

Adolescents with atopic disorders have an attenuated cortisol response to laboratory stress

Marianne Z. Wamboldt, MD,^{a,b} Mark Laudenslager, PhD,^b Frederick S. Wamboldt, MD,^{a,b} Kim Kelsay, MD,^{a,b} and John Hewitt, PhD^c *Denver and Boulder, Colo*

Background: Patients with allergic disorders have been noted to have variations in cortisol patterns under natural conditions as well as a differential cortisol response to stress.

Objective: The main goal of this study was to examine hypothalamic-pituitary-adrenal (HPA) axis differences in atopic adolescents.

Methods: Subjects were a community sample of 202 adolescents (52% male; mean age, 16.2 years). Atopic status was determined by skin testing and clinical history. Saliva samples for cortisol assay were obtained 4 times during a "typical day" and at 4 time points during laboratory procedures.

Results: One third of the sample (33%) had a clinical atopic disorder, primarily allergic rhinitis; 39% had positive skin test results without clinical symptoms; and 27% had no signs or symptoms of allergic disorders. There were no significant effects of atopic status on home cortisol patterns. Presence of clinical atopy was significantly ($P < .05$) associated with lower cortisol levels in response to laboratory stressors.

Conclusions: Adolescents with a history of atopic illnesses had an attenuated cortisol response to the stress of laboratory procedures compared with adolescents with positive skin test results alone or nonatopic adolescents. An attenuated cortisol response to a stressor may help us understand the link between stress and exacerbation of atopic illness. (*J Allergy Clin Immunol* 2003;111:509-14.)

Key words: Cortisol, reactivity, HPA axis, atopy, adolescents

Allergic disorders are common chronic illnesses of childhood and adulthood, with prevalence rates in the population ranging from 5% to 10% for asthma to as high as 20% for allergic rhinitis.¹ These atopic illnesses are thought to be due to genetic predisposition, chronic inflammation, and alterations in the immune system, pri-

Abbreviations used

ANOVA: Analysis of variance

DenDF: Degrees of freedom in the denominator

HPA axis: Hypothalamic-pituitary-adrenal axis

MANOVA: Multiple analysis of variance

NumDF: Degrees of freedom in the numerator

marily a Th-2 lymphocyte-predominant immune response,² and are noted to be sensitive to the effects of stress.³⁻⁷ Since the hypothalamic-pituitary-adrenal (HPA) axis is known to help regulate inflammation through regulation of cortisol, investigators have examined the role of the HPA axis and endogenous cortisol in the outcome of allergic disorders.

Several studies have looked at cortisol levels "at rest" in patients with allergic disorders versus nonatopic control patients. Kauffmann et al⁸ found that asthmatic subjects had a lower one-time serum cortisol level than nonasthmatic subjects in a study of 270 policemen. Landstra et al⁹ compared serum cortisol levels drawn in the laboratory at 6 time points throughout the day for children with stable allergic asthma and age-matched nonallergic control subjects. Asthmatic subjects had a lower mean cortisol level than control subjects ($P < .05$) and higher mean cortisol over a period of 24 hours correlated with higher FEV₁ in asthmatic subjects ($P < .05$). Fujitaka et al¹⁰ compared 118 non-steroid-taking asthmatic subjects with control subjects. The control subjects had the expected diurnal decline in serum cortisol levels, whereas asthmatic subjects in remission had cortisol levels in the morning that were not significantly different than those in the evening, and subjects with current asthma attacks had significantly higher cortisol levels in the evening than in the morning. In a classic treatise, Tromp¹¹ commented that contradictory findings regarding cortisol levels and asthma were due to infrequent, cross-sectional cortisol sampling. He studied patients with 24-hour urine 17-ketosteroid levels taken weekly over a period of months and demonstrated that over time, asthmatic patients (not taking corticosteroid drugs) had lower levels than nonasthmatic control subjects. Thus, there is some evidence that patients with asthma might have lower cortisol than nonasthmatic subjects and/or might have dysregulated diurnal cycles of cortisol secretion.

From the ^aNational Jewish Medical and Research Center, Denver, Colo; the

^bUniversity of Colorado Health Sciences Center, Department of Psychiatry, Denver, Colo; and the ^cInstitute for Behavioral Genetics, University of Colorado, Boulder.

