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The relationship of psychologic stress with childhood asthma

Gordon R. Bloomberg, MD[a,*], Edith Chen, PhD[b]

[a]*Division of Allergy and Pulmonary Medicine, Washington University Medical School, St. Louis Children's Hospital, One Children's Place, St. Louis, MO 63110, USA*
[b]*Department of Psychology, University of British Columbia, BC 2329 West Mall Vancouver, BC, Canada V6T 1Z4*

Asthma has a long tradition as a "psychosomatic disease" [1]. Previously seen as an episodic, periodic condition, asthma seemed to appear suddenly as exacerbations occurring with little warning and unidentified causes [2]. Asthma, classified as extrinsic or intrinsic depending on whether known factors such as allergens precipitated the acute episode, was considered by many to have strong psychologic causes [3,4]. Emotional causes were commonly sought as explanations for acute exacerbations. Leading physicians in the 1930s and 1940s saw childhood asthma in the context of a mother–child interaction with dependency conflict precipitating or aggravating symptoms as a result of the threat of separation [3]. Studies of the parental interaction during this period indicated a range of parental attitudes, from rejection to over-protection [3].

Later, allergens, upper respiratory infections, and exercise were recognized to be related to bronchial smooth muscle contraction. Biologic processes were identified. Continued investigation emphasized cellular and molecular explanations for the underlying pathophysiology that is responsible for the exacerbations and persistence of asthma activity [5–7], yet there is much interest in the interface and reciprocal interaction between biology of asthma, behavior, stress, and the immune system [1,8,9]. Asthma is considered a symptom complex resulting from the presence of chronic inflammation in the airways, whether it is the result of allergen sensitization, respiratory viral infection, exercise, or other

* Corresponding author. Division of Allergy and Pulmonary Medicine, Department of Pediatrics, St. Louis Children's Hospital, Suite 5 S 30, One Children's Place, St. Louis, MO 63110.
E-mail address: bloomberg@kids.wustl.edu (G.R. Bloomberg).

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nonidentified causes. The impact of psychologic factors on the prevalence of asthma does not distinguish between the fundamental mechanisms underlying the chronic inflammation immediately responsible for the expression of asthma. Yet, it is the mind-body paradigm linking psychologic stress to neuroendocrine and immune functioning that provides a framework to explore the relationship. The environment of the allergic child and the child with asthma is of substantial clinical importance. Genetic predisposition, allergens, exposure to respiratory viral infections, air contaminants, residence (ie, city or farm), and family size are important in determining the inception of asthma and its continuing activity. The environment also includes the experiences that result in stressful situations. Stressful experience may result in the inception of asthma, exacerbations, and inadequate control. In this article we explore the relationship between psychologic stress as an exacerbating factor of asthma and the mechanisms through which this relationship may exist.

The impact of asthma upon the child's psychologic adjustment

In 2001, the percentage of children with asthma was 8.7%, or 6.3 million children [10]. This number of children represents a significant degree of physical disability and financial cost, but, additionally, there are psychologic, social and educational consequences that affect the financial burden upon the family, restrict of the child's physical activities, impair of the child's development of social connections and adaptive resources, and cause general disruption in the family [11].

Many children with asthma have no psychologic difficulties as a result of their asthma, and, as a group, children with asthma do not exhibit higher psychologic disturbance than other children [12,13]. This may be related to the level of asthma severity because most asthma can be classified as mild to moderate. The subgroup of children with severe, poorly controlled disease is the group most disposed to increased psychopathology and family dysfunction [14] and poor compliance with prescribed management and in whom the risk of complications, including fatality, is high [12]. Although psychologic and disease risk factors are interactive and no single causal direction exists in the relationship between disease and psychopathology, it is instructive to sort out the effect of psychologic stress and its impact upon childhood asthma.

Stress and asthma

The concept of stress as a disease-causing stimulus was introduced in 1936 by Hans Selye [15]. Although his ideas have been modified, the consideration of stress as disease causing has been explored in many studies in laboratories involving animals and humans and under epidemiologic and clinical conditions. Stressful events occur in various forms. Public disaster, academic examinations,

public speaking, marital discord, family dysfunction, neighborhood conditions, and exposure to violence are stressful situations documented to be related to asthma symptoms. Stress may affect the organism through cognitive changes in health behavior and comorbid diseases or may have more direct physiologic effects through the pathways of neuroendocrine and neuroimmune systems.

Definitions of stress

In attempting to understand the effects of stress on health, researchers have used multiple approaches in defining stress. Many of these approaches are common to the studies of stress and asthma as reported in this article. Conceptualizations of stress fall into three primary approaches: (1) objective (or environmental) characteristics, (2) subjective characteristics, and (3) biologic responses [16]. Of the three, probably the most common approach is defining stress by the events that happen to an individual. Events that are judged by consensus to place demands on an individual are labeled as "stressors." This approach labels objective events that occur in individuals' lives as stress.

