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Sensitization and Exposure to Indoor Allergens as Risk Factors for Asthma among Patients Presenting to Hospital

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To investigate the role of indoor allergens in adult patients with acute asthma, we conducted a case-controlled study on patients presenting to an emergency room. One hundred and fourteen patients and 114 control subjects were enrolled over a 1-yr period in Wilmington, Delaware. Sera were assayed for total IgE, and for IgE antibodies to dust mites, cat dander, cockroach, grass pollen, and ragweed pollen. Dust was obtained from 186 homes and assayed for dust mite, cat, and cockroach allergens. IgE antibodies to mite, cat, and cockroach were each significantly associated with asthma, and this association was very strong among participants without medical insurance and among African Americans. Among 99 uninsured participants, sensitization to one of the indoor allergens (>200 RAST units) was present in 28 of 57 asthmatics and in one of 42 control subjects (odds ratio, 39; confidence interval, 9.4 to 166). For cat and cockroach the combination of sensitization and presence of allergen in the house was significantly associated with asthma. Furthermore, there was a strong inverse relationship between IgE antibodies to cat and to cockroach, and the risk of this sensitization was in large part restricted to homes or areas with high levels of allergen. Thirty-eight percent of the asthmatics, but only 8% of the control subjects, were allergic to one of the three indoor allergens, and had high levels of the relevant allergen in their houses (odds ratio, 7.4; confidence interval, 3.3 to 16.5). The results suggest that the risk for asthma related to sensitization to indoor allergens applies to a large proportion of adults with acute asthma and that this risk is prominent among the socioeconomic groups that have suffered the largest increase in both morbidity and mortality from asthma.

An increase in the severity of asthma during the past 20 years has been observed in several countries, but it has been particularly marked in urban areas and among African American populations in the United States (1-3). Over the same period it has been shown that asthma is an inflammatory disease of the bronchi characterized by eosinophil infiltration (4-6). In keeping with this model of asthma, experimental exposure of the lungs of sensitive patients to allergens can release inflammatory mediators, recruit eosinophils, and increase bronchial reactivity (7-9). This has led to the argument that year-round exposure to allergens may be important as a cause of bronchial hyperreactivity. Thus, it appears that the relationship between allergen exposure and asthma can be divided into two phases: exposure of genetically predisposed persons most commonly in childhood that leads to sensitization, and ongoing exposure of sensitized persons that contributes to chronic bronchial hyperreactivity (10-12). Given that most people spend 20 to 22 h per day indoors and at least half this time in their own homes, it is not surprising that increasing attention has focused on the role of foreign proteins that accumu-

late in houses (13-17). During the last 10 years population and clinical studies from many different parts of the world have established that exposure to allergens derived from the dust mite *Dermatophagoides pteronyssinus* is associated with sensitization and asthma (18-21).

Most previous epidemiologic studies have not included a sufficient number of asthmatics with acute disease to answer whether sensitization to indoor allergens was relevant to these patients. For this reason it is often implied that allergen exposure is relevant only to mild or seasonal asthma. Our previous study in Charlottesville, Virginia showed that sensitization to indoor allergens was associated with asthma (16). However, that study did not include any results on allergen exposure. Indeed, there has been no quantitative data relating exposure to indoor allergens other than dust mite to asthma. Furthermore, there has been very little data on the levels of allergen in houses of lower income patients. Recently, monoclonal antibodies to cat and cockroach allergens have been developed so that it is now possible to measure allergens derived from three separate sources in house dust (22-25). The present case control study investigated serum IgE antibodies and the levels of allergen in the houses of random adult asthmatics presenting to hospital emergency rooms in Wilmington, Delaware. The catchment area for these patients included both inner city and suburban zones.

METHODS

One hundred and fourteen patients 15 to 55 yr of age who presented to either of two emergency rooms in Wilmington with asthma were enrolled

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between September 1988 and June 1989. An equal number of age- and sex-matched control subjects were enrolled who presented to the same two emergency rooms (ER) within 1 wk of the patients with any condition other than breathlessness. Demographic data on the patients and control subjects (including details of medical insurance and smoking history) were taken from the hospital charts and from a questionnaire completed in the ER and confirmed at house visits. Asthmatics were patients presenting to the ER with breathlessness for whom the physician on call prescribed urgent treatment for airway obstruction. Airway obstruction was confirmed in all cases by measurement of peak expiratory flow rate, and in 110 cases reversal of obstruction was confirmed by $\geq 20\%$ increase after therapy. Peak expiratory flow rates were measured before and after treatment; for the 114 asthmatics values were 193 ± 99 and 320 ± 126 L/min (arithmetic mean $\pm$ SD), respectively.

