessary and are not under consideration for modification (pre-therapeutic zone). In contrast, the consequences of these factors are treatable or even altogether avoidable (optimum therapeutic zone). If those consequences are not averted, a complex dysregulation occurs which is extremely difficult to treat (post-optimal therapeutic zone). This dysregulation involves (a) variety of factors that are genetic and/or environmental and difficult or impossible to avoid (underlined text in light-colored boxes), (b) various systems of the body, including the immune system and metabolism (darkest colored boxes in the post-optimal therapeutic zone), and (c) a wide range of pathology (white boxes). Although the stratification presented in the diagram is complete, the components within the three strata are representative of a larger picture. For example, factors such as the Western diet and chronic psychological stress which undoubtedly contribute to pathology are not included.

adversely affect the other (Figure 1). Not only might chronic immune activation due to hyperimmune-associated disease utilize resources normally allocated to metabolism, but aberrant metabolism may lead to oxidative stress and/or the buildup of toxins, which may be immunostimulatory. It is likely beneficial that the human biome temporarily diverts resources from metabolism to immunity in times of infection, although chronic diversion of such resources may spell disaster.

What does a ‘normal’ immune system look like?

The concept of ‘normalcy’ is often a relative one. However, for the field of clinical immunology, at least one aspect of normalcy is relatively straight forward in the minds of the clinicians and the patients they treat; the normal immune system does not react to harmless components of the environment or to self antigens in a manner that leads to disease, and it does not have a high propensity for such reactions. In other words, a clinical definition of ‘normal’ involves freedom from hyperimmune-associated diseases and freedom from a high risk for those diseases. For patients, clinicians and biomedical

researchers alike, the concept of normal equates to healthy and is opposed to abnormal that relates to diseased or prone to disease. This view is imbedded in the field of medicine and is inescapable. Clinicians routinely use a variety of synonyms for abnormal, including aberrant, dysregulated, dysplasia, pathology, disorder, mutation, and impaired. In stark contrast, the concept of normal versus abnormal does not exist in evolutionary biology. Any given state at any given time, whether it results in disease or health, is part of the natural process, and thus cannot be described as abnormal.

Perhaps the easiest way to move forward in the multi-disciplinary field of evolutionary medicine is to establish that different fields have different definitions, and that those definitions are useful for those fields. As long as terms are clearly defined, any lack of progress due to miscommunication should be minimized. With that in mind, for the purposes of this manuscript, we will view the ‘normal’ state of the immune system as that which effectively mounts beneficial immune responses but is free from hyperimmune-associated diseases, and free from a propensity for such diseases. This is indeed the state which patients, clinicians, and biomedical researchers seek to establish and maintain.

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Unfortunately, clinicians and biomedical researchers alike often view the immune system of an individual in an industrialized population as normal if that system is free of disease. This viewpoint is problematic from a clinical perspective, since such individuals are glaring examples of evolutionary mismatches, being devoid of helminths and often lacking adequate vitamin D. Epidemiology indicates that even if these mismatched individuals have avoided immune-related disease for a time, they are still susceptible throughout their lifetime. Most importantly, classifying these individuals as 'normal' makes it virtually impossible to devise a cure for those individuals who have hyperimmune-associated disease. Thus, although the clinician and the biomedical researcher alike would like to have a normal standard that is both free of hyperimmune-associated disease and free of high risk for such disease, they instead have defined as normal a system that is at high risk for disease. We argue that the actual definition of 'normal' that should be sought by clinicians and biomedical researchers is a state where the consequences of evolutionary mismatches that lead to hyperimmune-associated diseases and the propensity for those diseases are avoided.

The immune systems of non-industrialized, developing populations have been studied²³. Some of these populations may be described, in part, as living predominately without some of the evolutionary mismatches described above. Compared to many of those in modern industrialized societies, these individuals have a relatively low prevalence of allergy and autoimmunity, high IgE levels, high numbers of eosinophils, higher numbers of cytotoxic T-cells but lower numbers of helper T-cells, increased HLA-DR⁺ cells in all examined T-cell subsets, a decreased proportion of naive CD4⁺ cells, an increased proportion of CD4⁺ memory cells, and decreased delayed-type skin hypersensitivity. Immune cells from these individuals demonstrate relatively reduced levels of transmembrane signaling and have reduced proliferation to recall antigen stimulation²³. In the current medical literature, the immune systems of these individuals are termed aberrant, with impaired immune function. We argue that the normal or healthy state of the immune system sought by clinicians and biomedical researchers is actually found in the disease-free inhabitants of a pre-industrial, developing populations, not in the disease-free inhabitants of most industrialized societies. The former have a biome sufficient to induce development and maintenance of a normal immune system, whereas the latter have no such biome.

