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The impact of stress on the development and expression of atopy

Rosalind J. Wright[a], Robyn T. Cohen[b] and Sheldon Cohen[c]

Purpose of review

Biological hypersensitivity to environmental stimuli is a fundamental feature of atopy predisposing to a number of clinically expressed disorders including allergic rhinitis, atopic dermatitis or eczema, and allergic asthma. There is provocative evidence that psychological stress constitutes an increased risk for atopy. This risk is thought to be mediated by the effects of stress on neuroimmunoregulation which in turn modulates the hypersensitivity response. The primary objective is to review recent evidence updating our understanding of the role for psychological stress in atopy.

Recent findings

The Th1–Th2 paradigm has been central to interpreting quantitative differences in cytokine expression in response to environmental stimuli like stress. Here we argue that examination of other mechanisms (e.g. oxidative stress pathways, glucocorticoid resistance, nerve–mast cell interactions, intestinal dysbiosis) and a broader range of cytokines and neuropeptides produced by cells both within and outside the immune system may better delineate the true complexity of the underlying mechanisms linking stress to allergic sensitization and asthma. The role of genetics and gene by environment interactions – based on evolving knowledge of candidate genes that may be relevant to both the stress response in general and pathways linked specifically to atopy – is also discussed.

Summary

Psychological stress may be conceptualized as a social pollutant that, when 'breathed' into the body, may disrupt biological systems related to inflammation through mechanisms potentially overlapping with those altered by physical pollutants and toxicants.

Keywords

allergic rhinitis, asthma, atopic dermatitis, atopy, neuroimmune, psychological stress

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Abbreviations

HPA hypothalamic–pituitary–adrenocortical
SAM sympathetic and adrenomedullary
TNF tumor necrosis factor

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Introduction

Atopy may be considered a genetically and environmentally determined predisposition to a number of clinically expressed disorders including allergic rhinitis, atopic dermatitis or eczema, and allergic asthma regulated through immune phenomena in which many cells (i.e. mast cells, eosinophils, and T lymphocytes) and associated cytokines, chemokines and neuropeptides play a role. Mechanisms of inflammation central to the pathophysiology of these atopic disorders overlap and involve a cascade of events that include the release of immunologic mediators triggered by both IgE-dependent and independent mechanisms. The exploration of host and environmental factors that may alter immune expression and potentiate the expression of atopic disorders is an active area of research. Indeed, atopy has been conceptualized as an epidemic of dysregulated immunity [1,2].

Mechanisms linking psychological stress, personality, and emotion to atopic disease continue to be elucidated. Hormones and neuropeptides released into the circulation when individuals experience stress are thought to be involved in regulating both immune-mediated and neurogenic inflammatory processes [3]. Dysregulation of normal homeostatic neural, endocrine, and immunologic mechanisms can occur in the face of chronic stress, leading to chronic hyperarousal or hyporesponsiveness that may impact disease expression [4–7]. This discussion updates a previous review [3] providing further insights into potential mechanisms linking stress to atopic disorders.

Psychological stress and the endocrine system

Psychological stressors have been associated with the activation of the sympathetic and adrenomedullary (SAM) system and the hypothalamic–pituitary–adrenocortical (HPA) axis (see Wright *et al.* [3] for a detailed review). Negative emotional responses disturb the regulation of the HPA axis and the SAM systems; that is, in the face of stress, physiological systems may operate at higher or

lower levels than during normal homeostasis. It is the disturbed balance of these systems that is relevant to disease. Immune, metabolic, and neural defensive biological responses important for the short-term response to stress may produce long-term damage if not checked and eventually terminated [5]. The potential detrimental cost of such accommodation to stress has been conceptualized as allostatic load (i.e. wear and tear from chronic under or overactivity of the allostatic system) [5]. This is exemplified by shifts in the circadian rhythm of cortisol found among persons under chronic stress [8].

There is evidence of increases in HPA, SAM, and inflammatory reactions in response to stress in patients with atopic dermatitis [9]. For example, there is increased responsiveness of the HPA axis in response to a heel prick stressor in newborns with a family history of atopy or elevated levels of cord blood IgE [10••]. This same group also found increased eosinophil counts and elevated IgE expression in response to stress in patients with atopic dermatitis [11]. Recent animal data suggest that increased maternal stress prenatally was associated with an elevated cortisol response to stress in the newborn affecting Th1/Th2 cell differentiation [12].

