The Hygiene Hypothesis and Multiple Sclerosis

Epidemiological studies indicate that the industrially developed world is characterized by a high and increasing burden of allergic and autoimmune diseases. For example, Holgate\(^1\) considers allergy a pandemic and points out that currently almost half of the populations of developed countries suffer from atopy, asthma, or another allergic condition. In the case of autoimmunity, Jacobson and colleagues\(^2\) estimate that 3 to 5% of the US population suffers from a serious immune-mediated disease such as insulin-dependent diabetes, inflammatory bowel disease, connective tissue disease, or multiple sclerosis (MS). In addition, Bach\(^3\) summarizes evidence suggesting that in the last 50 years the incidence of allergic and autoimmune diseases has increased dramatically, and the most persuasive supporting data for this trend come from conditions such as insulin-dependent diabetes,\(^4\) where acute treatment is life-saving and diagnosis is straightforward. In developing countries, by contrast, allergy and autoimmunity are uncommon. Clearly, this dichotomous epidemiological pattern requires a scientific explanation.

One account put forth to explain the observed global distribution and temporal changes in the incidence of allergy and autoimmunity is the hygiene hypothesis. Yazdanbakhsh and colleagues\(^5\) summarize the hygiene hypotheses as follows:

\[\ldots\] it has been proposed that the lack of intense infections in industrialized countries owing to improved hygiene, vaccination, and use of antibiotics may alter the human immune system such that it responds inappropriately to innocuous substances [leading to allergy or autoimmunity].

The hygiene hypothesis was first explicitly formulated by Strachan in 1989;\(^6\) however, many years previously, Leibowitz and colleagues\(^7\) had suggested that MS may be associated with high levels of sanitation. According to the hygiene hypothesis, allergy and autoimmunity are predominantly diseases of modern industrialized societies; immunopathology may thus be an unanticipated consequence of otherwise beneficial advances in sanitation and public health. It should be noted that the hygiene hypothesis is compatible with other explanations of immune-mediated diseases, such as well-established genetic associations; the hygiene hypothesis merely holds that a lack of “evolutionary normal” infectious exposures may be a critical factor that contributes to overt disease in an individual who is at risk because of genetic or other predispositions. Also, a rapid increase of disease incidence in a stable population in a short timeframe indicates that observed increase in allergy and autoimmunity cases is likely caused by environmental factors.

The hygiene hypothesis has been supported by investigations at the level of epidemiology,\(^8\) basic immunology,\(^13,16\) animal models,\(^17,22\) and human trials of probiotic agents.\(^23,26\) A prominent theme emerging from this research has been the finding of a relative deficiency of T-regulatory cell activity in allergy and autoimmunity;\(^27,29\) in addition, in some animal models, restitution of T-regulatory cell activity has been achieved by exposure to infectious agents, such as helminths or products derived from them.\(^20,30,31\)

Is the hygiene hypothesis relevant to MS? On one hand, a considerable body of evidence has indicated that infections may play a causative or exacerbating role in MS or animal models of MS.\(^32,35\) On the other hand, in support of the hygiene hypothesis, in some circumstances, immunomodulatory molecules produced by infectious agents can be beneficial and may prevent or ameliorate autoimmune disease (reviewed in Fallon and Alcamî\(^36\)). For example, in animal models of MS, such as experimental autoimmune encephalomyelitis, studies in our\(^37,38\) and other laboratories\(^39\) have shown that immunization or infection of mice with the helminth Schistosoma mansoni reduces the severity of disease; also, investigators have shown that spontaneous demyelination developed with high severity in immunodeficient anti-myelin basic protein T-cell receptor transgenic mice when they were kept in germ-free conditions.\(^40\) For epidemiology, we have recently shown that there is a dichotomous relationship between the global distribution of MS and parasitic infection,\(^41\) and some studies of MS incidence related to birth order or asthma association are supportive of the hygiene hypothesis.\(^42,43\) Longitudinal and migratory studies of MS, such as those conducted in the French West Indies, have been consistent with the hygiene hypothesis, showing, for example, that the incidence of MS increased in parallel with improved sanitation.\(^44\) Finally, among many immunological findings in MS has been a reduction in T-regulatory cell activity.\(^27,45\) Taken together, these studies provide support, albeit indirect, for the provisions of the hygiene hypothesis as possibly relevant to MS.