A prescription for immunology: restoration of immune normalcy

Several helminth species have been fine-tuned by hundreds of millions of years of natural selection not to

adversely affect a healthy host, and are known to cause few if any symptoms in healthy hosts^{20,42,43}. The oldest of these associations is probably that found between the tapeworms (cestodes) and vertebrates. For therapeutic purposes, one of the best candidates in this class for use in humans is the bovine tapeworm (*Taenia saginata*), which is considered by some as a 'commensal' rather than a parasite⁴². This organism colonizes humans in a self-limiting manner that protects the human host, and can live for more than 20 years. To make this organism readily available for therapy would require systematic utilization of cows as the intermediate hosts, and the means to prepare the cysticercoids found in the bovine tissue for human consumption. Given the lack of technical hurdles facing the accomplishment of this task, the very low risk to healthy humans, and the long lifespan of the organism, this therapy seems feasible. One of the few limitations to such therapy may be that use of the bovine tapeworm will be precluded when defecation in soil where cattle might graze is a possibility, since such activity might pose a risk to the cattle industry. The rat tapeworm (*Hymenolepis diminuta*) also colonizes humans, and offers the advantages that it can be reared in arthropods and rodents (as intermediate and definitive hosts, respectively), rather than in cows. The rat tapeworm also has the advantage that the adult is only about 20 cm in length, shorter than the bovine worm, which can reach a length of over 5 meters and thus pose some inconvenience when it dies and is expelled from the human host via the anus. In addition, the rat tapeworm can be administered in varying doses, ranging from one to perhaps a dozen or more organisms, whereas the bovine tapeworm is almost invariably a solitary guest, with the presence of one organism precluding the addition of others. These factors might make the rat tapeworm preferable to the bovine tapeworm as a therapeutic for humans. However, the lifespan of the rat tapeworm is only 4–5 years, several-fold shorter than that of the bovine tapeworm. Thus, therapy using rat tapeworms would need to be administered on a more frequent basis than therapy using a bovine tapeworm.

Two other species are known to have few adverse effects on healthy humans when found in low numbers, and have been widely considered for use in biome reconstitution. These are the human hookworm (*Necator americanus*) and the human whipworm (*Trichuris trichiura*), which inhabit the small and large intestines, respectively. Neither of these species can be readily transmitted by human-to-human contact, since the eggs of both require incubation periods in the soil before they can colonize another human. This property, and the absence of substantial adverse reactions from these organisms when present in low numbers, distinguish them from the human pinworm (*Enterobius vermicularis*), which can be easily transmitted by human-to-human contact and which has some unwanted, albeit nonlethal, symptoms.

Preliminary indications are that hookworm therapy might entail colonization by a few dozen organisms, whereas therapy with whipworms (*Trichuris trichiura*) might involve hundreds of organisms. Hookworms are delivered cutaneously, with the primary side-effect of some minor soreness in the skin where the organisms are delivered. Whipworms, on the other hand, are delivered orally. Hookworms generally live between 1 and 5 years, similar to the rat tapeworm, whereas the whipworm has a lifespan of 1 year. Widespread use of these organisms for biome reconstitution will require facilities and personnel to accept material from human donors and to prepare the donor material for therapeutic delivery. Importantly, use of these particular organisms will be precluded when defecation in soil is a possibility, since uncontrolled infections can have an adverse effect on human health.

