

The Environment and Asthma in U.S. Inner Cities

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The prevalence and severity of asthma has increased in the last 20 years, and the greatest increase has been seen among children and young adults living in U.S. inner cities. The reasons for this increase are obviously complex, but include environmental exposures to allergens and pollutants, changing patterns of medication, and the psychosocial stresses of living in poor inner-city neighborhoods. This paper presents an overview of environmental, immunologic, and genetic factors associated with asthma morbidity and mortality. This overview can be used to provide a framework for designing an interdisciplinary research program to address the complexities of asthma etiology and exacerbation. The strongest epidemiologic association has been found between asthma morbidity and the exposure of immunologically sensitive asthmatic patients to airborne allergens. Our current understanding of the process of sensitization suggests that there is a strong genetic predisposition to form IgE to allergenic proteins on airborne particles. Much of this work has been conducted with animal models, but in a number of instances, specific confirmation has been reported in humans. Sensitized individuals respond to inhaled exposure with immediate mast-cell dependent inflammation that may be augmented by pollutant particles, especially diesel exhaust particles. Relatively little is known about the methods of assessing exposure to airborne pollutants, especially biologically active particulates. However, to examine the relationship of morbidity in genetically predisposed individuals, it will be important to determine the most relevant method of making this assessment. *Key words:* air pollution, allergens, asthma, urban environment. — *Environ Health Perspect* 107(suppl 3):439–450 (1999). <http://ehpnet1.niehs.nih.gov/docs/1999/suppl-3/439-450eggleston/abstract.html>

Within the United States, asthma morbidity and mortality has increased disproportionately among poor, minority children living in the inner city (1–4). Poverty, ethnicity, and residence in the inner city are closely related in the United States, and considerable effort has been directed at dissecting these factors. There seem to be definite racial differences in prevalence that cannot be explained by socioeconomic status. According to National Health and Nutrition Survey (NHANES II) data (5), the rate of asthma among children 6 months to 11 years of age was 3.0% in whites, 7.2% in African Americans. Although the rate of asthma was related to age, gender, and residence in the inner city, even when adjusted for these factors, the ethnic differences were significant. Similarly, in the Six Cities Study (6), the unadjusted prevalence of asthma in white children 7–14 years of age was 4.8% and 6.7% in blacks—differences that were statistically significant after adjustment for confounding variables. Hispanic children also have a higher prevalence of asthma (3). Morbidity from asthma is also higher in minorities (3), generally, but poverty seems to explain these differences (7). Mortality from asthma is as much as three times higher in minorities (3), and the relation of

mortality to black and Hispanic ethnicity has been found by some (2) but not all (8) investigators to be explained by poverty. Together, these studies suggest that the three components of ethnicity, poverty, and residence cannot be dissected easily, and should be viewed together when trying to understand risk factors for asthma.

The reasons for these trends are obviously complex and must include many factors that have nothing to do with the environment. At the same time, current evidence suggests that environmental exposure is at least one of the most important causative factors. In addition, environmental exposures may be risk factors (like other public health measures) that are more amenable to change than are social or psychosocial problems. Perhaps, as in providing clean water supply and immunizations, we can introduce concrete measures that will have broad impact on health through an organized societal effort. This paper reviews the data relating exposure to environmental pollutants and airborne allergens and discusses the relationship of this exposure to asthma prevalence and morbidity.

Background

In approaching our understanding of the importance of environmental exposure, the

model shown in Figure 1 is a useful guide. In this model, environmental exposure to allergens and air pollutants such as particulate matter (PM), environmental tobacco smoke (ETS), and ozone (O₃) affect a susceptible host, resulting in airway inflammation and obstruction that leads to respiratory morbidity. Underlying and influencing each step of this process are societal susceptibility factors (e.g., psychosocial stress, high smoking rates, inappropriate medication use, inadequate resources, and poor access to quality health care) that are specific to the inner city and serve to increase asthma morbidity. Another critical factor that influences host susceptibility to environmental stimuli is the genetic background of the person exposed.

