



Editorial

Stress and immunity: bench to bedside approaches continue



Living in an increasingly complex world has advantages and disadvantages. Access to technologies that make many lives easier and/or more efficient has seen an explosion in most western societies and many other cultures around the world. With the good of technology comes the psychological challenge of living in an increasingly complex world with its economic, environmental, and geopolitical aspects. This increasing global development has occurred at the same time and rate as 2 other manifestations that are more directly germane to us as allergists and immunologists—changing external environments (increased pollution,¹ pollination,² and climate change³) and internal environments (multitasking, increased levels of perceived stress, anxiety, and depression)⁴—with a proposed direct impact on the increasing incidence and prevalence of allergy and asthma and increased difficulty in management⁵ despite new and exciting therapies being consistently introduced.

In this month's issue of *Annals*, we present 3 articles that examine the effects of living in our modern world, with its increased incidence of anxiety and depression, on asthma disease control, the clinical effects of increased exposure to oxidative stress, and a better understanding of the immune imbalances associated with chronic psychosocial stress. It is important for the reader to take these articles at their face value with self-described claims and limitations. Moreover, it is important to look at the bigger picture to address some possible reasons for the increase in disease morbidity in many of our patients.

Ciprandi et al⁶ examined the ongoing question of whether underlying anxiety and/or depression has negative clinical consequences in patients with asthma. From a diverse Italian outpatient population, 263 patients answered a questionnaire that quantified their levels of anxiety and depression, which was correlated with Asthma Control Test scores, forced expiratory volume in 1 second, fractional nitric oxide in the exhaled breath levels, and physical findings. Their results indicated a significant inverse correlation between anxiety scores and asthma control level in addition to rhinitis symptom scores. There was an inverse relation between anxiety and Asthma Control Test scores. Similarly, a significant correlation existed between depression scores and asthma symptoms, with a negative relation between depression and Asthma Control Test scores and forced expiratory volume in 1 second. These data further support evidence for the negative effects of chronic anxiety and/or depression on the clinical course of asthma and point to an important, although often neglected, target for intervention in patients with poorly controlled asthma.

Another article in this issue of the *Annals* addresses the relations associated with chronic stressful environments and their impact on cytokine balance.⁷ In this multicenter study (Urban Environment and Childhood Asthma Study), Gruenberg et al obtained a composite stressor score derived from an assessment of environmental

stressors, perceived stress level, and depression levels in 606 young inner-city mothers. These participants were selected because of the previously reported high levels of chronic stressor exposure and high prevalence of allergy and asthma in this population.⁸ Cytokine levels were determined from stimulated peripheral blood mononuclear cells and correlated with measurements of stress and depression. Interestingly, overall stress scores did not correlate with T-helper cell type 1 and 2 cytokine profiles as reported in other studies. However, individual environmental stressors (ie, interpersonal problems, housing factors, and neighborhood issues) significantly correlated with levels of proinflammatory and pro-allergic cytokines. These data do not fit directly into the stress-immune dysfunction paradigm for multiple possible reasons discussed by the investigators. However, this study does support the need for more consistently designed and controlled studies to develop immune profiles that can be accurately and reproducibly analyzed in stress-susceptible cohorts for future interventional studies.

Another form of stress that has known health consequences is oxidative stress. Indeed, antioxidant therapy (often in the form of dietary alterations) is increasingly popular globally. Oxidative stress has long been implicated as a factor to explain the effects of environmental pollution on allergic respiratory diseases,⁹ yet relatively little information about its impact on allergic rhinitis has been published. In their study, Sim et al¹⁰ compared the oxidative stress index, defined as the ratio of the serum total oxidant score to the total antioxidant score, in 90 children (mean age 9 years) with symptomatic allergic rhinitis vs 90 matched controls. Interestingly, the composite score and total oxidant and antioxidant scores were higher in the allergic rhinitis group than in the control group. Although the limited sample and cross-sectional design do not allow broad application, the investigators speculate that the total oxidant score (which would be expected to be increased in chronic inflammatory states) might have been moderated by an adaptive response in these patients. Factors influencing that inflammatory vs adaptive response remain to be determined in future larger longitudinal studies.

These articles in this issue of the *Annals* should add to our scientific and clinical awareness of the role that various forms of psychological dysfunction (high levels of perceived stress, anxiety, and depression) and environmental exposures can play in patients for whom we care on a daily basis. Adequately addressing these issues for our patients will demand a better approach to individual assessment of these factors and evidence from studies that will demonstrate the utility of pragmatic interventions to help us help our patients manage what many believe to be worsening levels of chronic stressor exposure in our increasingly complex world. The editorial team of the *Annals of Allergy, Asthma, and Immunology* is committed to finding and publishing high-quality evidence-based relevant articles that address the many facets of this important topic.

Gailen D. Marshall Jr, MD, PhD, FACP, DFACAAI
Editor-in-Chief
 University of Mississippi Medical Center
 Jackson, Mississippi
gmarshall@umc.edu

References

- [1] Zhang Q, Qiu Z, Chung KF, Huang SK. Link between environmental air pollution and allergic asthma: East meets West. *J Thorac Dis*. 2015;7:14–22.
- [2] Oswalt ML, Marshall GD. Ragweed as an example of worldwide allergen expansion. *Allergy Asthma Clin Immunol*. 2008;4:130–135.
- [3] D'Amato G, Holgate ST, Pawankar R, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. *World Allergy Organ J*. 2015;8:25.
- [4] Marshall GD Jr. Stress and allergic diseases—still under recognized and undertreated. *Ann Allergy Asthma Immunol*. 2014;112:275.
- [5] Baptist AP, Hamad A, Patel MR. Special challenges in treatment and self-management of older women with asthma. *Ann Allergy Asthma Immunol*. 2014;113:125–130.
- [6] Ciprandi G, Schiavetti I, Ridone E, Ricciardolo FLM. The impact of anxiety and depression on outpatients with asthma. *Ann Allergy Asthma Immunol*. 2015;115:408–414.
- [7] Gruenberg DA, Wright RJ, Visness CM, et al. Relationships between stress and cytokine responses in inner-city mothers. *Ann Allergy Asthma Immunol*. 2015;115:439–445.
- [8] Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med*. 2010;182:25–33.
- [9] Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. *J Allergy Clin Immunol*. 2002;110:349–356.
- [10] Sim CS, Lee JH, Kim SH, et al. Oxidative stress in schoolchildren with allergic rhinitis: propensity score matching case control study. *Ann Allergy Asthma Immunol*. 2015;115:391–395.