While the ability to activate an increase in cortisol in response to some stimuli in early life may be adaptive, prolonged exposure to stress may change the cortisol response if examined at a later developmental stage [13]. Chronic stress may induce a state of hyporesponsiveness of the HPA axis, whereby cortisol secretion is attenuated leading to increased secretion of inflammatory cytokines typically counterregulated by cortisol. A state of stress-induced HPA hyporesponsiveness has been demonstrated in some research participants with chronic inflammatory disorders [14]. Wamboldt and others [15•] found an attenuated cortisol response among adolescents with positive skin test reactivity and a clinical history of allergic rhinitis, atopic dermatitis, or asthma compared with those with skin test positivity alone or nonatopic individuals. Further studies are needed to examine relationships between individual patterns of cortisol response to stress across different developmental periods and the subsequent expression of atopy.

Other regulatory pituitary (i.e. corticotropin) and hypothalamic hormones (i.e. corticotropin-releasing hormone and arginine vasopressin) of the HPA axis have systemic immunopotentiating and proinflammatory effects [16]. Theoharides and colleagues [17] have shown that acute psychological stress (immobilization in rats) results in skin mast cell degranulation, an effect inhibited by anti-corticotropin-releasing hormone serum administered prior to stress [17]. Mast cell mediators are responsible for many of the immediate symptoms of nasal allergy and manifestations of atopic dermatitis. Mechanisms linking stress and mast cell function have been extensively reviewed [18••]. Although hormones of the sympathetic and adrenal medullary and HPA systems are those most often discussed as the biochemical substances involved in stress responses, alterations in a range of other hormones, neurotransmitters, and neuropeptides found in response to stress may also play a part in the health effects of stress and need to be further studied (e.g. prolactin, endorphins, enkephalins) [19].

Stress and autonomic control of airways

Further study of the balance among functional parasympathetic and functional sympathetic activity in relation to stress, emotional stimuli, and immune function in patients with asthma is needed. Local interactions between the immune system and the autonomic nervous system in the lung in particular are poorly understood and constitute an area of needed research [20••]. Increased activity of the parasympathetic nervous system was once thought to be the dominant mechanism responsible for the exaggerated reflex bronchoconstriction in asthma patients, although more recent work challenges this idea [21]. In the initial phases, narrowing of the airways in asthma is thought to result primarily from inflammation. Evidence suggesting a number of cholinergic antiinflammatory pathways triggered through vagus nerve activation including inhibition of macrophages and secretion of tumor necrosis factor (TNF)-α [22] complicate our understanding and need to be explored in the context of atopy.

More recent evidence demonstrating nerve–mast cell communication in response to stress and the potential import of these interactions in the respiratory system suggests this may be a fruitful area of research relative to stress and asthma [23]. Tachykinins produced by nonadrenergic noncholinergic (NANC) nerves influence airway smooth muscle contraction, mucus secretion, vascular leakage, and neutrophil attachment. In experimental studies, tachykinins, especially substance P, have been linked to neurogenic inflammation [24••] and regulation of stress hormonal pathways [25] as well as being implicated in asthma [26,27] and neurogenic skin disorders [28]. Recent data from a mouse model suggested that stress-induced airway hyperreactivity and enhanced allergic inflammation (OVA sensitization) was mediated by tachykinins [29••].

Stress and immune function

Atopic inflammation is thought to be orchestrated by activated T lymphocytes and the cytokines they produce. The T-helper cell Th2 cytokine phenotype promotes IgE production, with subsequent recruitment of inflammatory cells that may initiate or potentiate allergic

inflammation [3]. For most children who become allergic or asthmatic, the polarization of their immune system into an atopic phenotype probably occurs during early childhood [30].

These findings have sparked vigorous investigation into the potential influence of early life environmental risk factors for asthma and allergy on the maturation of the immune system, in the hope of understanding which factors will potentiate (or protect from) this polarization. There is evidence that parental reports of life stress are associated with subsequent onset of wheezing in children between birth and 1 year [31]. It has been speculated that stress triggers hormones in the early months of life which may influence Th2 cell predominance, perhaps through a direct influence of stress hormones on the production of cytokines that are thought to modulate the direction of differentiation. We examined relationships between caregiver stress on markers of early childhood immune response including IgE expression, mitogen and allergen-specific lymphocyte proliferative response, and subsequent cytokine expression (INF-γ, TNF-α, IL-10, and IL-13) in the same prospective birth cohort when the children were 2–3 years of age [32••]. In adjusted analyses, higher caregiver stress in the first 6 months after birth was associated with a greater allergen-specific proliferative response, higher total IgE levels, and increased production of TNF-α and reduced INF-γ.