The second approach argues for the importance of factoring in the individual's subjective reactions to the stressor. This approach states that the amount of stress experienced depends in large part on how an individual interprets, or appraises, a situation and that the same objective event may cause different stress reactions in different individuals depending on their perceived ability to handle the stressor [17].

The third approach relies on the ability to detect a biologic response to stress. This approach acknowledges that the same stressor may cause different reactions in different individuals but relies on biologic indicators of stress rather than an individual's self-report of stress.

How stress is measured

Each of these approaches to conceptualizing stress has its own methods of measuring stress. Studies that define stress based on environmental characteristics often involve querying subjects about the events that have occurred in their lives. For example, life-event checklists ask participants to indicate which of a list of events have happened during a specific time frame (eg, the previous 6 months) [18]. These are typically events that have been judged by raters to be objectively stressful (eg, death of a parent or loss of a job). Researchers can sum the total number of events that have happened or can create weights, meaning that different events count differentially depending on the seriousness of the event. Duration of events and timing of events can be ascertained as factors that may contribute to the association of stress with health.

Another type of stressor-based approach involves the collection of daily diary information [19]. Rather than interviewing subjects once every few months or every year, individuals can be asked to collect data every day about events that happen. Subjects can be prompted multiple times a day to answer questions about

whether negative events have occurred over much shorter intervals (eg, several hours). One advantage to the daily-diary approach is that subjects have better recall of events occurring that day (as opposed to trying to remember what has happened over the past 6 months). The disadvantage is that this type of data collection is burdensome and can be done only for short periods of time; thus, one might miss big life events that occur outside of the data collection window.

Measuring the subjective component of stress entails querying subjects about their appraisals of stress. Questionnaire measures of general perceived stress, such as the Perceived Stress Scale [20], assess the degree to which subjects generally find life to be stressful (ie, overloading, uncontrollable, and unpredictable). In addition, more specific appraisal questions can be asked regarding life events by probing subjects about their appraisals of a specific life event (rather than life in general). Last, laboratory-based approaches involve separating appraisals from stressor events by presenting subjects with identical stressors in a laboratory setting and asking for their subjective appraisal of each stressor [21]. By keeping the stressor constant across all subjects, one can test for individual differences in how subjects perceive the stressor.

Biologic approaches to measuring stress include assessing physiologic systems that are responsive to changing demands in the environment [22,23]. Frequently, measured systems in the stress literature include the autonomic nervous system (ANS), the neuroendocrine system, and the immune system [8,16,24]. ANS measures include assessing the activity of the sympathetic and parasympathetic nervous systems. Neuroendocrine measures commonly include the products of two identified stress response systems, the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis. These products include cortisol, epinephrine, and norepinephrine [16]. Immune measures typically include enumerative assays (measuring the numbers of different types of cells) and functional assays (eg, measuring how effective cells are at killing a target) [8,16]. Biologic measures can be taken at rest as an indicator of basal state or in response to an acute stressor to measure an individual's reactivity to stress. The biologic measures chosen for a study depend on the health outcome of interest. For example, in asthma, research has focused on inflammatory markers and on ANS effects on the airways.

Pathways between stress and illness

The two most commonly discussed pathways through which stress exerts its effects are the direct effects of stress on biologic systems and the effects of stress on behaviors that affect illness. Researchers have proposed that the cumulative wear and tear of stress can result in allostatic load—a detrimental physiologic toll on the body that can predispose one to disease [25–27]. In addition to this general physiologic load, effects of stress on biologic systems that are relevant to specific diseases may have implications for disease. For instance, inflammatory processes that relate to stress and asthma are important to understand. The Th1/Th2 balance may be affected in both situations. Cytokine secretion patterns characteristic of

this altered paradigm orchestrate the cellular events that relate to airway inflammation and hyper-responsiveness [28], and it is generally accepted that the inflammatory response in asthma involves a Th2 mechanism [28–30]. Research into the effects of stress related to asthma and the pathways by which this effect may occur is often directed toward evaluating alterations in the immune response by measuring cytokine changes.

In terms of behavioral pathways, stress could affect illness in at least two ways. One involves the changes in health behaviors that occur during times of stress. For example, individuals experiencing stress are more likely to smoke, have poorer diets, and be physically inactive [31–33]. These changes in health behaviors could place high-stress individuals at risk for developing or exacerbating illnesses. Second, among individuals with chronic illnesses, stress could affect behaviors such as adherence to medication regimens. For example, higher perceived stress has been associated with nonadherence to antiretroviral medications among HIV-positive women [34]. In addition, psychologic stressors, such as family dysfunction and depression, are associated with greater nonadherence in patients with asthma or HIV [35,36].