Serum was obtained from each subject and was assayed for total IgE and for specific IgE antibodies. Total serum IgE levels were measured by two-site monoclonal-antibody-based assay; the geometric mean value for the patients with asthma was 160 IU/ml, and for the control subjects it was 44 IU/ml (paired t test; $p < 0.001$). Among the asthmatics, only 21 had total serum IgE < 40 IU/ml, whereas 59 control subjects had levels below this. In keeping with previous studies, the increased levels of IgE were present in all age groups (16, 26). IgE antibodies were measured by a quantitative RAST technique using allergen extracts coated to cyanogen bromide activated cellulose discs as described previously (16). The allergens used were dust mites (*D. pteronyssinus* and *D. farinae*), cat (*Felis domesticus*) epithelium, cockroach extract (German, American and Oriental mixed), short ragweed pollen, and rye grass pollen. Extracts were obtained from Hollister-Stier (Spokane, WA). For each allergen the extract applied to the discs was standardized by measurement of major allergen content of the extract (16). Values for IgE antibodies were obtained from a standard curve using serial dilutions of a serum containing 1,000 units of IgE antibodies to *D. farinae*. Horse serum (50%) was used as a diluent to reduce nonspecific background. Preliminary studies confirmed that horse serum did not inhibit binding to any of the allergens studied. The units are standardized relative to an antimitic serum pool (NIBSC 82/528), which contains 1,800 RAST units of IgE antibodies to *D. farinae*; 1 RAST unit equals approximately 0.1 ng of IgE antibody (16, 27). In addition, the sera were assayed for IgE antibodies to the fungi *Alternaria* and *Aspergillus*, using commercial (Hollister-Stier) extracts; the results for these fungi were scored on a semiquantitative basis, and 2+ results were regarded as positive.

The houses of 93 patients and 93 control subjects were visited within 2 wk of enrollment in the study. By examining the housing conditions, it was possible to differentiate urban, i.e., predominantly overcrowded or rundown housing, from suburban housing. The urban boundary of Wilmington (an area of approximately 35 square miles) was defined by a long-time resident of New Castle County with extensive knowledge of local demographics. The area included the whole of postal areas 19701, 19720, 19801, 19802, 19805, and 19806, and it also included sections of 19804 and 19808 extending approximately half a mile on either side of route 2. Four dust samples were collected from each home using a handheld Douglas[®] vacuum cleaner modified with a cotton filter. The samples were obtained from bedding, bedroom carpets, sofas, and kitchens. The kitchen samples were obtained by vacuuming the accessible cabinet space above, below and adjacent to the kitchen sink and the surface of the floor adjacent to the kitchen cabinets. The remaining samples were collected by vacuuming a 1 square meter area for 2 min. Families were questioned about, and houses were examined for, the presence of cockroaches. Dust samples were assayed for Group I dust mite allergens (*Der f I* and *Der p I*), cat allergen (*Fel d I*), and for a German cockroach allergen, *Blattella germanica* allergen II (*Bla g II*), using two-site, monoclonal-antibody-based ELISA (23–25). The details of the assays have been reported elsewhere; the detection limits for the assays were 0.2 μ g/g for *Der p I* and *Der f I*, 0.2 μ g/g for *Fel d I*, and 0.5 units/g for *Bla g II*. In analyzing the results the highest level for each allergen (out of four samples) in a house was taken as an index of exposure to that allergen (10). Cutoff values for considering levels as significant were chosen based on previous results and the present study; for cat allergen ≥ 8 μ g *Fel d I*/g dust; for cockroach allergen ≥ 2 units *Bla g II*/g dust; for dust mite allergen ≥ 10 μ g Group I mite allergen/g of dust (10).

Odds ratio was calculated as the odds of disease occurring in persons with IgE antibodies, relative to the odds of disease occurring in those without IgE antibodies. Analysis of the data for sensitization and allergen exposure was for unmatched data since not all the houses were visited. Values for etiologic fraction (defined as the proportion of all cases in the target population attributable to a given risk factor) were obtained using the equation proposed by Schlesselman (28).