As seen in this diagram, both environmental allergen exposure and pollution can increase asthma morbidity. Environmental allergen exposure induces inflammation through two steps. A person with the appropriate genetic susceptibility develops specific IgE antibody to the allergenic protein following repeated or prolonged exposure. We currently believe that polymorphisms of a number of genes coding for critical regulatory proteins are responsible for the genetic susceptibility to sensitization to environmental allergens seen in patients with asthma. Once sensitized, the patient is susceptible to acute asthma episodes in response to very small exposures of airborne allergens (9). Pollutants, both O₃ (10,11) and PM (12), are associated with direct effects on the asthmatic airway and with indirect synergistic effects on allergic sensitization and inflammation. Underlying these processes are important social or psychosocial factors that increase

This article is part of the monograph on Children's Environmental Health and Disease Prevention Research.

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The authors thank M. Skolasky for her help with producing the manuscript.

Received 22 February 1999; accepted 7 April 1999.

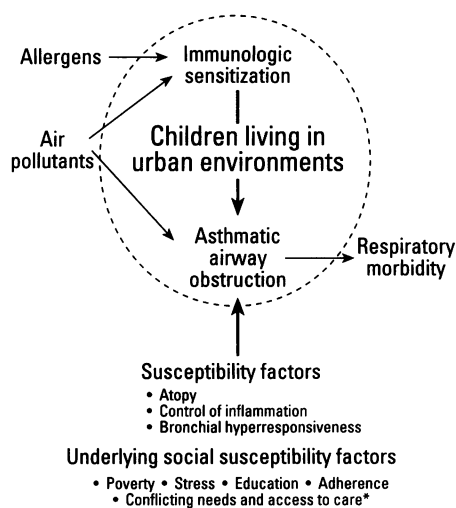


Figure 1. A model of the pathways in which environmental exposures and individual susceptibility interact to lead to symptomatic asthma.

susceptibility in poor inner-city residents. Other influences include impaired access to good medical care for acute or chronic treatment of asthma, inappropriate use of beta adrenergic agents, and emotional stress, depression, and anxiety.

A large number of cross-sectional, often population-based studies have described the association between prevalent asthma and presence or history of environmental exposures. Observations about the possible effect of dampness and mold problems was reported from such studies conducted in the United States (13,14), Canada (15), and Finland (16). Environmental tobacco smoke (17), gas cooking, and presence of pets have also been associated with asthma in cross-sectional studies. In a strictly cross-sectional study, the causal inference is based on a comparison of the prevalence of asthma in subjects currently exposed and unexposed. The major weakness of this approach is the uncertainty in temporality, which is an important criterion of causality; i.e., the cause has to precede the effect. Use of past exposure data from other sources such as monitoring stations, emission records, traffic statistics, or information on emission sources (such as building characteristics or surface materials) that most likely has not changed over time could partly resolve this critical issue of time sequence.

An example of a case-control study with prevalent cases of asthma is a study carried out in the Netherlands to assess the role of sensitization to dust mites and molds in chronic respiratory symptoms and asthma (18). With the use of a screening questionnaire, 78 cases with asthma and

257 controls without chronic respiratory symptoms were selected from a cross-section of 7,632 children from 38 schools. In this study, the presence of asthma was weakly associated with observed dampness and mold in the home in all children, but the association was stronger in a subgroup with elevated serum IgE to dust mites and/or mold. Prevalent case-control study allows a more efficient use of available resources, but shares some of the limitations of causal inference with cross-sectional studies.

In a longitudinal study, the outcome is defined as a new or incident case of asthma. Exposed and unexposed populations are followed over time, and incidence rates of asthma are compared. These studies can also address the effects of cumulative exposures or exposures during specific periods of time believed to be relevant, e.g., fetal exposure or exposure in early childhood. Two examples of large prospective cohort studies are the Tucson Cohort Study and the Oslo Birth Cohort Study. In the Tucson study, a total of 1,246 newborns were enrolled in the study between May 1980 and January 1984, representing 78% of eligible infants. These children were followed 3 years for lower respiratory tract illness, and at 6-year follow-up, questionnaire and skin prick testing were applied. The Oslo Birth Cohort Study was established by recruiting 3,754 children born in Oslo, Norway, during a period of 15 months in 1992-1993. Information on the child's health and environmental exposures were collected at birth and when the child was 6 months of age (follow-up rate = 95%), 12 months (92%), 18 months (92%), 24 months (81%), and 4 years. The effect of exposure to ETS on the risk of developing bronchial obstruction in the first 2 years of life was assessed (19). The risk of bronchial obstruction was increased in children exposed to ETS, with an adjusted odds ratio (OR) of 1.6 [95% confidence interval (CI) = 1.3-2.1]. The effect was seen for maternal smoking alone (OR = 1.6; 95% CI = 1.0-2.6), paternal smoking alone (OR = 1.5; 95% CI = 1.1-2.2), and both parents smoking (OR = 1.5; 95% CI = 1.0-2.2). A longitudinal study with prospective collection of exposure information provides valid information for causal inference, if the follow-up rates are sufficiently high or random to protect from selection bias.