For individuals with existing asthma, psychological stress may potentiate antigen-induced airway inflammation and contribute to exacerbations and disease severity. Liu and colleagues [33] reported a direct relationship between increased stress and increased eosinophilic airway inflammation to antigen challenge in patients with mild asthma.

Stress and glucocorticoid resistance

An alternative hypothesis linking stress, neuroendocrine and immune function and inflammatory disease expression considers a glucocorticoid resistance model [34]. As we have come to understand the central role of airway inflammation and immune activation in asthma pathogenesis, asthma treatment guidelines have focused on the use of antiinflammatory therapy, particularly inhaled glucocorticoids. Asthma patients, however, have a variable response to glucocorticoid therapy [35]. Although the majority of patients readily respond to inhaled glucocorticoids, a subset of patients have difficult to control asthma even when treated with high doses of oral steroids. The cellular and molecular mechanisms underlying steroid resistance in asthma and other inflammatory diseases have been recently reviewed [36•]. Notably, the majority of patients with glucocorticoid-resistant or glucocorticoid-insensitive asthma have an acquired form of steroid resistance induced by chronic inflammation or immune activation. Thus it is important to investigate those factors that may potentiate the development of functional steroid resistance. For example, studies have shown that allergen exposure effects glucocorticoid receptor binding affinity in T lymphocytes from atopic asthma patients [37]. It has been proposed that chronic psychological stress, resulting in prolonged activation of the HPA and SAM axes, may result in downregulation of the expression or function of glucocorticoid receptors, leading to functional glucocorticoid resistance [34].

Psychological stress and oxidative stress

Another potential mechanism linking stress to atopy and asthma is through oxidative stress pathways. A common feature of inflammation in living organisms is that it is frequently mediated by reactive oxygen species, either acquired exogenously or as by-products of normal metabolism. Individuals may differ in their ability to deal with oxidant burdens, either due to genetic factors or other environmental factors that induce or augment oxidative stress. It has been proposed that differences in host detoxification provide the basis for either resolution or progression of inflammation in atopic individuals after exposure to an environmental trigger. Spiteri and colleagues [38] postulated that the inability to detoxify reactive oxygen species among atopic patients leads to the release of chemotactic factors, the activation and recruitment of immune effector cells, prolonged inflammation, and the stimulation of bronchoconstricting mechanisms. Suggested factors which predispose susceptible individuals to asthma include chronic exposure to oxidative toxins (tobacco smoke, air pollution). An extension of the oxidative stress hypothesis is that psychological stress may be an additional environmental factor that could augment oxidative toxicity and increase airway inflammation.

There is evidence that psychological stress augments oxidative damage [39–41]. Irie and colleagues [42] used classical conditioning to illustrate the role of chronic stress and oxidative damage. In these experiments, rats treated with ferric nitrilotriacetate, an oxidant, and conditioned to associated treatment with taste aversion therapy, had increased 8-OhdG, a biomarker of oxidative toxicity, with further taste therapy compared with unconditioned animals.

Evidence also supports the notion that psychological stress modifies the host response to inflammatory oxidative toxins [43–46]. Recent animal data support a role for oxidative/antioxidative imbalance influencing a shift toward a Th2 phenotype in a model of autoimmunity in the rat [47•].

Environmental exposures that may interact with stress through these pathways include air pollution and tobacco

smoke. While epidemiologic evidence suggests that asthma symptoms can be worsened by air pollution, air pollution has not been clearly associated with increased risk of sensitization and induction of disease [48]. Several investigators have suggested that the ability of air pollution to generate reactive oxidative species may explain its role in asthma and other respiratory diseases [49–51]. Ultrafine particles ($<0.1\ \mu$m in diameter) have been demonstrated to increase oxidatively mediated inflammation in the lungs of rats [52,53]. In-vitro studies demonstrate that PM10 is responsible for the production and release of inflammatory cytokines by the respiratory tract epithelium as well as the activation of the transcription factor nuclear factor κB and that these properties are mediated by the production of reactive oxygen species [53]. Air pollution contains other oxidative toxins, such as reactive quinones and polycyclic aromatic hydrocarbons [51]. Tobacco smoke also contains a number of compounds with oxidative potential, at least 50 of which are procarcinogens [54]. These include polycyclic aromatic hydrocarbons [54–56]. Elevated levels of biomarkers linked to oxidative stress have been found among smokers relative to nonsmokers [57,58]. Young children exposed to environmental tobacco smoke have increased levels of 8-OhdG, a biomarker of oxidative toxicity in infants [59].