RESULTS

Sensitization and Relationship to Other Demographic Factors

Measurement of serum IgE antibodies by RAST demonstrated that for each of the five common inhalant allergens the prevalence of sensitization was greater among asthmatics than among control subjects (figure 1). As expected for atopic persons, some patients (and control subjects) had IgE antibodies to multiple allergens. Sensitivity (defined as IgE antibody > 40 RAST units) to at least one of the five inhalants was present in 83 of 114 asthmatics and 42 of 114 control subjects. For the three indoor allergens results for IgE antibodies were analyzed at levels of 40 and 200 RAST units, and the results for uninsured participants and for African Americans were analyzed separately (table 1). The results show that in these groups there was a very strong association between sensitivity to indoor allergens and asthma. In particular, for the uninsured, there were 28 asthmatics with > 200 units of IgE antibody and only one control subject with a comparable level (odds ratio, 39; confidence interval, 9.4 to 166). In addition to race and insurance status, information was available about the geographic location of housing. Geographic location, race, and insurance status were each strongly related to each other, and this applied equally to asthmatics and control subjects (table 2). For example, in the urban area among the uninsured, 48 were nonwhite and 13 were white. By contrast, in the suburban area among the insured, 78 were white and 11 were nonwhite. Smoking histories showed no relationship to disease. Among 49 patients who presented with asthma and who had no detectable IgE antibodies to one of the three indoor allergens, 23 were active smokers and seven were passive smokers (overall, 61%). The figures for smoking were very similar among all asthmatics (66 of 114 or 58%) and also among the whole population (139 of 228 or 61%).

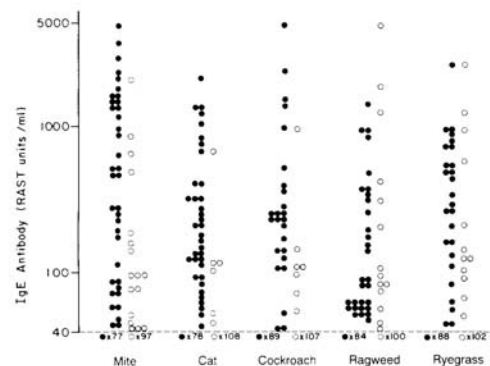


Figure 1. IgE antibodies to five common allergens in sera from 114 patients presenting with asthma (closed circles) and 114 age- and sex-matched control subjects (open circles). The numbers given below the level of 40 units/ml are the numbers of patients and control subjects with less than this level. The RAST units of IgE antibody are approximately equivalent to 0.1 ng IgE.

TABLE 1
SENSITIZATION TO ONE OF THE INDOOR ALLERGENS AMONG ASTHMATICS AND CONTROL SUBJECTS*

	RAST (units)	All Patients		Uninsured		African American	
		Asthmatics (n = 114)	Control Subjects (n = 114)	Asthmatics (n = 57)	Control Subjects (n = 42)	Asthmatics (n = 46)	Control Subjects (n = 42)
Sensitization to one of three indoor allergens	> 40	65	23	34	8	32	10
	> 200	44†	5	28	1	26	1

* Sensitization was judged by serum IgE antibodies and evaluated at levels of > 40 and > 200 RAST units/ml.

† Among patients with > 200 RAST units specific for at least one of the three indoor allergens, the results for asthmatics and control subjects were: mite, 24:4; cat, 18:1; cockroach, 16:1.

Concentrations of Dust Mite, Cat, and Cockroach Allergens in House Dust

Dust samples were obtained from 186 houses (four samples per house): 93 asthmatics and 93 control subjects. Of the 186 houses studied 98 had greater than the proposed threshold levels of cat or cockroach allergen. Fifty-seven houses were found to have significant cat allergen ($\geq 8 \mu\text{g}$ *Fel d* l/g dust) (table 3); 75% of these houses were in the suburban area, and only 25% were in urban locations. In contrast, of 68 houses with cockroach allergen (> 2 units *Bla g* II/g dust), 84% were urban, and only 16% were suburban. This difference was highly significant statistically (chi-square, $p < 0.001$). Only 46 of the houses contained greater than $10 \mu\text{g}$ Group I mite allergen/g, and there was no significant difference between urban and suburban houses ($p \approx 0.31$). In keeping with previous results, the highest levels of mite allergen were most commonly found in bedding (32%) or in living rooms (48%); in only 3% of houses was the highest level of mite allergen found in the kitchen. By contrast, the highest levels of cockroach allergen were generally found in the kitchen samples (i.e., in 53 of 68 houses or 78%) (figure 2). In analyzing the results, the levels of

allergen in dust were taken as an index of exposure; 66% of control subjects and 74% of asthmatics had significant exposure to one of the three indoor allergens. These results suggest that current exposure alone was not a major risk factor for asthma.

