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:

> . . . 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,[8–12] 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 Alcami[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

Published by Wiley-Liss, Inc., through Wiley Subscription Services

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,[47,48] 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[46] 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[46]) 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.[49,50] Certainly, the intriguing and positive results that Correale and Farez[46] note should not be an impetus to uncontrolled or faddish alternative treatments with parasitic or probiotic agents outside of scientific trials.

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.[51–54] In a recent review, Sheikh and Strachan,[55] who initially formulated this concept, remind us that it is only a hypothesis, not a validated theory. Finally, van Schayck and Knottnerus[54] 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."[54]

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[46] groundbreaking study by means of rigorous, prospective, double-blinded clinical MS trials. The rationale for these studies is set out by Fallon and Alcami,[36] 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[56] have developed means of evading or attenuating the effects of immune responses, providing the basis for possible immunomodulatory therapies as Fallon and Alcami[36] 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[18] and pilot safety studies in humans,[57] 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 helminth 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 immunomodulary 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, nonpathogenic 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.

John Fleming, MD,[1] and Zsuzsanna Fabry, PhD[2]

[1]Departments of Neurology and [2]Pathology
University of Wisconsin
Madison, WI

References

1. Holgate ST. The epidemic of allergy and asthma. Nature 1999; 402(suppl 1):B2–B4.
2. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopath 1997; 84:223–243.
3. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347: 911–931.
4. Gale EA. The rise of childhood type 1 diabetes in the 20th century. Diabetes 2002;51:3353–3361.
5. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. Science 2002;296:490–494.
6. Strachan DP. Hay fever, hygiene, and household size. Br Med J 1989;299:1259–1260.