In this issue of the Annals of Neurology, Correale and Farez\(^46\) report on an important experiment of...
nature that may provide the first direct test of the hygiene hypothesis as it applies to MS. During the course of longitudinal studies conducted at a research MS clinic, the authors identified 12 patients at the onset of their eosinophilia, subsequently determined to be caused by mild, asymptomatic intestinal parasitism. The infected patients were matched with 12 uninfected MS patients, and the 2 groups were found not to vary significantly in clinical characteristics during either the previous 2 years or at baseline, defined as the onset of eosinophilia. Following standard medical practice for endemic areas and the recommendations of tropical medicine authorities that asymptomatic adult patients usually do not require treatment, the infected MS patients were not given antihelminth medications. Both groups were then followed for approximately 4.5 years and compared for serial clinical, magnetic resonance imaging (MRI), and immunological parameters. In comparison with the uninfected control patients, infected MS patients had a dramatic reduction in relapses, disability accumulation, new or enlarging T2 MRI lesions, and enhancing MRI lesions after gadolinium administration; remarkably, the relative reduction of activity in infected MS patients exceeded 90% for these parameters. In addition, immunological investigations showed that infected MS patients were characterized by cytokine responses that were predominantly of an antiparasitic Th2 type, rather than the proinflammatory Th1 type thought to be most characteristic of the natural history of MS. Also, increased numbers and activities of T-regulatory cells were found in infected MS patients in comparison with uninfected MS patients. Mechanistic studies indicated that immunological changes in infected MS patients may have been driven, in part, by downregulation of Smad7 signaling.

In summary, Correale and Farez’s investigation suggests that parasitism in MS is associated with substantial clinical, MRI, and immunological benefits, findings that are consistent with the provisions of the hygiene hypothesis. This study raises the exciting possibility that new insights into the cause and treatment of MS may follow from this research. Nevertheless, caution is necessary in interpreting the study, given its lack of blinding, small size, and observational design. Also, although the choice of an epitope of myelin basic protein as the main antigen for the study is reasonable, reliance on a single peptide does narrow the scope and implications of the investigation to some extent. In addition, although the apparently benign outcome observed during parasitic infection in MS patients suggests that low-grade parasitism causes no paradoxical or harmful immunological changes, only carefully designed prospective studies of safety can address these possible dangers definitively. For example, whereas polarization of the immune response toward an antiparasitic Th2 type immune response (evidenced by eosinophilia and cytokine changes in Correale and Farez’s study) rather than a proinflammatory Th1 type immune response would ordinarily be considered beneficial in MS, it is important to recall that in some circumstances Th2 activity has been associated with immunopathology, including, potentially, in MS itself.

It is also important to note that although the investigations cited earlier have been supportive of the hygiene hypothesis, evidence from other studies has been equivocal or contradictory. In a recent review, Sheikh and Strachan, who initially formulated this concept, remind us that it is only a hypothesis, not a validated theory. Finally, van Schayck and Knottnerus indicate that the acceptance of the hygiene hypothesis sometimes appears to have been based on unsupported conviction or ideology, rather than evidence; as they point out, scientists and physicians should be careful that “messages imparted to the general public do not go beyond or conflict with existing evidence.”

Where should research on MS and the hygiene hypothesis go from here? There is a pressing need to follow up on Correale and Farez’s groundbreaking study by means of rigorous, prospective, double-blinded clinical MS trials. The rationale for these studies is set out by Fallon and Alcami, who state:

Some of the major human diseases are caused by malfunctions in the immune response. The immune system did not evolve to cause these diseases but developed primarily to control bacterial, viral, fungal, and parasitic infections.

Of course, during millions of years of coevolution with the immune system, pathogens such as helminths have developed means of evading or attenuating the effects of immune responses, providing the basis for possible immunomodulatory therapies as Fallon and Alcami proposed:

The use of pathogens as therapeutics is well established through the exposure of people to live or attenuated pathogens as vaccines for infectious disease. An extension of this strategy is using the potentially desirable immune-modulating effects...
of pathogen infection for treating unrelated inflammatory diseases.

At first blush, the idea of intentionally treating patients with live, attenuated parasites may appear odd or repulsive. Nevertheless, after preparatory laboratory animal investigations\(^1\) and pilot safety studies in humans,\(^2\) researchers at the University of Iowa conducted controlled trials showing that oral administration of the whipworm *Trichuris suis* to patients with active inflammatory bowel disease was safe and effective in more than 120 subjects, some of whom were treated for more than 4 years\(^25,26,58\); these investigators also found that *T. suis* was noninvasive, and patients were essentially asymptomatic during transient colonization of the gastrointestinal tract. Additional studies of *T. suis* treatment in inflammatory bowel disease patients will be conducted shortly in Australia, and a large phase 3 study is anticipated in Europe. Also, an exploratory trial of helmint treatment for asthma has begun at the University of Nottingham, and a MRI-controlled phase 2 study of *T. suis* administration for MS has been funded by the National Multiple Sclerosis Society.