Supported by the General Clinical Research Center at NJCIRM, grant M01-RR00051, and NIH grants K8MH01486, RO1HL45157, and MH37373.

Received for publication May 29, 2002; revised September 18, 2002; accepted for publication November 18, 2002.

Reprint requests: Marianne Wamboldt, MD, National Jewish Medical and Research Center, 1400 Jackson St, #A109, Denver, CO 80206.

© 2003 Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.140

Cortisol is also known to increase after a variety of stressors, as part of the body's homeostatic regulatory systems.¹² This cortisol response to stress has not yet been tabulated in large population samples such that there is no "normal value" for an appropriate increase after specific stressors. However, several investigators have examined the cortisol increase after a stressor in atopic subjects compared with nonatopic control subjects. Kallenbach et al¹³ demonstrated that asthmatic subjects had a significantly attenuated cortisol response at 5 and 20 minutes after exercise compared with nonatopic control subjects. Children with atopic dermatitis in remission have a significantly lower cortisol response at 10 and 20 minutes after a public speaking task than age- and sex-matched nonatopic control subjects.¹⁴

Having an adequate cortisol response to stress may attenuate the course of allergic illnesses. For example, an asthma attack is a stressor that can raise cortisol levels,¹⁵ and an attenuated cortisol response may lead to more inflammation and more severe asthma. In support of this, non-steroid-taking patients with an asthma attack that lasted longer than 24 hours did not have an increase in endogenous cortisol, whereas patients with an attack that lasted less than 24 hours did have an increase in endogenous cortisol levels over the levels they had during remission.¹⁰ A similar study in children found that although there was no difference in cortisol levels between children with asthma during remission and non-asthmatic control subjects, children with asthma whose attack lasted longer than 5 days had a smaller elevation in cortisol than children whose attack was shorter.¹⁶ In a laboratory paradigm, during which subjects underwent a bronchial allergen challenge, subjects whose lung functions returned to normal faster had a greater cortisol response to the allergen challenge.¹⁷ Similarly, Herrscher et al¹⁸ found that endogenous cortisol protected subjects from a late phase skin response to an intradermal allergen challenge.

The goals of the current report were to replicate evidence of HPA axis differences in atopic versus nonatopic adolescents in addition to determining other sources of individual differences. A community sample was recruited to eliminate the concerns of sample selection bias (ie, more patients who seek medical care have comorbid disorders than are found in the community). The study was designed to examine both diurnal variations in cortisol under naturalistic settings as well as cortisol changes in response to a laboratory experience in adolescents and compare the results with atopic status.

METHODS

Subjects

Subjects were 202 adolescents, ages 12 to 19 years of age (mean age, 16.2 years). Ninety percent of the sample was white and 52% of the sample was male. Seventy-eight percent of the children lived with both biological parents. The sample was primarily middle class. A letter was sent to a random sample of 250 families with twins (from the Colorado Twin Registry¹⁹) between the ages of 12 and 20 years, asking if they were willing to be contacted regarding this study. One hundred eighty-one families (72%) responded to the

letters. Of these 181 families, 158 (87%) could be contacted by phone, and 109 (69%) agreed to participate. Reasons for nonparticipation included geographic distance, scheduling difficulties, and reluctance to have blood drawn. Seven families were excluded because at least one twin had a chronic medical illness or developmental delays that interfered with completing the protocol. A total of 101 families participated (40% of initial sample.)

Procedures

The subjects and their parents were contacted by phone and told about a study of the genetics of allergies and emotions, which was approved by the National Jewish Medical and Research Center Institutional Review Board. If they agreed to participate, they were scheduled for a laboratory assessment and mailed both assent and consent forms and 8 salivettes with instructions for both twins to collect saliva at 8 AM, noon, 4 PM, and 8 PM on a "typical" day. These samples were to be stored in a refrigerator at approximately 5°C until they came to the laboratory (mean time from home collection to laboratory session was 2.2 days). Teens also completed a questionnaire about activity level, sleep, meals, illness, substance use, and menstrual cycle for the day of saliva collection.