Evidence for stress and illness relationships

The objective and subjective components of stress have been linked to infectious and inflammatory illnesses. Objective measures refer to the occurrence of specific stressor experiences, such as marital and job-related stressors as exemplified by the relation to clinical exacerbations of multiple sclerosis (MS) [37] and minor stressors in rheumatoid arthritis [38,39]. A stressor may have a delayed effect, with a period of 2 weeks between the occurrence of the stressor and an exacerbation [40]. Cumulative effects have an independent effect, as noted in studies of HIV infections [41–44]. The factors of objective stressors, timing, and cumulative effects are apparent in asthma as related in the studies reviewed in this article.

Subjective, or perceived, stress has been found to be related to infectious and inflammatory illnesses. For example, subjects who reported higher levels of perceived stress were more likely to become infected and to develop clinical colds (based on physician examination and antibody titers) after experimental exposure to a virus that causes the common cold [45]. Subjective assessments, such as perceived conflict and disruption in one's routine, have been found to predict the development of new MS-related brain lesions 8 weeks later [46].

Studies in children relating stress and asthma

Asthma has long been a prototype for psychosomatic disease [47]. Stress related to asthma has been studied in the laboratory, by daily diary of life events, and by survey. Changes in airway function, as measured by spirometry, methacholine challenge, and airway resistance, have been demonstrated in laboratory

studies where children with asthma were asked to watch a movie or perform a stressful task. Participants in these studies did not experience overt asthma symptoms [48–51]. Alternatively, a sense of breathlessness that was considered excessive was observed in the asthma group in a study of adolescents, asthmatics, and control subjects experiencing stress induction by a frustrating computer task. The subjects experienced high levels of negative emotion and stress, but no participant developed airways obstruction or reduction in lung function [52]. These investigators previously studied patients with asthma before and after watching an emotional film and performing standardized physical exercise. It was concluded that negative emotions affect subjective rather than objective symptoms of asthma. There was relatively high breathlessness irrespective of the objective symptoms of asthma. They suggested that children in a negative emotional state who are uncertain about the condition of their airways are inclined to interpret exercise-related general sensations, such as fatigue, heart pounding, and sighing, in line with expectations as symptoms of airways obstruction [53].

Daily diary studies of patients with asthma show that life stressors have been associated with lower same-day peak expiratory flow rate and greater self-report of asthma symptoms. Psychosocial variables, such as activities, location, social contacts, mood, and stressors, are strongly related to peak expiratory flow rate (PEFR) and asthma symptoms and are a major contributor to the observed diurnal cycle in PEFR and symptoms [54]. Sandberg [55] used continuous monitoring by diaries and daily peak flow measurements in a prospective study of children with moderate to severe asthma, all receiving inhaled corticosteroid medication. Asthma exacerbations, severely negative life events, and chronic stressors were key measures. The authors interpreted their results as demonstrating that severely negative life events increase the risk of children's asthma attacks over the coming few weeks. This risk is magnified and brought forward in time if the child's life situation is also characterized by multiple chronic stressors. In this group of children, the risk of new exacerbations was significantly greater during the autumn and winter months and lowest in the summer, suggesting a mechanism at least partly explained by reports of the detrimental effect of stress on the resistance to childhood respiratory viral infections [56,57]. In children without high chronic stress, most of the severely negative events were unpredictable and frequently involved loss. However, in the group of children with a high level of background stress, the situation was different. In this group, with backgrounds including poverty, poor housing, parental psychiatric and physical illness, parental alcohol dependence, family discord, and school problems, severe events immediately preceding an acute asthma exacerbation in most instances arose directly from an existing chronic adversity. This clinical study is consistent with laboratory studies showing that when persons who are undergoing chronic life stress are confronted with an acute psychologic challenge, exaggerated psychologic, sympathomedullary reactivity is present and associated with immune changes [58].

Sandberg et al [59] studied the effect of positive experiences in the relation between stress and asthma in children. In the cohort reported previously [55],

they assessed whether life events involving substantial positive effects on the child could protect against the increased risk associated with stressful life events. They demonstrated that a life event with a definite positive effect can counteract the increased risk of an asthma exacerbation precipitated by a severely negative life event provided that the chronic stress was of low to medium level, noting that the protective effect did not apply where there was chronic stress.