The eventual goal of research based on immunomodulatory pathogens such as helminths is to identify molecules for immunotherapeutic application in allergy and autoimmunity, on analogy of the isolation of digitalis from foxglove. Currently, however, a controversial issue is the best starting strategy: Should initial studies be conducted with specific molecules or whole organisms? Each approach has theoretical advantages and disadvantages. Administration of purified, well-characterized immunomodulatory molecules would be rational and obviate the risks associated with active infection; however, this strategy might entail drawbacks such as the development of neutralizing antibodies or hypersensitivity reactions or a bad guess as to which is the “right” molecule to test in a clinical trial. Also, although some studies have shown that purified molecular preparations have active immunomodulatory effects in animal models,\(^16,56,59,60\) other research has indicated that in reality the parasitic armamentarium is complex and involves mixtures of immunoactive molecules, each of which possibly has an optimal concentration and temporal niche in vivo.\(^61\) In this context, Ruby and colleagues\(^62\) state that “animals have coevolved and continue to coexist with diverse assemblages of microorganisms that are required for normal health and development,” and this view of complex organisms and their endogenous microbes as interconnected ecosystems has received increasing attention by evolutionary biologists and ecologists.\(^63,64\) The challenge for future research is to understand beneficial host–microbe interactions and incorporate this growing knowledge into our treatment of diseases. For initial clinical trials, a reasonable approach, such as that taken by investigators at the University of Iowa,\(^58\) might be to start with oral administration and transient gastrointestinal colonization with a highly attenuated, non-pathogenic organism such as *T. suis*, and work toward eventual identification of active parasitic components and mechanisms of their action.

In this regard, one vexing issue is determining the proper regulatory review for novel probiotic or parasitic-based therapies, which do not fit neatly into the paradigms established for conventional pharmaceuticals, vaccines, or biologics. The parameters that are typically relevant in drug testing (eg, pharmacokinetics, metabolism, drug interactions, dose range, receptor interactions) are usually quite different from those that are important during transient colonization by a probiotic or attenuated parasite (eg, avoidance of tissue invasion, effects of coinfections, paradoxical immune responses to the organism, effects specific to different life stages of the agent, unforeseen consequences of xenoinfection). In fact, considering microbes as something they are not (ie, drugs) may obscure the real safety issues raised by such treatment.\(^58,65–67\) Currently, the important, provocative findings of Correale and Farez\(^46\) reported in this issue of the *Annals of Neurology* must be interpreted with caution and await confirmation or refutation. Nevertheless, the intriguing and careful data presented in this report justifies controlled scientific studies to determine whether novel approaches based on the hygiene hypothesis will be safe and effective for allergic and autoimmune diseases, including MS.

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References


Models for Infantile Spasms: An Arduous Journey to the Holy Grail...

Infantile spasms (IS) is a relatively common and severe epilepsy of infants and young children. IS likely contributes to up to 10% of all mental retardation, and it evolves into further epilepsies in about 50% of cases. Although this catastrophic epilepsy was first identified more than 160 years ago, its cause and mechanism are poorly understood and treatment is unsatisfactory, particularly in preventing the postulated effects of these seizures on cognitive function.1,2

These questions are difficult to address in human studies; thus, valid animal models for IS are needed.3 However, defining and characterizing suitable models for IS has been a daunting problem. Prominent among the issues facing investigators interested in developing a model for IS are the numerous causes of this disorder: IS occurs in infants with metabolic disorders, many gene mutations, brain malformations, tuberous sclerosis, congenital or postnatal infections and strokes, among other causes. This multitude of apparent “causes” has made it difficult to sort out the essential elements within any of these entities that are required and sufficient to provoke IS.4,5

Models for IS proposed to date fit one of two general categories: those that recapitulate a specific cause of IS (eg, loss of interneurons in the ARX mouse, artificial stroke/hemispherectomy), and models that attempt to define and recreate a “final common pathway” for all of the causes that elicit IS. This latter approach has been taken by Velisek’s group,6 as described in this issue of *Annals*.

The unusual, rapid, and robust response to adrenocorticotropic hormone (ACTH), the current recommended therapy,7 has been considered a crucial clue for defining a common or converging mechanism for IS.4,8,9 Because ACTH is a component of the neuroendocrine stress response the possibility was raised that the common denominator or “final common pathway” of the many causes of IS involves stress response within the developing brain. Activation of specific components of the stress response, in turn, may promote hyperexcitability and provoke the abnormal neuronal activity (hypsarrhythmia) and seizures (spasms).4,10,11

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