7. Leibowitz U, Antonovsky A, Medalie JM, et al. Epidemiological study of multiple sclerosis in Israel. II. multiple sclerosis and level of sanitation. J Neurol Neurosurg Psychiatry 1966;29: 60–68.
8. Bach JF. Infections and autoimmune diseases. J Autoimmun 2005;25(suppl):74–80.
9. Cooke A, Zaccone P, Raine T, et al. Infection and autoimmunity: are we winning war, only to lose the peace? Trends Parasitol 2004;20:316–321.
10. Elias D, Wolday D, Akuffo H, et al. Effect of deworming on human T cell responses to myobacterial antigens in helminth-exposed individuals before and after bacille Calmette-Guerin (BCG) vaccination. Clin Exp Immunol 2001;123:219–225.
11. McKay DM. The beneficial helminth parasite? Parasitology 2006;132:1–12.
12. Nyan OA, Walraven GE, Banya WA, et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. Clin Exp Allergy 2001;31: 1672–1678.
13. Maizels RM. Infection and allergy helminths-hygiene and host immune regulation. Curr Opin Immunol 2005;17:656–661.
14. Vercelli D. Mechanisms of the hygiene hypothesis-molecular and otherwise. Curr Opin Immunol 2006;18:733–737.
15. Yazdankbakhsh M, Matricardi PM. Parasites and the hygiene hypothesis: regulating the immune system? Clin Rev Allergy Immunol 2004;26:15–24.
16. Zaccone P, Fehervari Z, Phillips JM, et al. Parasitic worms and inflammatory diseases. Parasite Immunol 2006;28:515–523.
17. Boitelle A, Scales HE, Di Lorenzo C, et al. Investigating the impact of helminth products on immune responsiveness using a TCR transgenic adoptive transfer system. J Immunol 2003;171: 447–454.
18. Elliott DE, Li J, Blum A, et al. Exposure to schistosome eggs protects mice from TNBS-induced colitis. Am J Physiol Gastrointest Liver Physiol 2003;284:G385–G391.
19. Fox JG, Beck P, Dangler CA, et al. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces Helicobacter-induced gastric atrophy. Nat Med 2000;6:536–542.
20. Kitagaki K, Businga TR, Racilia D, et al. Intestinal helminths protect in a murine model of asthma. J Immunol 2006;177: 1628–1635.
21. Saunders KA, Raine T, Cooke A, et al. Inhibition of type 1 diabetes by gastrointestinal helminth infection. Infect Immun 2007;75:397–407.
22. Wohlleben G, Trujillo C, Muller J, et al. Helminth infection modulates the development of allergen-induced airway inflammation. Int Immunol 2004;16:585–596.
23. Floch MH, Montrose DC. Use of probiotics in humans: an analysis of the literature. Gastroenterol Clin N Am 2005;34: 547–570.
24. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? Br J Derm 2005;152: 202–216.
25. Summers RW, Elliott DE, Urban JF Jr, et al. *Trichuris suis* therapy in Crohn's disease. Gut 2005;54:87–90.
26. Summers RW, Elliott DE, Urban JF Jr, et al. *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology 2005;128:825–832.
27. Baecher-Allan C, Hafler DA. Human regulatory T cells and their role in autoimmune disease. Immunol Rev 2006;212: 203–216.
28. Randolph DA, Fathman CG. $CD4^+CD25^+$ regulatory T cells and their therapeutic potential. Annu Rev Med 2006;57: 381–402.
29. Wing K, Sakaguchi S. Regulatory T cells as potential immunotherapy in allergy. Curr Opin Allergy Clin Immunol 2006;6: 482–488.
30. Harnett W, Harnett MM. Filarial nematode secreted product ES-62 is an anti-inflammatory agent: therapeutic potential of small molecule derivatives and ES-62 peptide mimetics. Clin Exp Pharm Physiol 2006;33:511–518.
31. Wilson MS, Taylor MD, Balic A, et al. Suppression of allergic airway inflammation by helminth-induced regulatory T cells. J Exp Med 2005;202:1199–1212.
32. Buljevac D, Flach HZ, Hop WC, et al. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 2002;125:952–960.
33. Correale J, Fiol M, Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. Neurology 2006;67: 652–659.
34. Gilden DH. Infectious causes of multiple sclerosis. Lancet Neurol 2005;4:195–202.
35. Goverman J, Woods A, Larson L, et al. Transgenic mice that express a myelin basic protein-specific T cell receptor develop spontaneous autoimmunity. Cell 1993;72:551–560.
36. Fallon PG, Alcami A. Pathogen-derived immunomodulatory molecules: future immunotherapeutics? Trends Immunol 2006; 27:470–476.
37. Sewell DL, Reinke EK, Hogan LH, et al. Immunoregulation of CNS autoimmunity by helminth and mycobacterial infections. Immunol Lett 2002;82:101–110.
38. Sewell D, Qing Z, Reinke E, et al. Immunomodulation of experimental autoimmune encephalomyelitis by helminth ova immunization. Int Immunol 2003;15:59–69.
39. La Flamme AC, Ruddenklau K, Backstrom BT. Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis. Infect Immun 2003;71:4996–5004.
40. Lafaille JJ, Nagashima K, Katsuki M, Tonegawa S. High incidence of spontaneous autoimmune encephalomyelitis in immunodeficient anti-myelin basic protein T cell receptor transgenic mice. Cell 1994;78:399–408.
41. Fleming JO, Cook TD. Multiple sclerosis and the hygiene hypothesis. Neurology 2006;67:2085–2086.
42. Ponsonby AL, van der Mei I, Dwyer T, et al. Exposure to infant siblings during early life and risk of multiple sclerosis. JAMA 2005;293:463–469.
43. Ponsonby AL, Dwyer T, van der Mei I, et al. Asthma onset prior to multiple sclerosis and the contribution of sibling exposure in early life. Clin Exp Immunol 2006;146: 463–470.
44. Cabre P, Signate A, Olindo S, et al. Role of return migration in the emergence of multiple sclerosis in the French West Indies. Brain 2005;128:2899–2910.
45. Viglietta V, Baecher-Allan C, Weiner HL, Hafler DL. Loss of functional suppression by CD4+CD5+ regulatory T cells in patients with multiple sclerosis. J Exp Med 2004;199: 971–979.
46. Correale J, Farez M. Parasite infections modulate the immune response in multiple sclerosis. Ann Neurol 2007;61: 97–108.
47. Gopinath R, Keystone JS. Ascariasis, trichuriasis, and enterobiasis. In: Blaser MJ, Smith PD, Ravdin JI, et al., eds. Infections of the gastrointestinal tract. New York: Raven Press, 1995: 1167–1177.
48. Liu LX, Weller PF. Intestinal nematodes. In: Rustgi VK, ed. Gastrointestinal infections in the tropics. Basel: Karger, 1990: 145–169.
49. Lassmann H, Ransohoff RM. The CD4-Th1 model for multiple sclerosis: a critical re-appraisal. Trends Immunol 2004;25: 132–137.