That stressful life events increase the risk of onset of asthma comes from a large study by postal survey of risk factors for asthma and atopic disease among 10,667 Finnish first-year university students 18 to 25 years of age. Stressful life events, such as severe disease or death of a family member and parental or personal conflicts, were retrospectively recorded during the preceding year and in grouped yearly intervals before the survey response. Concomitant parental and personal conflicts increased the risk of asthma when adjusted by parental asthma, education, and passive smoke exposure at an early age [60].

A link between stress-related immunosuppression and health is demonstrated by studies of first-year medical students during examination periods [45,61]. These studies indicated that an increased susceptibility to upper respiratory infections was mediated by immune suppression as reflected by significant decrements in interferon (IFN)-γ secretions upon mitogen stimulation of lymphocytes. Additional evidence of immune suppression was uncovered by the finding that antibody titers to Epstein-Barr virus (EBV) increased during the examination periods, suggesting that reactivation of latent EBV had occurred, consistent with decreased cellular immune control of latent virus. Concurrently, there was an increase in the incidence of self-reported symptoms of infectious illness [24].

Bronchospasm in asthma may occur through mechanisms involving immune/inflammatory and cholinergic/vagal pathways [62]. Emotions therefore might influence airway function through psychobiologic pathways that are psychoneuroimmunologic and psychophysiologic (the autonomic system) [62]. Emotions have long been considered an exacerbating factor in asthma, with negative emotions exacerbating asthma and resulting from having asthma [63]. One mechanism assumed to relate asthma symptoms triggered by emotion takes place through the ANS: alpha sympathetic activation and parasympathetic activation. It is thought that ''individual response stereotypy,'' a predisposition among patients with asthma to respond to many diverse stressors with bronchoconstriction, is responsible [63].

Altered immune function is considered a pathway by which stress is possibly mediated toward asthma. The changes that occur are consistent with a cytokine milieu that could worsen asthma [30]. This has been studied in several situations where students undergoing academic examinations are evaluated for changes in cytokine patterns, an examination stress model. Marshall [64] demonstrated cytokine alterations occurring in healthy nonasthmatic medical students undergoing examination stress. The effect of examination stress on regulatory cytokines was assessed by measuring Th-1 cytokines (IFN-γ) and Th-2 cytokines (interleukin [IL]-10) from mitogen-stimulated peripheral blood mononuclear cells 4 weeks before and 48 hours after the examination. A decreased IFN-γ and

increased IL-10, resulting in a decreased IFN-¬/lL-10 ratio, was demonstrated during examination stress, with significant correlation between cytokine pattern response and the number and degree of subjective adjustment to daily hassles. The authors suggest that the data showed that psychologically stressful situations shift type-1/type-2 cytokine balance toward a type-2 pattern and result in an immune dysregulation rather than overall immunosuppression. The authors state, ''This may partially explain the increased incidence of type-2 mediated conditions such as increased viral infections, latent viral expression, allergic/asthmatic reactions, and autoimmunity reported during periods of high stress.''

The influence of academic examination stress on cellular immune response has been confirmed in additional studies of asthmatic subjects and healthy control participants. Immunologic responses were found to be similar in both groups [65,66]. Lung function was not changed in the asthmatic subjects. The authors concluded that there is no aggravation of inflammatory disease in well-managed patients with asthma. Further studies by this group of investigators showed that high social support attenuated the magnitude of examination-induced immune changes during times of stress [67]. The importance of social support is noted again in our discussions of the effect of stress related to family, neighborhood, caregiving, and comorbid conditions such as depression.

In addition to studies of cytokine profiles and in contrast to previous studies, evidence of airway inflammation has been found in response to examination stress [68]. Antigen challenge was evaluated in college students with mild asthma during a low-stress phase and a stress phase determined by the timing of the final examination. Questionnaires assessed psychologic state for anxiety and depression. An inhaled antigen challenge was completed, and sputum samples were collected before challenge and at 6 hours, 24 hours, and 7 days postchallenge. Sputum eosinophils and eosinophil-derived neurotoxin levels significantly increased at 6 and 24 hours postchallenge and were enhanced during the stress phase. IL-5 generation from sputum cells was increased at 24 hours during stress and correlated with airway eosinophils. The investigators suggested that stress can act as a cofactor to increase eosinophilic airway inflammation to antigen challenge and in this way enhances asthma severity. However, in this study, as in the other academic examination studies that demonstrated cytokine changes, there was no significant deterioration in lung function or worsening of asthma symptoms.