Exposure and Sensitization

Among the 15 participants with both exposure to cat allergen and sensitization (> 40 RAST units/ml), all but one presented with asthma (estimated odds ratio, 16.3; confidence interval, 3.4 to 78). Similarly, among the 19 with both sensitization (> 40 RAST units/ml) and exposure to cockroach, 16 presented with asthma (estimated odds ratio, 6.2; confidence interval, 1.9 to 19.5). Comparable figures for mite sensitization and exposure were 11 asthmatics and three control subjects. A striking feature of the results was the inverse relationship between cat and cockroach allergen levels (table 4) and the complete lack of relationship between IgE antibody to cat and cockroach allergens (table 5). By contrast, among patients

TABLE 2
DEMOGRAPHICS OF PATIENTS ENROLLED IN THE STUDY

Race*	Insurance†	Location	
		Urban	Suburban
White	No	13	29
	Yes	20	78
Nonwhite	No	48	9
	Yes	20	11

* The nonwhite patients included six Hispanics.

† Insurance status was derived from hospital records; 11 patients with Medicaid were included with uninsured patients, but one patient with Medicare was included as insured.

TABLE 3
LEVELS OF CAT ALLERGEN IN HOUSES WITH OR WITHOUT CATS PRESENT*

Cat Allergen <i>Fel d</i> I† ($\mu\text{g/g}$ dust)	Cat Present	No Cats in the House
> 80	37 (19:18)	0
> 8–< 80	12 (8:4)	8 (3:5)
> 1–< 8	0	54 (26:28)
≤ 1	0	75 (37:38)

* Values in parentheses indicate the number of patients and control subjects, respectively, in each category.

† Values for cat allergen were the highest level found in any sample from the house.

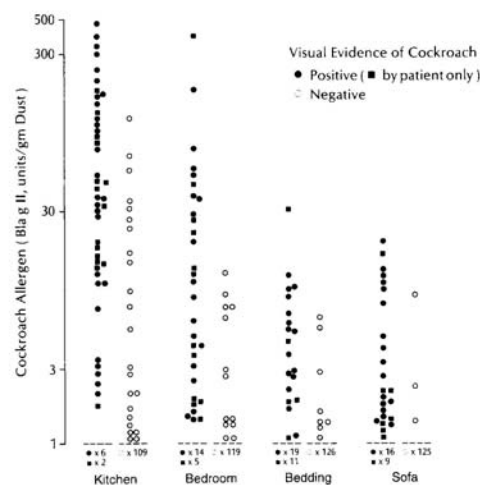


Figure 2. Levels of cockroach allergen *Bla g* II (units/g dust) in dust obtained from 186 houses. In general, houses with visual evidence of cockroach infestation (closed circles) or reported infestation (closed squares) had raised levels of allergen. However, cockroach allergen at high levels was found in some houses with no signs of infestation or report of infestation (open circles).

TABLE 4
COCKROACH (*Bla g* II) AND CAT (*Fel d* I) ALLERGEN LEVELS IN
DUST FROM THE HOUSES OF PATIENTS AND CONTROL SUBJECTS*

Highest Level of Cockroach Allergen <i>Bla g</i> II (units/g)	Highest Level of Cat Allergen <i>Fel d</i> I		
	< 8 (μ g/g)	$\geq$ 8 (μ g/g)	$\geq$ 80 (μ g/g)
$\geq$ 20	33 (18:15)	2 (1:1)	2 (2:0)
$\geq$ 2- < 20	23 (16:7)	5 (3:2)	3 (0:3)
< 2	115 (50:65)	13 (7:6)	32 (17:15)

* Values for each allergen are in each case the highest level found in any sample from the house. The probability of finding > 2 units of cockroach allergen was inversely related to the concentration of cat allergen, $p < 0.001$, using chi-square test for trend. Values in parentheses indicate the number of patients and control subjects in each group.

TABLE 5
SENSITIZATION (SERUM IgE ANTIBODY) TO COCKROACH AND CAT
ALLERGEN AMONG PATIENTS AND CONTROL SUBJECTS*

IgE Antibody to Cockroach Allergen (RAST units/ml)	IgE Antibody to Cat Allergen†		
	< 40 (RAST units/ml)	$\geq$ 40- < 200 (RAST units/ml)	$\geq$ 200 (RAST units/ml)
$\geq$ 200	14 (13:1)	2 (2:0)	1 (1:0)
$\geq$ 40- < 200	12 (6:6)	2 (2:0)	1 (1:0)
< 40	160 (59:101)	19 (14:5)	17 (16:1)

* Serum IgE antibodies measured by RAST. The units are approximately equal to 0.1 ng IgE antibody. Values in parentheses indicate the number of patients and control subjects, respectively, in each category.