Subjects and their parents came to the General Clinical Research Center of National Jewish, where informed consent/assent was reviewed and written signatures were obtained. Subjects were scheduled to report either at 8 AM (52% of sample) or 1 PM (48% of sample). Subjects and their parents completed questionnaires. Each twin underwent a physical examination, had their blood drawn, underwent pulmonary function testing, and had prick skin testing for allergies. Finally, each twin participated in a semistructured psychiatric interview.²⁰ Each subject was asked to rate how stressful each procedure was on a 7-point Likert scale.

At set points during these interventions, saliva samples were collected for cortisol assay. Time points for the saliva collection were as follows: after consent forms were filled out (baseline), 30 minutes after blood draw, 30 minutes after the start of skin testing, and 45 minutes after the start of the psychiatric interview. These time points were chosen to reflect the stress of the procedure preceding the saliva collection: that is, baseline values reflect anticipatory anxiety upon coming into the laboratory; the saliva collected 30 minutes after blood draw reflects the stress of venipuncture and physical examination; the saliva 30 minutes after explanation of skin test reflects the anticipatory anxiety of skin testing; and the saliva collected 45 minutes after the start of the interview corresponded to that portion of the interview during which the subject answered questions regarding parent-child conflict, thought to be the most stressful portion of the interview.

During the study, new research indicated that cortisol levels in the saliva might increase more immediately than 30 minutes after a serum level of cortisol increased. To test this, the remainder of subjects ($n = 78$) had a fifth saliva sample taken immediately after the blood draw to assess the correlation of immediate salivary cortisol with serum cortisol.

Saliva collection

Saliva was collected with a Salivette (Sarstedt, Inc). Subjects chewed on the cotton plug for 30 to 45 seconds. The moistened cotton plug was returned to the centrifuge tube. Tubes were later centrifuged at 350g for 15 minutes, and saliva was expressed in the bottom of the tube. The saliva was then transferred to an O-ring sealed microcentrifuge tube and stored at -20°C until assayed for cortisol.

Cortisol radioimmunoassay

Salivary cortisol was measured with a commercially available radioimmunoassay kit (Diagnostic Products Company). The kit

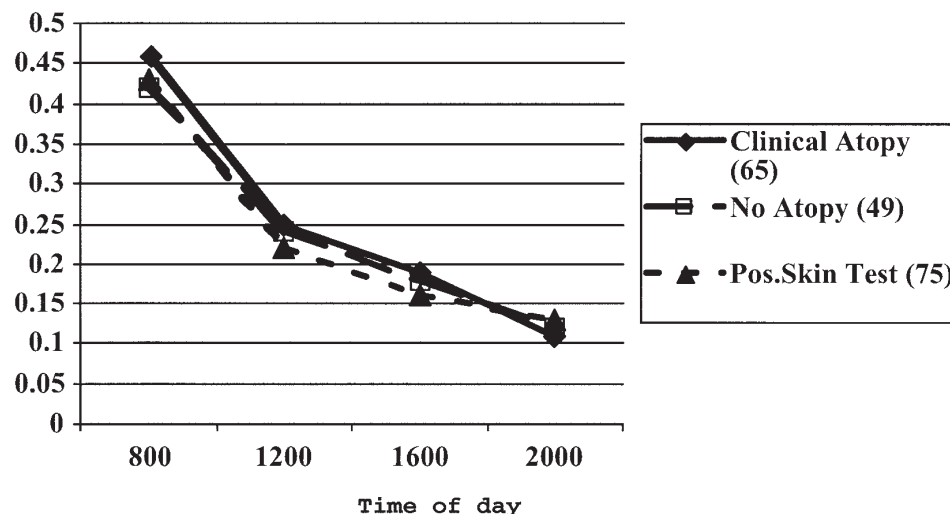


FIG 1. Salivary cortisol values (in µg/dL) at home by atopy status.

instructions were modified to permit the determination of lower levels of cortisol found in saliva. A 100-µL saliva sample rather than the 25-µL recommended by the manufacturer was transferred to triplicate assay tubes coated with antibody. The median of triplicate determinations is used for determination of cortisol level. The standard curve was modified by serial dilutions of the standards supplied with the kit to include standards of 0.01, 0.05, 0.1, 0.25, 0.5, 1.0, 2.0, 5.0, and 10 µg/dL. The standards were added in volumes of 100 µL. Finally, the incubation time of the assay was increased from 30 minutes to 3 hours. Commercial calibrator standards were inserted in 2 to 6 different locations in the assay, depending on the size of the assay for the determination of intra-assay and interassay coefficients of variation. Subjects were never split across assays. Intra-assay and interassay coefficients of variation for this assay are less than 5%.