The effects of environmental toxins (air pollution, tobacco smoke) on atopy and asthma may be mediated by the common pathway of oxidative stress, a process that could be potentiated by chronic psychological stress. Further research is needed to examine these relationships.

Genetics

Studies to determine the role of genetics in modifying the risk of the social/physical environment experienced through psychological stress may further inform pathways through which stress may impact asthma expression [60]. Genetic factors of potential import include those that influence immune development and airway inflammation in early life, corticosteroid regulatory genes, adrenergic system regulatory genes, biotransformation genes, and cytokine pathway genes.

Genes expressed in the lung involved in determining the effects of oxidative stress, specifically the glutathione S tranferases, have been found to be functionally [61] and clinically [62,63] significant in recent studies related to atopic risk. Gilliland and colleagues [64•] found that specific glutathione-S transferase P1 variants are associated with increased histamine and IgE responses to air pollution oxidants and allergen *in vivo*. Maternal genetics related to oxidative stress genes may influence the child's atopic risk beginning *in utero* [65•]. The fetal immune response is influenced prenatally [66]. Seasonal sensitization of cord blood mononuclear cells to pollens has been demonstrated [67,68].

Variants of the glucocorticoid receptor gene may contribute to interindividual variability in HPA axis activity and glucocorticoid sensitivity in response to stress [69•,70]. Studies related to factors regulating the feedback mechanisms involved in the glucocorticoid response to stress are also of interest [71•]. A recent study examined polymorphisms of the TNF-α promoter region (TNF-α –308G/A) and linked specific variants to increased C-reactive protein, a proinflammatory marker [72•]. These are potentially interesting candidate genes to include in future studies of risk for atopic disease. Such studies that consider gene–environment interactions (i.e. stress by pathway genes) may inform specific mechanisms related to stress and atopy.

Stress and dysbiosis

Recently there has been growing interest in the integrity of the indigenous microflora of the gastrointestinal tract in early life and the relationship to atopic disorders. Epidemiological and clinical studies suggest that nonpathogenic microbes including *Lactobacillus* in the gut play a role in the maturation of the immune system toward a nonatopic phenotype [73]. Intestinal dysbiosis – or alterations in the integrity of indigenous microflora in the gastrointestinal tract – is now believed to be a contributing factor to atopic diseases among others [74•]. Factors including antibiotics, psychological and physical stress, and dietary components have been found to contribute to intestinal dysbiosis. A number of prospective intervention studies modifying the gut flora from birth have yielded results supporting the notion that this may be a promising approach to primary prevention of atopy in the future [75–77]. Studies have shown that psychological and physical stress may disrupt the normal balance of intestinal microflora that may contribute to later disease. Bailey and Coe [78] showed that separation of infant monkeys from their mothers, a psychological stressor, was associated with a significant decrease in protective fecal flora, particularly lactobacilli. This same group demonstrated that this influence may begin even before birth. Bailey and colleagues [79•] documented alteration in the intestinal microflora in newborn and infant monkeys when their mothers were exposed to an acoustical startle stress paradigm during pregnancy.

Evidence suggests that shifts in the population dynamics of enteric bacteria can be modulated by psychological stress. Stress results in increased bacterial adherence and decreased luminal lactobacilli in the gut [80]. These data suggest another pathway through which stress may be operating to influence risk for atopy.

Insights from psychological intervention studies

Clinical studies demonstrating the efficacy of alternative modalities that reduce stress and alter mood states in treating atopic disorders add further support to the hypothesized link with stress and suggest alternative treatment approaches. These have been reviewed elsewhere [81•].

Conclusion

Although the Th1–Th2 paradigm remains an important functional dichotomy to consider when interpreting quantitative differences in cytokine expression in response to environmental stimuli like stress, examination of other mechanisms (e.g. oxidative stress pathways, neural–immune interactions, intestinal dysbiosis) or a broader range of cytokines and neuropeptides produced by cells both within and outside the immune system may better delineate the true complexity of the underlying mechanisms linking stress to allergic sensitization and asthma. Psychological stress should be conceptualized as a social pollutant which can be 'breathed' into the body and disrupt a number of physiological pathways similar to how air pollutants and other physical toxicants may lead to increased risk for atopy. Stress may have independent effects as well as influencing atopy through the enhancement of neuroimmune responses to other environmental factors operating through similar pathways.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

1 Umetsu DT, McIntire JJ, Akbari O, *et al.* Asthma: an epidemic of dysregulated immunity. Nat Immunol 2002; 3:715–720.

2 Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: an overview. Psychother Psychosom 2001; 70:6–16.