† The probability of finding sensitization to cockroach allergens (> 40 units) was unrelated ($p = 0.8$) to the presence of sensitization to cat. By contrast, among patients with sensitization to mite allergen, there was a significant increase in sensitization to either cat ($p < 0.01$) or cockroach allergen ($p < 0.001$).

with sensitization (i.e., > 40 RAST units/ml) to mite allergens, there was a significant increase in sensitization to cat ($p < 0.01$) or to cockroach allergen ($p < 0.001$, chi-square). Comparing urban and suburban areas, it was clear that the combination of cat exposure and sensitization was associated with asthma in the urban area (table 6). As discussed previously, race, insurance status, and geographic location were each interrelated, and this applied also to asthmatics. The combination of sensitization and relevant ex-

posure to at least one of the indoor allergens was found in 35 of 93 asthmatics and seven of 93 control subjects. When this combination was analyzed for uninsured patients the figures were 22 of 48 asthmatics and two of 20 control subjects (odds ratio, 7.6; confidence interval, 1.8 to 31).

DISCUSSION

There are many factors that can contribute to bronchial hyper-reactivity or trigger acute attacks of asthma among patients with underlying BHR. The present study was designed to investigate the role that indoor allergens play in asthmatics presenting to hospitals, particularly among uninsured and/or urban populations. Wilmington was chosen because it is one of the larger towns in the United States where it is easy to visit houses in the urban area. Other risk factors were not addressed, e.g., air pollution, dietary factors, and the role of acute viral infections. Our study was not designed to study the effect of outdoor air pollution since the patients and control subjects were enrolled within a few days of each other. However, analyzing the admission figures for the Wilmington hospitals did not indicate peaks that could be related to changes in air pollution. Smoking histories showed no relationship to asthma in our study population. This is in keeping with the results of a recent population study in the United States (26).

The allergens studied here were chosen both from the results of skin testing in clinics in Delaware and Virginia and because it is possible to measure dust mite, cat, and cockroach allergen in house dust. There are many other allergens that also may play a role in individual cases. We found a significant number of patients with sensitivity to *Alternaria* (15 patients and five control subjects), and this may be an underestimate because enrollment was predominantly in the fall and spring, i.e., not the peak period for *Alternaria* spores (29). We consider, based on the results of skin testing, that other outdoor allergens are unlikely to account for more than 10% of cases in this area.

In analyzing the relationship between asthma, sensitization, and exposure, it was necessary to define thresholds both for IgE antibodies and allergen levels. The reason for a cutoff of 40 RAST units for IgE antibody was primarily to exclude effects of total IgE on RAST background (16). Using a higher cutoff, i.e., 200 RAST units, increased the specificity but reduced the sensitivity of the association between indoor allergens and asthma. The level of mite allergen in house dust that increases the risk of symptomatic asthma ($> 10 \mu$ g Group I allergen/g) was proposed by an international workshop, and it has been reaffirmed by several re-

TABLE 6
GEOGRAPHIC SEPARATION OF THE RISK FOR ASTHMA ASSOCIATED WITH
CAT AND COCKROACH EXPOSURE AND SENSITIVITY

	Cockroach			Cat		
	Exposure*	IgE ab†	IgE ab & Exposure‡	Exposure*	IgE ab†	IgE ab & Exposure‡
Urban area						
Asthmatics, n = 43	32	16	15	8	12	4
Control subjects, n = 38	21	4	3	6	0	0
Suburban area						
Asthmatics, n = 50	8	5	1	22	16	10
Control subjects, n = 55	7	1	0	21	5	1

* Exposure to cockroach was considered to be present in houses where at least one dust sample had ≥ 2 units *Bla g* II/g dust. Exposure to cat allergen was considered to be present where at least one sample had $\geq 8 \mu$ g *Fel d* I/g dust.

† IgE antibody (IgE ab) levels ≥ 40 units/ml were considered to represent significant sensitization.