Determination of atopic status

Subjects were considered to have an atopic disorder if they had at least one positive skin test result and had a consistent positive clinical history for atopic dermatitis, allergic rhinitis, and/or asthma.

Skin testing

This testing was performed in the GCRC by certified technicians with a standard clinical protocol used with 24 common allergens. A positive skin test result was defined as one in which the diameter of the wheal was at least 5 mm greater than the diameter produced by a saline control.

Clinical history of atopic disorders

Parents filled out questions on the medical history of each child, including history of atopic dermatitis, allergic rhinitis, otitis media, sinusitis, asthma, history of respiratory arrests and seizures, and allergies to specific food or medications. The questionnaire was developed for use in the Childhood Asthma Management Program,²¹ an NHLBI-funded, multisite study of mild and moderate asthma in children.

Data analysis

All data were first cleaned and assessed for normal distribution. Cortisol was transformed by log₁₀. Correlation coefficients were calculated for serum cortisol with the immediate saliva sample and with the 30-minute post-blood draw saliva sample. Groups were

defined as those with clinical atopy, positive skin tests only, or no signs or symptoms of allergy. Group differences were tested for Tanner stage and age by means of *t* tests, sex, and time of testing with χ^2 tests. Final overall model was tested by using a repeated measures (over time) multiple analysis of variance (MANOVA), with the log-transformed cortisol levels at 4 times in the laboratory as the dependent measures. This controls for differences at baseline as well as differences over time. Post hoc testing was performed with ANOVA. All analyses were performed on a Macintosh G4 using JMP 4.0.4 (Copyright 1989–2001 SAS Institute, Inc) statistical program.

RESULTS

The description of the sample is shown in Table I. One third of the sample (*n* = 66) had at least one atopic disorder: 61 with allergic rhinitis, 12 with atopic dermatitis, and 1 with asthma. Another 39% (*n* = 79) had positive skin test results without clinical symptoms, and 28% (*n* = 56) had no signs or symptoms of allergic disorders. There were no significant differences in age, sex, Tanner stage, time of day of testing, or reported levels of stress in the laboratory between the three groups.

Home cortisol

Only 65.3% of the adolescents were able to collect the home cortisol samples exactly as they were asked to do. Approximately one third (34.6%) of the subjects made one or more mistakes on the collection of their home samples, including collecting samples on different days (*n* = 43), collecting samples at incorrect times (*n* = 21), keeping poor records of the time the samples were collected (*n* = 7), or missing a collection time (*n* = 13). Samples were used if they were within 90 minutes of the targeted time. Samples were also used if they were taken on consecutive days but at the right time. Samples were not used if there was no legible recording of time or if they were taken on more than 2 days. All usable samples from each subject were analyzed. Thus, the usable number of samples varied by