3 Wright R, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. Thorax 1998; 53:1066–1074.

4 Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 1995; 345:99–102.

5 McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998; 338:171–179.

6 Holgate ST. Asthma: a dynamic disease of inflammation and repair. In: Chadwick DJ, Cardew G, editors. The rising trends in asthma. West Sussex, UK: John Wiley & Sons; 1997. pp. 5–34.

7 Busse WW, Rosenwasser LJ. Mechanisms of asthma. J Allergy Clin Immunol 2003; 111(3 Suppl):S799–S804.

8 Ockenfels MC, Porter L, Smyth J, *et al.* Effect of chronic stress associated with unemployment on salivary cortisol: overall cortisol levels, diurnal rhythm, and acute stress reactivity. Psychosom Med 1995; 57:460–467.

9 Buske-Kirschbaum A, Geiben A, Hollig H, *et al.* Altered responsiveness of the hypothalamus–pituitary–adrenal axis and the sympathetic adrenomedullary system to stress in patients with atopic dermatitis. J Clin Endocrinol Metab 2002; 87:4245–4251.

10 •• Buske-Kirschbaum A, Fischbach S, Rauh W, *et al.* Increased responsiveness of the hypothalamus–pituitary–adrenal (HPA) axis to stress in newborns with atopic disposition. Psychoneuroendocrinology 2004; 29:705–711.
Neonates with an atopic family history and elevated cord IgE were shown to have significantly more elevated cortisol response to the heel prick stressor when compared with their counterparts without a family history of atopy. This demonstrates that those potentially at risk for atopy may show a different hormonal response to stress depending on the developmental stage at which they are assessed.

11 Buske-Kirschbaum A, Gierens A, Hollig H, Hellhammer DH. Stress-induced immunomodulation is altered in patients with atopic dermatitis. J Neuroimmunol 2002; 129:161–167.

12 von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. J Allergy Clin Immunol 2002; 109:923–928.

13 Miller GE, Cohen S. Psychological Interventions and the immune system: a meta-analytic review and critique. Health Psychol 2001; 20:47–63.

14 Buske-Kirschbaum A, Jobst S, Wustmans A, *et al.* Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. Psychosom Med 1997; 59:419–426.

15 • Wamboldt MZ, Laudenslager M, Wamboldt FS, *et al.* Adolescents with atopic disorders have an attenuated cortisol response to laboratory stress. J Allergy Clin Immunol 2003; 111:509–514.
This study examines the HPA axis response in atopic adolescents in a community sample. Adolescents with a history of atopic illnesses with clinical symptoms had an attenuated cortisol response to laboratory stressors compared with adolescents with positive skin test results alone or nonatopic adolescents.

16 Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med 1995; 332:1351–1362.

17 Theoharides TC, Singh LK, Boucher W, *et al.* Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology 1998; 139:403–413.

18 •• Theoharides TC, Donelan JM, Papadopoulou N, *et al.* Mast cells as targets of corticotropin-releasing factor and related peptides. Trends Pharmacol Sci 2004; 25:563–568.
This manuscript provides an excellent overview of known neural–mast cell interactions and the relationship with the hormonal stress response.

19 Rabin BS, Cohen S, Ganguli R, *et al.* Bidirectional interaction between the central nervous system and the immune system. Crit Rev Immunol 1989; 9:279–312.

20 •• Undem BJ, Weinreich D. Neuroimmune interactions in the lung. In: Bienenstock J, Goetzle EJ, Blennerhassett MG, editors. Autonomic neuroimmunology. New York: Taylor & Francis; 2003. pp. 279–294.
This overview provides an excellent summary of current knowledge in the field and underscores several gaps in research.

21 Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract. Am Rev Respir Dis 1991; 144:1187–1198, 1391–1399.

22 Tracey KJ. The inflammatory reflex. Nature 2002; 420:853–859.

23 van der Kleij HPM, Blennerhassett MG, Bienenstock J. Nerve–mast cell interactions: partnership in health and disease. In: Bienenstock J, Goetzl JE, Blennerhassett MG, editors. Autonomic neuroimmunology. New York: Taylor & Francis; 2003. pp. 139–170.

24 •• Weinstock JV. Substance P (SP) and the immune system. New York: Taylor & Francis; 2003.
Interactions between substance P and the immune system are reviewed.