‡ The association between sensitization and exposure to cockroach allergen and asthma was significant in the urban area ($p < 0.05$) but not in the suburban area. The association between sensitization and exposure to cat allergen was significant in the suburban area ($p < 0.05$) but not in the urban area. The difference between the results for the two allergens was highly significant ($p < 0.001$).

cent studies (10, 12, 20, 30). The levels of mite allergen found in the houses were lower than we had expected, probably because the summer of 1988 was very dry. The value used for cat allergen 8 µg/g is a level at which almost all patients allergic to cats experience symptoms and it is the minimal level found in a house with a cat. This value has been reported in several studies, and it could be taken as a proposed threshold. The level for cockroach allergen was based on sampling approximately 350 houses in Charlottesville, Virginia; Atlanta, Georgia; and the present study, as the level that best distinguishes significant cockroach infestation. The relevance of these proposed thresholds for cat and cockroach exposure is supported by the inverse relationships seen in tables 4 and 5. Thus, patients who are exposed to cat allergen generally have < 2 units *Bla g II* cockroach allergen in their house dust, and they do not become sensitized to cockroach allergens. Furthermore, none of 65 children in England who were followed for 10 yr developed IgE antibodies to cockroach allergens, and none of the dust samples contained > 2 units *Bla g I* (12, 25). Similarly, patients who live in the inner city have less than threshold levels of cat allergen, and they generally do not develop sensitivity to cat allergen. The clinical significance of threshold levels is increased because it is possible to change the levels of allergen in houses. Mite allergen levels can be controlled either by house design (e.g., no carpets, low humidity, good ventilation) or by a combination of physical measures and the use of acaricides (22, 31). For cat allergen it appears that the factors influencing airborne allergen, and methods of reducing exposure, are completely different from those for dust mites. Recent evidence suggests that it is possible to reduce cat allergen levels even with the cat present (32, 33). It is important to evaluate whether the available methods for killing cockroaches can reduce allergen levels below 2 units/g.

Although it is not possible to prove that the relationship between sensitization to indoor allergens and asthma is causal, the evidence increasingly suggests that exposure to indoor allergens is a major cause of asthma. First, the association between asthma and sensitization has been consistently reported from many parts of the world, and it is extended by our data from Wilmington and Charlottesville to patients presenting with acute asthma. Second, the association is very strong (see table 1). Third, it is well established that inhaling dust mite, cat, or cockroach allergens experimentally can provoke both bronchospasm and inflammatory changes in the lung. Finally, intervention studies have demonstrated improvement in asthma when patients have been moved to an environment with low allergen levels, or their houses have been changed (10, 22, 34). The present results do not establish a role of current exposure to indoor allergens since the levels of cat and cockroach allergens were probably stable and the mite allergen levels did not show their normal seasonal rise in the fall of 1988. However, the results do demonstrate for the first time that many of the patients presenting to the ER were both sensitized to and had exposure to a relevant allergen in their homes. Thus, although sensitization is strongly associated with asthma, and there is a quantitative relationship between exposure and sensitization, the present data do not establish, or refute, a quantitative relationship between current exposure and the risk of acute asthma among sensitized persons. Indeed, our results could equally be explained if chronic exposure to indoor allergens maintained bronchial hyperreactivity and acute attacks were precipitated either by a large dose of allergen or a variety of other "trigger factors," including viral infection, tobacco smoke, emotional factors, etc.

Using the Wilmington and previous Charlottesville data, and assuming that the control population in the ER reflects the population from which the asthmatics came, we used the equation for

etiologic fraction proposed by Schlesselman (28). For these calculations the results of two ER studies were combined so that values are based on 188 asthmatics and 202 control subjects (16). Sensitization to one of the five allergens gave an etiologic fraction of 46%, whereas sensitization to one of the indoor allergens gave a value of 40%. The population of New Castle County between the ages of 15 and 55 yr is estimated to be 256,000, which is ~ 0.18% of the population this age in the United States (35). During the year ending May 1989, 663 patients were treated for acute asthma in the Medical Center of Delaware, which we estimate was two-thirds of the cases treated in the County. These figures suggest that there may be as many as 550,000 ER visits/year in the United States among people 15 to 55 yr of age. From the calculated etiologic fraction, i.e., 40%, this suggests that among this age group as many as 200,000 episodes of acute asthma/year might be attributable to that risk which is associated with sensitization to mite, cat, or cockroach allergens. Our results suggest that among African American or uninsured adult patients the risk associated with indoor allergens is at least as strong as in the whole population. Furthermore, similar data for children with asthma in an inner city have recently been reported (36). Given the evidence that the prevalence and mortality of asthma in inner cities is both higher and increasing, it is clearly important to identify potentially treatable causes of asthma in this population. Our results suggest that housing conditions play an important role in asthma among lower income populations, and they also imply that recognition of this risk and education about methods of reducing it should be part of the management of the disease.

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