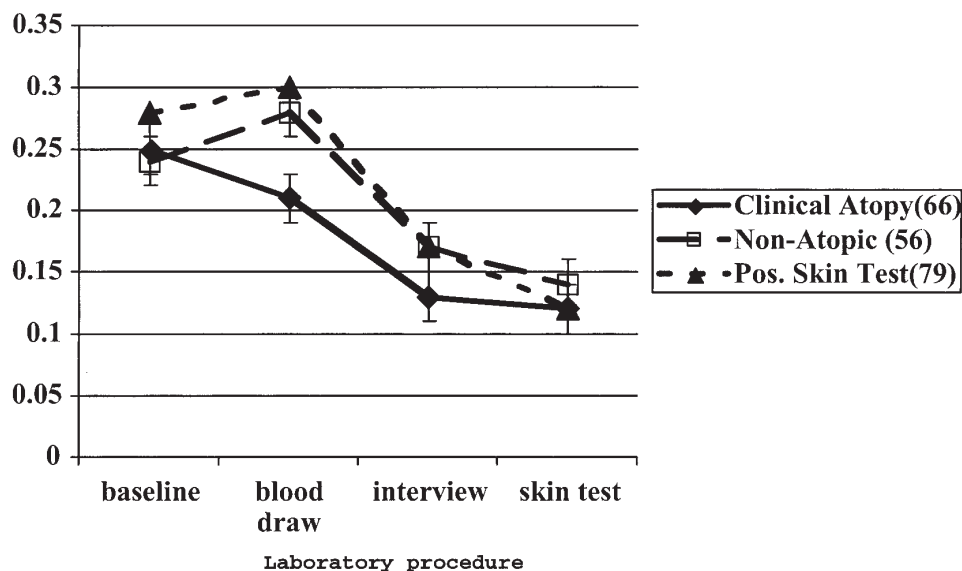


FIG 2. Salivary cortisol values (in µg/dL) in the laboratory by atopy status.

TABLE I. Baseline characteristics of the sample

	Clinical atopy (n = 66)	Positive skin tests; no symptoms (n = 79)	No signs or symptoms of atopy (n = 56)
Percent tested in AM	50.0	55.4	50.6
Percent male	51.5	54.4	48.2
	Mean ± SEM	Mean ± SEM	Mean ± SEM
Age	16.3 ± 0.2	16.1 ± 0.2	16.3 ± 0.3
Tanner stage	4.8 ± 0.1	4.6 ± 0.1	4.7 ± 0.1
Reported stress level via Likert scale 1–7			
Baseline	2.2 ± 0.2	2.3 ± 0.2	2.4 ± 0.2
Blood draw	3.2 ± 0.2	2.2 ± 0.2	3.8 ± 0.2
Interview	3.0 ± 0.2	3.3 ± 0.2	3.5 ± 0.2
Skin test	3.2 ± 0.2	2.9 ± 0.2	2.9 ± 0.2

collection time, from 188 to 191. The home saliva cortisol levels were not significantly associated with sex, age, Tanner stage, or any of the psychological variables. Fig 1 shows the mean cortisol values for each atopy group. As can be seen, there is a diurnal decline for all three groups, and the groups were not significantly different at any time point.

The serum cortisol correlated significantly with saliva cortisol samples taken both immediately after ($r = 0.81$, $P < .001$) and 30 minutes after blood draw ($r = 0.48$, $P < .001$), thus further validating salivary cortisol as a marker of total cortisol measured in blood. Subjects rated their perceived stress after each laboratory procedure on a Likert scale of 1 to 7. The subjective stress ratings did not correlate significantly with the cortisol levels after the corresponding procedure: r values ranged from -0.13 to 0.12 . Blood draw was rated as most stressful by 50%; interview by 22.3%; baseline by 16.8%; and skin test by 10.4%. These percentages did not differ by atopic group ($\chi^2 = 6.57$; $P = .389$).

MANOVA analysis examined age, sex, time of day of testing, and atopic group status as predictive variables for repeated laboratory cortisol levels. As can be seen in Table II, main effects were found to be significant for age (older have higher cortisol), sex (boys greater than girls), and time of day of testing (AM levels higher than PM). Atopic status tended toward significance at the level of $P = .07$. However, the only variable significant for an interaction over time, or a significantly different rise in cortisol over baseline levels, was atopic status ($P < .05$). Fig 2 visually clarifies this by showing the raw values of the saliva cortisol variables in the laboratory by each atopic group. Those subjects with at least one atopic illness had significantly lower cortisol samples after the blood draw than those without atopic illness (post hoc 1-way ANOVA, $F = 4.33$; $P < .01$). Thus, it can be concluded that age, time of day of testing, and sex were all significantly associated with overall levels of cortisol but not with cortisol change over the various cortisol stressors. However, adolescents with clinical atopic status had a

significantly lower rise of cortisol under the stress of laboratory procedures than those without atopic disorders.