25 Jessop DS, Renshaw D, Larsen PJ, *et al.* Substance P is involved in terminating the hypothalamo–pituitary–adrenal axis response to acute stress through centrally located neurokinin-1 receptors. Stress 2000; 3:209–220.

26 Ichinose M, Miura M, Yamauchi H, *et al.* A neurokinin 1-receptor antagonist improves exercise-induced airway narrowing in asthmatic patients. Am J Respir Crit Care Med 1996; 153:936–941.

27 Tomaki M, Ichinose M, Miura M, *et al.* Elevated substance P content in induced sputum from patients with asthma and patients with chronic bronchitis. Am J Respir Crit Care Med 1995; 151:613–617.

28 Singh LK, Boucher W, Pang X, *et al.* Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of corticotropin-releasing hormone receptors. J Pharmacol Exp Ther 1999; 288:1349–1356.

29 •• Joachim RA, Sagach V, Quarcoo D, *et al.* Neurokinin-1 receptor mediates stress-exacerbated allergic airway inflammation and airway hyperresponsiveness in mice. Psychosom Med 2004; 66:564–571.
This study investigated whether stress-induced increase in airway inflammation and hyperreactivity is mediated by tachynins.

30 Yabuhara A, Macaubas C, Prescott SL. Th-2 polarised immunological memory to inhalant allergens in atopics is established during infancy and early childhood. Clin Exp Allergy 1997; 27:1261–1269.

31 Wright RJ, Cohen S, Carey V, *et al.* Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. Am J Respir Crit Care Med 2002; 165:358–365.

32 Wright RJ, Finn PW, Contreras JP, *et al.* Chronic caregiver stress and IgE
•• expression, allergen-induced proliferation and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol 2004; 113:1051–1057.

This is the first prospective study linking higher levels of early caregiver stress and subsequent immune function suggestive of a proinflammatory, atopic phenotype. Whether these immune factors mediate the relationship between stress and subsequent diagnosis of asthma or atopy remains to be examined.

33 Liu LY, Coe CL, Swenson CA, *et al.* School examinations enhance airway inflammation to antigen challenge. Am J Respir Crit Care Med 2002; 165:1062–1067.

34 Miller GE, Ritchey AK, Cohen S. Chronic psychological stress and regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol 2002; 21:531–541.

35 Lee TH, Brattsand R, Leung DYM. Corticosteroid action and resistance in asthma. Am J Respir Cell Mol Biol 1996; 154:S1–S79.

36 Leung DYM. Update on glucocorticoid action and resistance. J Allergy Clin
• Immunol 2003; 111:3–22.

Glucocorticoids are widely used to treat atopic diseases. However, many individuals have a suboptimal response to steroid therapy. A number of known and unknown parameters determine glucocorticoid responsiveness and are reviewed here.

37 Nimmagadda S, Spahn J, Surs W, *et al.* Allergen exposure decreases glucocorticoid receptor binding affinity and steroid responsiveness in atopic asthmatics. Am J Respir Crit Care Med 1997; 155:93–97.

38 Spiteri MA, Bianco A, Strange RC, Freyer AA. Polymorphisms at the glutathione S-transferase, GSTP1 locus: a novel mechanism for susceptibility and development of atopic airway inflammation. Allergy 2000; 55: 15–20.

39 Adachi S, Kawamura K, Takemoto K. Oxidative damage of nuclear DNA in liver of rats exposed to psychological stress. Cancer Res 1993; 53:4153–4155.

40 Kosugi H, Enomoto H, Ishizuka Y, Kikugawa K. Variations in the level of urinary thiobarbituric acid reactant in healthy humans under different physiological conditions. Biol Pharmaceut Bull 1994; 17:1645–1650.

41 Tomei LD, Kiecolt-Glaser JK, Kennedy S, Glaser R. Psychological stress and phorbol ester inhibition of radiation-induced apoptosis in human peripheral blood leukocytes. Psychiatry Res 1990; 33:59–71.

42 Irie M, Asami S, Nagata S, *et al.* Classical conditioning of oxidative DNA damage in rats. Neurosci Lett 2000; 288:13–16.

43 Moller P, Wallin H, Knudsen LE. Oxidative stress associated with exercise, psychological stress and life-style factors. Chem Biol Interact 1996; 102:17–36.

44 Capel ID. The effect of isolation stress on some hepatic drug and carcinogen metabolising enzymes in rats. J Environ Pathol Toxicol 1980; 4:337–344.