The risks of biome reconstitution

The potential for biome reconstitution to improve human health and quality of life is vast, with more than 40% of children in the United States currently having chronic illnesses⁴⁴. However, the risks of reconstitution deserve consideration²², since substantial morbidity and mortality is incurred, particularly among individuals weakened by malnutrition and dehydration, when uncontrolled infections of pathogenic helminths are encountered in developing countries. The overriding consideration here is that three safety mechanisms must be put in place. First, screening of potential recipients for anemia and malnourishment as well as other conditions that may preclude therapy (e.g., coagulopathy) would be routinely performed prior to therapeutic biome reconstitution. Second, the ability of patients to reliably utilize routine sanitation practices (e.g., toilets) would be ascertained before they can receive at least some forms of biome reconstitution therapy, thus preventing uncontrolled infections and high burdens of helminths. Finally, only those organisms that are not harmful to a healthy host would be utilized in biome reconstitution therapy. In this manner, we have the luxury of selecting controlled colonization with helminths, not pathologic infection. The fact that modern medicine can quickly and effectively remove helminths in the event that therapy is no longer needed adds an additional level of safety of this approach.

Roadblocks to biome reconstitution

Despite the great theoretical potential of biome reconstitution for human health, the feasibility of the approach, the low risks involved, and the initial successes, some initial trials have failed to deliver a cure for disease. For example, a well known study found that porcine whipworms

(*Trichuris suis*) failed to cure allergies⁴⁵. Similarly, a well known attempt to curtail asthma in humans using the human hookworm met with a lack of any statistically significant effect⁴⁶. These trials have proven understandably discouraging for clinicians and patients, but it is imperative that these results do not undermine further work in this field for two very important reasons. First, it seems highly likely that the trials undertaken to date may not have sufficiently reconstituted the biome. These early experiments have involved only one organism, and a full range of dosage for even that one organism has not been determined. The porcine whipworm, in particular, does not colonize the human, being eliminated within days, and may thus be one of the poorest immune modulators that could be considered. The authors of the study using the human hookworm in asthmatic patients⁴⁶ acknowledged that there was a trend toward a positive effect, and that a larger dose might be more effective. To be discouraged at this point in terms of the ongoing research seems extremely premature in light of the vast number of possibilities which might be pursued and the limited number of trials that have been conducted.

A second, even more compelling reason not to be discouraged by initial negative results is that these were all efforts at a cure, not at prevention. Biome reconstitution offers a great hope of reversing the primary evolutionary mismatch affecting the human immune system in industrialized populations, and as such it holds great promise for prevention. However, there is no promise of a cure. It remains unknown under what circumstances pathologic immune reactivity might be reversed. Biome reconstitution apparently works as a cure or effective treatment for multiple sclerosis and for inflammatory bowel disease, but whether it might work for other diseases *as a cure* remains to be seen. Particularly when developmental diseases such as autism are considered, a microgram of prevention may be worth several metric tons of cure. It is thus imperative that very early clinical experiments do not deter an exhaustive, thorough, and efficient examination of the potential for biome reconstitution, both for a cure and for prevention.

An additional issue has emerged which has guided people away from the idea that biome depletion and thus biome reconstitution are important. Unfortunately, when specific triggers that cause disease are identified, the idea that biome depletion is not important is sometimes erroneously embraced. As discussed previously in detail²², the central paradigm of biome depletion is that keystone species are lost from the human biome, thereby creating an evolutionary mismatch that makes the immune system prone to mounting pathologic reactions against a wide range of factors. These factors are in fact 'triggers' for disease, and may include food, drugs, common viral and bacterial infections, self antigens, and harmless environmental antigens such as ragweed pollen.

Although these factors are indeed triggers, it must be kept in mind that (a) it is biome depletion which rendered the triggers dangerous, and (b) avoidance of all potential triggers is probably a fruitless endeavor and certainly a tiresome task. Thus, in lieu of trying to avoid the vast array of triggers that face industrialized populations, it is expected that biome reconstitution as a means to defuse that vast array be taken as a course of action.

The current approach versus biome reconstitution

Research in the basic science of immunology has focused long on molecular details associated with immune dysfunction, relying almost exclusively on laboratory and clinical models not reflective of the evolutionary conditions experienced by these species. Clinical science, in turn, has focused largely on (a) genetic and epigenetic factors, (b) persistent and intensive efforts to understand the pathogenesis of disease without understanding that the biome is destabilized by ubiquitous environmental conditions (e.g., depletion of keystone species), (c) intensive efforts to treat symptoms and not the cause, and (d) the existence of certain 'triggers' which, in the face of immune system destabilization, are associated with disease. Such efforts are focused almost exclusively on the 'post-optimal therapeutic zone' described in Figure 1, and result in the chronic and widespread use of pharmaceutical products that have varying degrees of success in alleviating symptoms of disease, but which do not address the underlying causes. Indicative of the widespread nature of this approach, more than 2 billion dollars per year is spent in the United States on prescription and non-prescription medications for allergic rhinitis alone⁴⁷, with about 4% of the population using prescription anti-allergy drugs each month⁴⁸.