50. Tremlett HL, Evans J, Wiles CM, Luscombe DK. Asthma and multiple sclerosis: an inverse association in a case-control general practice population. Q J Med 2002;95:753–756.
51. Amre DK, Lambrette P, Law L, et al. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. Am J Gastroenterol 2006;101: 1005–1011.
52. Cooper PJ, Chico ME, Vaca MG, et al. Effect of albendazole treatments on the prevalence of atopy in children living in communities endemic for geoheminth parasites: cluster-randomized trial. Lancet 2006;367:1598–1603.
53. Sadovnick AD, Yee IML, Ebers GC. Multiple sclerosis and birth order: a longitudinal cohort study. Lancet Neurol 2005; 4:611–617.
54. van Schayck CP, Knottnerus JA. No clinical evidence base to support the hygiene hypothesis. Prim Care Respir J 2004;13: 76–79.
55. Sheikh A, Strachan DP. The hygiene theory: fact or fiction? Curr Opin Otolaryngol Head Neck Surg 2004;12:232–236.
56. Dunne DW, Cooke A. A worm's eye view of the immune system: consequences for the evolution of human autoimmune disease. Nat Rev Immunol 2005;5:420–426.
57. Summers RW, Elliott DE, Qadir K, et al. *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. Am J Gastroenterol 2003;98: 2034–2041.
58. Summers RW, Elliott DE, Weinstock JV. Why *Trichuris suis* should prove safe for use in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:783–784.
59. Hokke CH, Yazdanbakhsh M. Schistosome glycans and innate immunity. Parasite Immunol 2005;27:257–264.
60. Thomas PG, Harn DA. Immune biasing by helminth glycans. Cell Microbiol 2004;6:13–22.
61. Rzepecka J, Lucius R, Doligalska M, et al. Screening for immunodulatory proteins of the intestinal parasitic nematode *Heligmosomoides polygyrus*. Parasite Immunol 2006;28: 463–472.
62. Ruby E, Henderson B, McFall-Ngai M. We get by with a little help from our (little) friends. Science 2004;303: 1305–1307.
63. McFall-Ngai M. Love the one you're with: vertebrate guts shape their microbiota. Cell 2006;127:247–249.
64. Woolhouse MEJ, Webster JP, Domingo E, et al. Biological and biomedical implications of the co-evolution of pathogens and their hosts. Nat Genet 2002;32:569–577.
65. Van Kruiningen HJ, West AB. Potential danger in the medical use of *Trichuris suis* for the treatment of inflammatory bowel disease. Inflamm Bowel Dis 2005;11:515.
66. Kradin RL, Badizadegan K, Auluck P, et al. Iatrogenic *Trichuris suis* infection in a patient with Crohn disease. Arch Pathol Lab Med 2006;130:718–720.
67. Summers RW, Elliott DE, Weinstock JV. Therapeutic colonization with *Trichuris suis.* Arch Pathol Lab Med 2006;130: 1753–1754.

DOI: 10.1002/ana.21092

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.[1] 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]

Published by Wiley-Liss, Inc., through Wiley Subscription Services