DISCUSSION

There have been several reports that both adults and children with atopic disorders have dysregulated cortisol patterns, both during “typical” days⁸⁻¹¹ and after a specific stressor.^{13,14} We studied a large community sample of adolescents, approximately a third of whom had a clinical atopic disorder, primarily allergic rhinitis, assessed by clinical history and skin tests. Through the use of noninvasive saliva sampling, daily cortisol levels at home were determined. Using this technology, there were no differences in cortisol levels or diurnal patterns during a “typical day” between the adolescents with an atopic disorder and those without. However, those who had an atopic disorder had a significantly lower cortisol response to the stress of laboratory procedures, primarily a blood draw, even after controlling for the effects of sex, age, and time of testing.

The results of this study seem to refute the studies of the Kauffmann, Landstra, and Fujitaka groups,⁸⁻¹⁰ who all found differences in cortisol during a “typical” day between asthmatic subjects and normal control subjects. The current study clearly showed no differences during a “typical” day in a naturalistic setting. One possibility is that these teens had milder atopic illness, that is, primarily allergic rhinitis, while the other studies examined patients with varying severity of asthma. Another interpretation is that the prior studies obtained cortisol samples through venipuncture and were performed in a hospital setting. Given the findings from this study, it is very possible that the subjects found the laboratory procedures stressful, or at least different from their typical pattern at home. Thus, these investigators may have tapped into a differential response of atopic subjects to the general stress of being in a hospital and having blood drawn. However, the current study replicated the prior work of Kallenbach et al¹³ and Buske-Kirschbaum et al,¹⁴ who showed that atopic subjects had an attenuated response to a specific stressor, either exercise or public speaking. Thus, the balance of evidence suggests that patients with atopic disorders do not have a different pattern of cortisol secretion during typical days at home but do have less of a cortisol rise after a stressor than nonatopic subjects.

As reviewed by Schleimer,²² a growing body of evidence suggests that the regulation of endogenous cortisol is thought to be a key regulator of allergic disease expression and allergic inflammatory responses. He cites evidence that lung function varies along with plasma cortisol levels, that the number of circulating inflammatory cells varies with plasma cortisol levels, and that low levels of endogenous cortisol may be associated with risk for asthma. It is of note that in this current study, those subjects with positive skin tests but no clinical symptoms had a similar HPA response to stress, as did the subjects with negative skin tests and no symptoms. It is possible that having a hyporeactive HPA axis to stress and being under

TABLE II. MANOVA fit predicting log-transformed cortisol values over time in the laboratory

	Exact F	NumDF	DenDF	Prob > F
Between subjects variable				
All between	15.16	5	183	<.0001
Intercept	84.85	1	183	<.0001
Atopy	2.65	2	183	0.07
AM vs PM	31.99	1	183	<.0001
Sex	29.34	1	183	<.0001
Age	4.90	1	183	0.03
Within subjects variable				
All within	1.38	15	500.06	0.02
Time	1.37	3	181	0.25
Atopy × time	2.10	6	362	0.05
AM vs PM × time	1.04	3	181	0.38
Sex × time	1.31	3	181	0.27
Age × time	0.21	3	181	0.89

stress at a critical time period may be necessary to convert from a “positive skin test result” status to a clinical atopic disorder. Having an attenuated cortisol response to a stressor may make one more likely to develop inflammatory cascade in response to that stressor and thus have a worsening of symptoms after the stress. This hypothesis has been elegantly demonstrated in the work with LEW/N rats, which are susceptible to developing autoimmune and inflammatory illnesses in response to an immune challenge due to their defective regulation of glucocorticoids (see review in Reference 23).²³ If this hypothesis holds true in human beings as well, it may explain why emotional stress or life changes can precipitate or exacerbate allergic symptoms in one with underlying propensity for allergic disease. Whether the HPA response to stress is genetically determined or environmentally impacted, is a trait or state, is still unknown.

The current study suggests that an attenuated HPA axis response to stress occurs in adolescents with atopic illness. Although this study supports prior findings of differential cortisol responses to stress in atopic individuals, there are several limitations of this study. First, although this is the largest sample size reported in the literature, future analyses with a larger sample size will be needed to confirm the finding and determine the genetic and environmental contributions to this trait. Second, this was a cross-sectional design and as such could not determine whether an attenuated cortisol response preceded or followed from atopic illness. It would be necessary to design a prospective study to make this determination. Third, although the finding was statistically significant, the effect size was relatively small. The clinical significance of this finding is not yet clear; it primarily leads research into new areas of understanding the various components that lead to eventual presentation of atopic disorders, as well as to understanding the potential role of stress and atopic illness exacerbation. Finally, this was a community sample, and subjects were not selected for

atopic disorders. Results may be different in clinical populations. Nonetheless, the results are intriguing, and replication should be attempted.