Essentially, *modern medical science is trying to stabilize an entire system that is inherently unstable* (prone to pathologic over-reactivity) due to evolutionary mismatches. Further, modern science is generally dependent on pharmaceuticals that are directed at a single target or at best a very limited number of targets. The idea that such a limited approach can never recapitulate the multi-faceted activity of helminths has been previously reviewed²², and illustrates the shortcoming of the pharmaceutical approach in terms of potential therapeutic targets, immune regulation, drug delivery, and the burden of healthcare costs. Although new discoveries periodically energize the basic science of immunology and drive new trends in research and funding, we argue that the past inability of this approach to halt pandemics of immune-related disease¹ foreshadows the future. A reversal of immune-related pandemics will require new approaches. Further, we argue that

it is not overly useful to dissect the thousands of molecular details that are affected by evolutionary mismatches. For example, vitamin D may affect the expression of thousands of genes, and elucidating such details may take decades or longer, offering no solution for vitamin D deficiency other than what is already obvious (widespread use of vitamin D supplements). Similarly, each helminth species produces dozens if not hundreds of molecules, and each molecule, in turn, potentially has profound and extensive effects on immunity. Although detailed studies of the molecular nature of the normal immune system are certainly interesting, we argue that such studies are not likely to resolve the *immediate* problems faced by clinical immunology today any more than studies of the evolutionarily mismatched immune system have resolved clinical problems in the past. By way of analogy, understanding the complexities associated with obesity and type 2 diabetes are interesting, but proper diet and exercise regimens do not depend on such understanding. The molecular details are sometimes only a distraction from what would otherwise be obvious. Such details do not generally drive a return to 'normalcy', but rather drive the production of expensive therapeutics with suboptimal efficacy and often with substantial side-effects. In lieu of this, development of a new approach, described below, is prescribed.

Research needed for biome reconstitution

As described recently²², a wide range of research needs to be conducted that will have a tremendous impact on human health: some questions need to be addressed concisely with the utmost urgency, while work on others will likely be ongoing for generations to come:

- (1) Which helminths or combination of helminths are safe and effective to utilize as therapeutics? How is the answer to this question affected by such variables as host age, pregnancy, disease state, gender, current state of the biome, state of the patient's maternal biome, and other factors?
- (2) What is the range of effective dosage (number and frequency) of helminths, and how does this vary with disease state? Is there a maximum safe dosage?
- (3) Which diseases can be cured or effectively treated with biome reconstitution, versus which can be prevented but not cured by biome reconstitution?
- (4) What are the risks versus the potential benefits for reconstituting the biome of patients who have medical conditions (e.g., suppressed immune system, anemia, and coagulopathy) that might make biome reconstitution more risky?
- (5) Can biome reconstitution be improved by individualized medicine? (Can biome reconstitution be tailored to the genotype of the patient?)

- (6) How will reconstitution of the biome affect modern medical practice? For example, will practices in the production and administration of vaccines and immunosuppressive drugs need to be modified so that they are effective on individuals with a healthy (reconstituted) biome?
- (7) What are the effects of biome reconstitution on human biology? For example, how does biome reconstitution affect reproduction, development, senescence, cognition and other factors?
- (8) Can modern science use naturally occurring helminths as a starting point, and improve them? The use of transgenic helminths and longer lived helminths are examples that might be considered. Biotechnology to improve production of helminths, including *in vitro* culture of helminths or cultivation of human specific helminths in genetically modified animals (e.g., humanized or immunosuppressed mice) might also be considered. In addition, irradiation of organisms to achieve sterility and eliminate the possibility of transmission is a possibility. As a specific example, a 'designer helminth' might be envisioned which has many of the properties of the bovine tapeworm (long life span, self-limiting colonization) but which is substantially smaller in size, thus eliminating much of the inconvenience when the organism dies and is eliminated from the body.