With regard to the above studies and the notion that stress causes a change in immune balance that might favor asthma activity in susceptible patients, there is a rationale for stress management. In chronically stressed adult populations, stress management intervention has been found to be beneficial for producing changes in immune functioning [69]. Adults with mild to moderate severe asthma were asked to write about the most stressful event of their lives or about emotionally neutral topics. Patients who wrote about stressful life events had clinically relevant changes in health status at 4 months compared with the control group. The asthma patients in the experimental group showed improvement within 2 weeks [70]. Stress management has also been evaluated in a 4-week intervention in young adults with asthma. The treatment group showed significant improve-

ment in measures of lung function compared with a placebo group, but no differences were found in measures of perceived stress [71].

Asthma and socioeconomic status, the neighborhood, and the community

Health problems in general are increasingly recognized as the result of influences operating at several levels, among which the individual, family, and community are included [72]. The influence upon health that socioeconomic status imposes is well recognized. Individuals in lower socioeconomic status (SES) experience higher rates of morbidity and mortality in almost every disease category than those within higher levels [73]. Low social support and high numbers of negative life events are associated with higher rates of morbidity and mortality among adults with asthma [74]. Among younger age groups, there is evidence to support the traditional SES relationship with respect to prevalence of asthma and respiratory illnesses, but among children age 9 and older these health associations are not apparent [75]. Among the older children, SES seems to have a reverse association or no association with the prevalence rates of asthma and respiratory illnesses. This may be important to take note of when assessing the relationship of community and neighborhood stress to asthma events. However, in contrast with prevalence rates, severe asthma does seem to consistently display the traditional SES relationship across all childhood ages [75]. Based on this pattern, there seems to be preliminary support for the persistence model for SES and severe asthma. This is consistent with epidemiologic data reported by Akinbami [76], where prevalence is not increased among African American children as much as in other groups, but morbidity is greatly increased. An association between socioeconomic status and the prevalence of severe asthma has also been reported in German grade-school children. The prevalence of severe asthma was found to be significantly higher in low as compared with the high socioeconomic group. This association could not be explained by established risk factors [77]. This may vary by country because socioeconomic status had no impact on prevalence in a prospective study of a birth cohort in Dunedin, New Zealand [78].

Within American cities, asthma prevalence, morbidity, and mortality are disproportionately increased among children living in central urban areas and low socioeconomic conditions [79]. Among the risk factors present in this environment, psychologic factors need to be considered [72,80]. Neighborhood disadvantage comprises many characteristics that may act individually and collectively to produce chronic stress. Stressful events have been identified among African American and Hispanic children living in urban neighborhoods, with the younger children and those children living in the most disadvantaged neighborhoods experiencing the more stressful events [81–83]. Stress in the context of neighborhood and community life seems to influence the prevalence and exacerbations of asthma. One such instance is the presence of community violence [83–85]. The prevalence of exposure to violence is substantial, with several surveys confirming that children from preschool through elementary school and adolescence

have had knowledge or exposure to drug deals, shootings, stabbings, rape, woundings, killings, and dead bodies in their immediate community [86–91]. Many children report psychologic disturbance of depression and anxiety about their own safety, and these feelings are correlated with the degree of stress. Depression is a significant comorbidity for asthma severity possibly as a result of cognitive and behavioral interferences with asthma management.

The association between exposure to violence and asthma is reported in the reports given by the caregivers of children studied within the Inner-City Asthma Study [92]. Increased exposure to violence predicted a higher number of symptom days, and caretakers reported losing sleep on more nights even after controlling for socioeconomic status, housing deterioration, and negative life events. Psychologic stress and caretaker behaviors only partially explained the association between higher exposure to violence and increased asthma morbidity. Although the mechanisms mediating this association are not fully explained, exposure to violence was not considered to be merely a marker for factors of the usual concerns of income, employment status, caretaker education, housing problems, and other life events.

On an individual basis, exposure to violence may have an immediate and proximal effect on asthma exacerbations [93]. Among African American patients with hypertension, the factor of violence in the community may be real or perceived, but it has a profound impact as a barrier to appropriate health care [94]. This continues to be an important issue for children because, although there is an overall decline in violence rates in the United States, homicides, firearm-related mortality, and homicide-related arrests among children and adolescents are increasing [95]. In this regard, the effect of violence may be attenuated by neighbors willing to intervene on behalf of the common good, an example of social support, and by the fact that ''collective efficacy'' is negatively associated with variations in violence [84].

Stress, as a factor related to childhood asthma, may mediate its effect through the caregiver in the family, as reported in an earlier study of the inner-city environment in relation to childhood asthma (National Cooperative Inner-City Asthma Study) [96]. The caretakers of these children reported elevated levels of psychologic distress, and 50% had symptoms at a level of clinical severity. They also experienced a large number of undesirable life events. High levels of life stress were identified as significant concerns, placing children in inner-city communities at increased risk for problems related to adherence and asthma morbidity. This model assumes that individual or child psychologic variables influence asthma morbidity through asthma management behaviors [97]. However, low socioeconomic status and psychologic stress may be linked through immunologic alterations of the markers implicated in asthma, as noted by Chen et al [73] in a study of adolescents with persistent asthma living in high or low socioeconomic neighborhoods. The authors note that the path through individually encountered stressors, interpretations of stress, and immune markers should be considered among the many possible mechanisms linking socioeconomic disadvantage with disease.