The authors thank Doug Curran-Everett, PhD, for statistical consultation, and Joan Bihun, PhD, Kayte Fulton, MA, Emily Millikan, MA, and Theresa O'Lonegan, MA, for their help in recruiting and testing the subjects.

REFERENCES

1. Lundback B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998;28(Suppl 2):3-10.
2. Cookson WO. Asthma genetics. *Chest* 2002;121:7S-13S.
3. Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: an overview. *Psychother Psychosom* 2001;70:6-16.
4. King RM, Wilson GV. Use of a diary technique to investigate psychosomatic relations in atopic dermatitis. *J Psychosom Res* 1991;35:697-706.
5. Rietveld S, Everaerd W, Creer TL. Stress-induced asthma: a review of research and potential mechanisms. *Clin Exp Allergy* 2000;30:1058-66.
6. Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, et al. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356:982-7.
7. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax* 1998;53:1066-74.
8. Kauffmann F, Guiochon-Mantel A, Neukirch F. Is low endogenous cortisol a risk factor for asthma? *Am J Respir Crit Care Med* 1999;160:1428.
9. Landstra AM, Postma DS, Boezen HM, van Aalderen WM. Role of serum cortisol levels in children with asthma. *Am J Respir Crit Care Med* 2002;165:708-12.
10. Fujitaka M, Nomura S, Sakura N, Ueda K, Matuura R, Yumiba C. Morning and afternoon serum levels of cortisone and cortisol in asthmatic patients. *Clin Chim Acta* 2000;299:101-8.
11. Tromp SW. Influence of weather and climate on asthma and bronchitis. *Rev Allergy* 1968;22:1027-44.
12. McEwen BS. Stress, adaptation, and disease: allostasis and allostatic load. *Ann N Y Acad Sci* 1998;840:33-44.
13. Kallenbach JM, Panz V, Gerson MS, Joffe BI, Seftel HC. The hormonal response to exercise in asthma. *Eur Respir J* 1990;3:171-5.
14. Buske-Kirschbaum A, Jobst S, Hellhammer DH. Altered reactivity of the hypothalamus-pituitary-adrenal axis in patients with atopic dermatitis: pathologic factor or symptom? *Ann N Y Acad Sci* 1998;840:747-54.
15. Cydulka RK, Emerman CL. Adrenal function and physiologic stress during acute asthma exacerbation. *Ann Emerg Med* 1998;31:558-61.
16. Nomura S, Fujitaka M, Sakura N, Ueda K. Adrenocortical function in asthmatic children: low levels of adrenocortical hormones in children with persistent attacks. *Eur J Pediatr* 1997;156:323-8.
17. Peebles RS Jr, Togias A, Bickel CA, Diemer FB, Hubbard WC, Schleimer RP. Endogenous glucocorticoids and antigen-induced acute and late phase pulmonary responses. *Clin Exp Allergy* 2000;30:1257-65.
18. Herrscher RF, Kasper C, Sullivan TJ. Endogenous cortisol regulates immunoglobulin E-dependent late phase reactions. *J Clin Invest* 1992;90:596-603.
19. Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. *Am J Med Genet* 2000;96:684-95.
20. Wamboldt MZ, Wamboldt FS, Gavin L, McTaggart AS. A parent-child relationship scale derived from the child and adolescent psychiatric assessment (CAPA). *J Am Acad Child Adolesc Psychiatry* 2001;40:945-53.
21. Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999;103:376-87.
22. Schleimer RP. Interactions between the hypothalamic-pituitary-adrenal axis and allergic inflammation. *J Allergy Clin Immunol* 2000;106:S270-4.
23. Tonelli L, Webster JI, Rapp KL, Sternberg E. Neuroendocrine responses regulating susceptibility and resistance to autoimmune/inflammatory disease in inbred rat strains. *Immunol Rev* 2001;184:203-11.