Another series of questions can be asked of reconstitution of the microbiome. For example, how and under what conditions should reconstitution of the microbiome be accomplished? This issue is currently being addressed in studies using probiotics and fecal transplants^{49,50}. One question of critical importance is whether intentional and controlled exposure to a normal microflora in a manner that recapitulates natural child birth should replace current practices in obstetrics. Other critical questions deal with how and when to reconstitute the microbiome following the use of antibiotics, or following infections that result in a depletion of the microbiome.

The prognosis

Promoting proper nutrition, including sufficient vitamin D intake, is not controversial. Similarly uncontroversial is the idea that assaults on the microbiome by antibiotic use and other factors should be limited as much as possible. These ideas, like much of preventative health practices, are often *not* effectively implemented, but at least they are not controversial. On the other hand, reconstituting the human biome with helminths, which is arguably the single most important factor in returning the immune system to normal¹²², has met with very limited enthusiasm and even some open opposition. Some argue that molecular

therapeutics are preferable to the restoration of normalcy using helminths. Arguments against using therapeutic helminths generally include the ideas that helminths (a) will not be widely accepted by patients, (b) are complex and thus will produce effects beyond our control, and (c) are dangerous as judged by the tremendous morbidity and mortality caused by helminths in developing countries. Fortunately, these arguments as they relate to industrialized populations are all easily negated²². Not only are *some* species of helminth (the ones that would be considered for use in modern industrialized populations) expected to be safe when used as a therapeutic²², but previous marketing of biological therapeutics (e.g., probiotics) to the general public has proven overwhelmingly effective. It seems highly unlikely that irrational fears would prevent patients from accepting life-saving therapy, especially if their children are at risk. More importantly, it seems highly unlikely that a pharmaceutical can be devised which will recapitulate the effects of an intimate association with another species. Thus, given the incredible morbidity and mortality associated with hyperimmune-associated disease, it seems imperative that we redirect our clinical science efforts toward restoration of a 'normal' immune system. The association of immune activation with some cognitive disorders such as autism⁵ and chronic fatigue syndrome³ supports the idea that pandemics of these diseases are also biome depletion-associated, and adds further to the sense of urgency.

The need for research aimed at returning the modern industrialized immune system to normal is directly proportional to the impact of biome depletion-associated pandemics on the population. Although the morbidity and mortality resulting from a variety of immune disorders is readily quantifiable, the complete impact of biome depletion-associated pandemics may be impossible to assess. For example, the pathogenesis of autism remains enigmatic, despite a wide range of circumstantial evidence suggesting that it is biome depletion-associated^{5,22}. Even if autism could be conclusively labeled as a biome depletion-associated pandemic, the complex phenotype associated with this disease and related disorders makes quantification of the impact difficult. Regardless of the impact on modern industrial societies, it is evident that biome depletion-associated pandemics are the single most pressing issue facing immunology today. Thus, clinical research is urgently needed to systematically address the best way to restore normalcy, whether restoration must be preventative, what new technologies might facilitate such restoration, and how restoration of normalcy for the immune system will affect other areas of medicine (e.g., immunization technology, cancer biology, aging, cognition, infectious disease, etc.). Given the ability of modern science to respond rapidly when a solution is envisioned, the prognosis for clinical immunology is considered excellent.

Conclusion

Data supporting the need for biome reconstitution as a readily available tool for modern medical practice are considerable, and argue that a substantial redirection of our biomedical research complex is needed. Several 'pills' which should facilitate reconstitution are readily available, and the future holds great promise for the development of new pills using modern biotechnology. Although the pills are ready, the leaders who will pioneer their use face some challenges. Not the least among these is funding for the testing of therapeutics which, although they hold great promise for public health, may hold limited promise for industrial profit. Another challenge involves regulation to ensure safe utilization of these therapeutics, especially given the wide-spread nature with which their eventual use is anticipated. The classification of helminths that have been a usual part of the human biome for thousands of years or longer as 'investigational new drugs' might impede their utilization, and seems ironic at best. However, prior work with a wide range of agents, including other living biological therapeutics (fly (*Phaenicia sericata*) larvae and leeches (e.g., *Hirudo medicinalis*)), blood, fecal material, and human milk may be considered as potential starting points for safe regulation of biome reconstitution.

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