Intervention based on the knowledge that psychosocial factors influence health behavior has recently shown to be effective. Attention to these aspects using a nurse-directed intervention program has been shown to reduce high health care use [98].

Family dysfunction as a stress factor for childhood asthma

A family in turmoil is stressful for all and especially for children, although in the case of an child with asthma, the problem may be bidirectional. Mothers of children with asthma report more perceived parenting stress, and the quality of the mother–child relationship is more problematic than for a comparison group of mothers with healthy children [99]. Noncompliance with prescribed medication is predicted by problems of psychologic adjustment and degree of family conflict [100,101]. This may not be the only pathway by which family stress causes illness. Biologic interaction may also be factor, and family dysfunction, such as marital conflict, has been shown to affect immune functioning [102].

Health care use in relation to asthma is an outcome that is affected by family dysfunction. Among the risk factors examined in relation to prior hospitalization in the Childhood Asthma Management Program, the results of the psychologic evaluations of patients with prior hospitalization demonstrate that family psychologic characteristics may affect the risk of hospitalization. The children without hospitalizations had higher Child Behavior Check List Total Competence scores, indicating greater social and academic capability than that reported by parents of the hospitalized children [103]. This capability may be a modulating factor in withstanding environmental and psychologic stressors. Families with less psychologic resources may have greater difficulty effectively managing the child's illness well enough to avoid hospitalization [103,104]. For instance, caretaker characteristics were found to be associated with a high degree of lifetime hospitalizations and predictive of readmissions over the following year [104]. This emphasizes the bidirectional effects of psychologic stress in asthma whereby poorly managed asthma becomes a stressor for a family with less resources to cope and intensifies asthma complications.

Caregiver stress and the inception of childhood asthma

There is evidence that psychosocial factors such as stress affect patients with existing asthma [55]. There is also evidence that disturbed family interaction and caregiver stress may affect the infant as a predictor of wheezing illness [92, 105–110]. If it is considered that there are critical times of vulnerability for atopic sensitization, the development of allergy may be a function of age and events that modulate asthma or allergy that occur early in life [111]. Wheezing frequently begins in early life [112,113], and the interaction between genetic and environmental factors seems to be an important key in unraveling pathogenic mecha-

nism [114,115]. Among the predictors of repeated wheeze in the first year of life, maternal smoking during pregnancy, lower respiratory illnesses in the first year of life, low birth weight, and cockroach allergen level in the family room are found to be predictors by multivariate analysis [116]. Early problems in the parenting of genetically predisposed children have also been linked to the onset of asthma [117]. The child's immediate environment is first contacted through parental influences. Parenting difficulties include problems with infant caregiving and components of maternal functioning, such as postpartum depression and inadequate marital support [106,118]. Given parental influence upon the predisposition for asthma, environmental factors from birth on determine the expression of symptoms thereon. From the many studies noting that psychologic stress modifies immune function and cytokine production, the relationship of stress in early childhood may be considered an additional factor predisposing to atopy and asthma. Family functioning as an environmental variable may, along with exposure to allergens and respiratory infections, be a contributing factor in the onset of asthma and its persistence into later childhood.

Considering that Th-2–polarized memory to allergens is established in infancy [119], much of the investigation into the effect of stress on the developing immune system is based on the Th-2 paradigm response [120–125]. This work often measures the immune alterations by evaluating cytokine expression as an indication of imbalance in the Th-2/Th-1 activity with augmented Th-2 cell response together with downregulated Th-1 response [28,29]. There is reduced production of the cytokine IFN-γ by T cells from asthmatic patients, and this correlates with disease severity [126]. Defective IFN-γ production may be important in asthma, and this is frequently examined in studies of infants in relation to the impact of psychologic stress and the evaluation of cytokine TNF-α [28,127,128].

If stress can alter the immune system to a Th-2 paradigm response, it is pertinent to ask if stressful experience early in life is related to the appearance of asthma in children of parents who have a history of asthma. Stress in this case would be mediated through the parent's psychologic state measured as parenting problems, maternal coping, and perceived stress. An important aspect of measuring parental stress as a stressful event affecting the infant is how the mother responds to the stressful episode. An infant whose parents experience stressful life events but who are able to manage their own responses and maintain a positive environment of the child would presumably have a different emotional experience than an infant whose parents are not able to provide this buffering [106]. The adult stress literature indicates that social support is a key factor in explaining why some individuals are more adversely affected than others by stressful events [129]; therefore, studies need to take into account paternal support and maternal perception of stress [106].