45 Capel ID, Dorrell HM, Smallwood AE. The influence of cold restraint stress on some components of the antioxidant defence system in the tissues of rats of various ages. J Toxicol Environ Health 1983; 11:425–436.

46 Chen D, Cho SI, Chen C, *et al.* Exposure to benzene, occupational stress, and reduced birth weight. Occup Environ Med 2000; 57:661–667.

47 Wu Z, Holwill SD, Oliveira DB. Desferrioxamine modulates chemically in-
• duced T helper 2-mediated autoimmunity in the rat. Clin Exp Immunol 2004; 135:194–199.

These data buttress the notion that oxidative/antioxidative balance plays a role in polarization of the immune system and may play a role in atopic disease. These findings may have implications for understanding the role of stress in atopy as stress may also influence this balance.

48 Peden DB. Air pollution in asthma: effect of pollutants on airway inflammation. Ann Allergy Asthma Immunol 2001; 87(6 Suppl 3):12–17.

49 Prahalad AK, Inmon J, Dailey LA, *et al.* Air pollution particles mediated oxidative DNA base damage in a cell free system and in human airway epithelial cells in relation to particulate metal content and bioreactivity. Chem Res Toxicol 2001; 14:879–887.

50 Ghio AJ, Carter JD, Richards JH, *et al.* Diminished injury in hypotransferrinemic mice after exposure to a metal-rich particle. Am J Physiol Lung Cell Mol Physiol 2000; 278:L1051–L1061.

51 Donaldson K, Gilmour MI, MacNee W. Asthma and PM10. Respir Res 2000; 1:12–15.

52 Oberdorster G. Pulmonary effects of inhaled ultrafine particles. Int Arch Occup Environ Health 2001; 74:1–8.

53 Baeza-Squiban A, Bonvallot V, Boland S, Marano F. Airborne particles evoke an inflammatory response in human airway epithelium: activation of transcription factors. Cell Biol Toxicol 1999; 15:375–380.

54 Ford JG, Li Y, O'Sullivan MM, *et al.* Glutathione S-transferase M1 polymorphism and lung cancer risk in African-Americans. Carcinogenesis 2000; 21:1971–1975.

55 Kelsey KT, Spitz MR, Zuo ZF, Wiencke JK. Polymorphisms in the glutathione S-transferase class mu and theta genes interact and increase susceptibility to lung cancer in minority populations (Texas, United States). Cancer Causes Control 1997; 8:554–559.

56 Rahman I, MacNee W. Oxidative stress and regulation of glutathione in lung inflammation. Eur Respir J 2000; 16:534–554.

57 Lodovici M. Levels of 8-hydroxydeoxyguanosine as a marker of DNA damage in human leukocytes. Free Radic Biol Med 2000; 28:13–17.

58 Zhou JF, Yan XF, Guo FZ, *et al.* Effects of cigarette smoking and smoking cessation on plasma constituents and enzyme activities related to oxidative stress. Biomed Environ Sci 2000; 13:44–55.

59 Hong YC, Kim H, Im MW, *et al.* Maternal genetic effects on neonatal susceptibility to oxidative damage from environmental tobacco smoke. J Natl Cancer Inst 2001; 93:645–647.

60 Steckler T. The molecular neurobiology of stress: evidence from genetic and epigenetic models. Behav Pharmacol 2001; 12:381–427.

61 Hu X, O'Donnell R, Srivastava SK, *et al.* Active site architecture of polymorphic forms of human glutathione S-transferase P1-1 accounts for their enantioselectivity and disparate activity in the glutathione conjugation of 7beta,8alpha-dihydroxy-9alpha,10alpha-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene. Biochem Biophys Res Commun 1997; 235:424–428.

62 Fryer AA, Bianco A, Hepple M, *et al.* Polymorphism at the glutathione S-transferase, GSTP1 locus: a new marker for bronchial hyperresponsiveness and asthma. Am J Respir Crit Care Med 2002; 161:1437–1442.

63 Aynacioglu AS, Nacak M, Filiz A, *et al.* Protective role of glutathione S-transferase P1 (GSTP1) Val105Val genotype in patients with bronchial asthma. Br J Clin Pharmacol 2004; 57:213–217.

64 Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-
• transferase M1 and P1 geotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. Lancet 2004; 363:119–125.

These findings may have implications on future hypotheses to be tested related to stress and atopy. Glutathione S-transferase P1 promises to be an important candidate gene to explore interactions with stress and the impact on atopic risk. Such studies may further inform mechanisms linking stress to atopy.