For infants, the quality of parenting is hypothesized to serve as a mediator between life events that affect the family and the emotional experience of very young infants. The mother is considered an emotional regulator for the infant. Studies include children who are genetically vulnerable to asthma, and evalua-

tions are made early in the infant's life before the onset of wheezing illnesses. Allergic and immune markers are measured as serologic levels of IgE and cytokine patterns. Questionnaires and interviews are used to evaluate caregiver stress, anxiety, depression, and marital tension or support. Mrazek [105] showed that early problems in coping and parenting were associated with the later onset of asthma. Klinnert [106] added that although neither parenting stress nor parenting risk was a significant predictor of asthma onset, the interaction effect between the two was a significant predictor of asthma onset. A further study of this population found that frequent illness, elevated IgE levels, and parenting difficulties entered into a predictive model were independently related to the development of asthma [107]. In another birth cohort, prospectively studied, caregiver stress was shown to influence immunologic function. Caregiver stress was measured repeatedly, and blood was drawn from the children at 21 to 46 months of age. A stimulation index was used as a response of lymphocyte proliferation to mitogen and antigen. Persistently higher household stress levels were observed for high responders, and it was concluded that higher family stress in early childhood may enhance allergen-induced lymphocyte proliferations [130]. The population reported by Klinnert et al [108] was followed to school age with confirmation that parenting difficulties rated in the first year of life were significantly and independently associated with asthma at school age, providing further support for the supposition that psychosocial factors contribute to asthma onset and persistence into childhood. Further studies have confirmed the effect of caregiver stress on early childhood wheeze as independent of caregiver smoking, breast feeding behaviors, allergen exposure, birth weight, and lower respiratory illness [109]. In this study it is significant that caregiver stress prospectively predicted wheeze in infants, whereas wheeze in the children did not predict subsequent caregiver stress.

Wright et al [92], in a prospective birth cohort predisposed to atopy, examined the relationships between caregiver stress on the markers of early immune response (ie, IgE expression, mitogen induced, and allergen-specific proliferative response) and subsequent cytokine expression (INF-γ, TNF-α, IL-10, IL-13). Immune alteration in the direction of atopy was demonstrated. Higher caregiver stress in the first 6 months of life was associated with significant stimulation by dust mite antigen (Df1) and nominally by cockroach antigen (Bla g 2). Higher stress levels between ages 6 and 18 months were associated with a high total IgE level. There was significant association of higher stress with increased production of TNF-α and a trend toward reduced INF-γ production. Although much of the work on the effect of caregiver stress upon immune alterations in infants is based on the Th-2 hypothesis, some researchers have challenged this model, pointing out the role of IFN-γ in asthma [131].

Not all studies are in agreement with the reports noted previously. Some prospective studies do not show these same relationships. Gustafson [132] concluded that dysfunctional family interaction was the result rather than the cause of wheezing in infancy. In a whole population cohort followed from birth through 10 years of age, genetic and environmental risk factors were collected

prospectively to determine the role of these factors in whether persistent childhood wheezing phenotypes had an early or late onset. Low social class, recurrent chest infections at 2 years of age, and parental smoking demonstrated independent significance for early-onset persistent wheeze, but inherited factors showed only independent significance in the development of late-onset persistent wheeze [133]. The authors concluded that inheritance was of prime significance in the cause of persistent childhood wheeze but that environmental factors early in life may combine with genetic predisposition to produce an early onset.

Overall, chronic stress may affect cytokine expression, allergic inflammation, and asthma expression. Dysregulation in the balance of neuroimmunologic mechanisms that occur with chronic stress may alter the immune balance, and the infant's stress response is linked to the level of caregiver stress [92].

Comorbid conditions as exacerbating stress in childhood asthma

Depression can be a significant comorbidity for illness and can lead to behaviors that increase the risk of further disease. For instance, among rural adolescents there is a strong longitudinal relationship between baseline depressive symptoms and several important risk behaviors/factors, such as tobacco, substance abuse, depression, and a history of physical/sexual abuse [134]. Depression is a common comorbid psychiatric diagnosis in children with severe asthma, and the predominant evidence suggests that children with more severe asthma are at higher risk for the development of two types of psychiatric disturbances: depression and anxiety [117,135]. Children with severe asthma and children with asthma plus additional chronic conditions have a significant risk for emotional and behavioral problems. This comes from a national survey of United States in which these two groups were compared with children who did not report chronic conditions and children who had the same chronic conditions but without asthma [136]. Among the subscales scores examined in relation to these groups, anxiety/depression was elevated only for asthma. In a population-based study in Puerto Rico of children with asthma, depression and separation anxiety was common, and children with severe asthma had significant degrees of potential internalizing disorders [137]. These findings are reflected in the child's ability to adjust to school activity. Severely ill children with asthma without comorbid psychiatric illness are able to cope with their increased school absenteeism, but the combination of depression and asthma is associated with problematic school performance [138].

The effect of depression as a comorbidity may be mediated through the caretaker, again bringing up the importance of considering the parental environment of the child. Considering the disparate burden of increased morbidity among inner-city children, mental health of the children and their caretakers was found to be a significant factor among the psychosocial factors in predicting asthma morbidity [139]. Maternal depression is a strong predictor of emergency department visits [140]. Poor mental health in the children or their caretakers had

the strongest relationship to asthma morbidity. Although a child with any chronic disease can lead to depression in the caregiver, a depressed caregiver can compound the difficulty of treating a child with a chronic disease [141]. Children whose caregivers have more depressive symptoms are more likely to have higher morbidity [142]. Maternal depression is reported to be associated with a constellation of beliefs and attitudes that significantly influence adherence to asthma management [143].

Although biologic mechanisms may be in play [8,144], the pathway of depression related to higher morbidity seems most likely to be in the area of noncompliance to medications [138,144]. Compared with nondepressed patients, the odds are three times greater that depressed patients will be noncompliant with medical treatment recommendations [145]. Depression involves hopelessness and cognitive problems related to remembering and following through on medications. Research suggests that family support and social network are important in promoting and maintaining the patient's compliance to prescribed medical treatments [145]. An opportunity for intervention is indicated by the finding that social support is associated with reductions in the need for acute care among a low-income Medicaid minority group [146].

Fatal asthma

The occurrence of depressive symptoms in severely asthmatic children is a risk factor for a fatal attack [117]. Psychologic factors implicated in pediatric asthma death are the most serious issues to be considered in patients with severe asthma. Emotional stress, particularly separation and loss, are of special psychologic significance [147], and a common theme of depression, emotional precipitation of attacks, unsupportive families, and a tendency to deny symptoms is present in all samples where psychologic factors have been investigated [148–153].

In a case-controlled study of physiologic and psychologic characteristics associated with deaths due to asthma in childhood, Strunk et al [148,150] identified eight variables that could discriminate cases from control subjects. A subsequent study of patients matched for severity of illness, age, and sex revealed that most of the clinical characteristics previously thought to place patients at greater risk for a fatal attack were equally frequent in the children who died and in control cases. This emphasized the important role of psychologic issues as risk factors for a fatal outcome in severe asthma [149]. A family disturbance, an abnormal reaction to separation or loss, and expressed hopelessness and despair are warning signs that a fatality may be imminent [151]. Many of the psychologic stress factors and comorbid conditions described in the preceding sections are noted in relation to this most dramatic and tragic outcome of childhood asthma. These include patient–staff conflict, patient–parent conflict, deficient self-care, noncompliance with prescribed care, depressive symptoms, emotional or behavioral reactions to separation or loss, and family dysfunction [150]. The vul-

nerable age groups centered in early or mid-adolescence. This resonates with a study of adolescents considered at risk for adjustment problems secondary to lower economic strata and educational or vocational failure. When examined on multiple measures of psychologic distress, those with asthma had higher scores for anxiety, depression, and global distress than those without asthma [154]. This study suggested that asthma is an additional and significant independent stressor or risk factor among adolescents who already are at high risk for multiple adjustment problems and emphasizes the bidirectional aspects of asthma and psychologic stress. Additional attention to psychologic issues is needed in the child with severe and difficult-to-manage asthma [155].

Summary

Psychologic stress can have a biologic effect upon the immune system, altering cytokine patterns in the direction of Th-2 response. Negative life events represent acute and chronic stresses that can affect asthma, causing symptoms and poor control. The family and neighborhood environment represent significant potential stressors. The mental health of the caregiver is an important mediator in the child's state of asthma and potential inception of asthma expression. Depression is particularly dangerous especially in the context of severe asthma. Social support should be examined as an attenuating factor in children with asthma because this may be a most important adjunct to appropriate medical management.

The National Heart, Lung, and Blood Institute's National Asthma Education Program calls for a number of psychologic components in the comprehensive treatment of asthma [156]. Psychologic stress may be present at every level of the child's interaction with the environment. Especially in the child whose asthma is more severe and in whom management is difficult, attention to the psychologic environment is important and relevant. There are many opportunities for intervention at every level.

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