65 Child F, Lenney W, Clayton S, *et al.* The association of maternal but not
• paternal genetic variation in GSTP1 with asthma phenotypes in children. Respir Med 2003; 97:1247–1256.

These data underscore the potential import of interactions of environmental exposures *in utero* with maternal genetics in the child's subsequent risk for atopy. Future studies of the effects of prenatal stress on childhood asthma risk should consider this paradigm.

66 Devereux G, Seaton A, Barker RN. In utero priming of allergen-specific helper T cells. Clin Exp Allergy 2001; 31:1686–1695.

67 Piccinni MP, Mecacci F, Sampognaro S, *et al.* Aeroallergen sensitization can occur during fetal life. Int Arch Allergy Immunol 1993; 102:301–303.

68 Van Duren-Schmidt K, Pichler J, Ebner C, *et al.* Prenatal contact with inhalant allergens. Pediatr Res 1997; 41:128–131.

69 Wust S, Van Rossum EF, Federenko IS, *et al.* Common polymorphisms
• in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. J Clin Endocrinol Metab 2004; 89:565–573.

Glucocorticoid receptor polymorphisms will be important candidate genes to consider in exploring the role of stress in disease risk.

70 Yamada Y, Nakamura H, Adachi T, *et al.* Elevated serum levels of thioredoxin in patients with acute exacerbation of asthma. Immunol Lett 2003; 86:199–205.

71 Uhart M, McCaul ME, Oswald LM, *et al.* GABRA6 gene polymorphism and an
• attenuated stress response. Mol Psychiatry 2004; 9:998–1006.

This study examines polymorphisms in the GABA receptors that are involved in the GABAergic inhibitory system which modulates the stress response. The T1521C polymorphism of the GABA6 gene was associated with attenuation in the HPA axis and blood pressure response to stress, suggesting a role for genetic-mediated regulation of the stress response. Again, these data implicate another candidate gene to be explored in the context of atopic disease risk.

72 Jeanmonod P, von Kanel R, Maly FE, Fischer JE. Elevated plasma C-reactive
• protein in chronically distressed subjects who carry the A allele of the TNF-alpha −308 G/A polymorphism. Psychosom Med 2004; 66:501–506.

This study examines another potential candidate gene that may be of interest in examining the influence of stress on risk for not only cardiovascular disease but also atopy – the TNF-α –308G/A polymorphism in the TNF-α promoter region. Cultured cells from individuals homozygous for the A allele produce more TNF-α than those with the G allele. Subjects with the A allele may also be more susceptible to stress.

73 Kalliomaki M, Isolauri E. Pandemic of atopic diseases: a lack of microbial exposure in early infancy? Curr Drug Targets Infect Disord 2002; 2:193–199.

74 Hawrelak JA, Myers SP. The causes of intestinal dysbiosis: a review. Altern
• Med Rev 2004; 9:180–197.

This review examines our understanding of factors, including physical and psychological stress, as an influence on dysbiosis which may implicate new hypotheses relating stress to atopy.

75 Bjorksten B. Effects of intestinal microflora and the environment on the development of asthma and allergy. Springer Semin Immunopathol 2004; 25:257–270.

76 Kalliomaki M, Salminen S, Arvilommi H, *et al.* Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001; 357:1076–1079.

77 Lodinova-Zadnikova R, Cukrowska B, Tlaskalova-Hogenova H. Oral administration of probiotic Escherichia coli after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years). Int Arch Allergy Immunol 2003; 131:209–211.

78 Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev Psychobiol 1999; 35:146–155.

79 Bailey MT, Lubach GR, Coe CL. Prenatal stress alters bacterial colonization of
• the gut in infant monkeys. J Pediatr Gastroenterol Nutr 2004; 38:414–421.

These data suggest the importance of the in-utero environment when considering the effects of maternal stress on risk of atopy in their offspring. It will be important to reproduce these types of studies in humans.

80 Hart A, Kamm MA. Review article: mechanisms of initiation and perpetuation of gut inflammation by stress. Aliment Pharmacol Ther 2002; 16:2017–2028.

81 Wright RJ. Alternative modalities for asthma that reduce stress and modify
• mood states: evidence for underlying psychobiological mechanisms. Ann Allergy Asthma Immunol 2003; 92:1–6.

This article reviews evidence supporting the influence of interventions that reduce stress on the expression of asthma and atopy exploring the pathways mediating these effects. Conceptual and methodological limitations in existing research are explored.