In an incident case-control study, only newly identified cases of asthma are recruited as cases with appropriate controls at risk of asthma selected from the source population that produced the cases.

Infante-Rivard carried out a case-control study of asthma in Quebec (17). The 457 cases of children with a newly diagnosed asthma were recruited from a hospital emergency room. Controls ($n = 57$) were chosen from welfare files and were matched with case children on age and census tract. Mother's heavy smoking (OR = 2.77; 95% CI = 1.35-5.66), use of a humidifier in the child's room (OR = 1.89; 95% CI = 1.30-2.74), and the presence of an electric heating system in the home (OR = 2.27; 95% CI = 1.42-3.65) were found as environmental determinants of asthma. The presence of other smokers in the home was not quite significant (OR = 1.82; 95% CI = 0.98-3.38). Another case-control study of Norwegian infants (20) demonstrated that bronchial obstruction was related to the presence of polyvinyl chloride flooring (OR = 1.89; 95% CI = 1.14-3.14) and textile wall materials (adjusted OR = 1.58; CI = 0.98-2.54) compared with a reference category of wood/parquet floor and painted walls and ceilings in the home.

Environmental Pollutants and Asthma

It has been suggested that urban pollution might contribute to increased asthma morbidity in the inner city. However, most ambient pollutants have declined steadily in U.S. cities (8) at the same time that asthma morbidity and mortality have increased. This does not exclude the importance of indoor pollutants, but much less published data is available regarding indoor pollutants.

Among indoor pollutants, ETS is most closely linked with increased asthma prevalence and morbidity (6,9,21). In a general population survey, smoking exposure is similar among Caucasians, African Americans, and Hispanics in the United States. As reported from the Six Cities Study (6), cigarette consumption of over a pack a day was reported by 29.9% of white mothers and 16.8% of African American mothers. The same study reported smoking by 2.4% of 14-year-old white boys, 11.7% of white girls, 4.1% of black boys and 6.7% of black girls. These figures represent the total population and do not separate ethnic groups by income. Although no direct comparisons between middle-class and inner-city populations are available, a study in an urban emergency room (ER) may provide figures for inner-city populations. In this study, over 50% of the children had at least one smoker in their homes, and over 38% had elevated urinary

cotinine compatible with heavy exposure to ETS (9). Similar findings were found in eight urban medical centers in the National Cooperative Inner City Asthma Study (NCICAS). In this study, 59% of the families included at least one smoker, 39% of the primary caretakers smoked, and urinary cotinine was elevated (above 30 mg/gm creatinine) in 48% of the children. These figures suggest that exposure to ETS in the home is more common in inner-city homes, but it is not known how important this is as a cause of increased morbidity.

Another indoor pollutant considered in relation to asthma is nitrogen dioxide (NO_2). NO_2 is an industrial pollutant that is generated as a by-product of hydrocarbon combustion and is considered to be an important component of urban smog. It is generated in homes by gas stoves and space heaters, but indoor concentrations are rarely elevated to levels that are considered health risks. Indoor NO_2 was measured in the NCICAS and was as high as 480 parts per billion (ppb), with 24% of the families exposed to levels of 40 ppb or greater (22). These excessive levels were thought to relate to the gas stoves used by 89% of the families and to the fact that 24% of the kitchens did not have functioning windows. To put this in context, the U. S. Environmental Protection Agency (U.S. EPA) air standards consider annual average levels of 50 ppb to constitute a risk factor for acute and chronic lung disease. Computer modeling of data from the Six Cities Study demonstrated that levels over 30 ppb would result in annual exposures of > 50 ppb (23). Thus, inner-city homes frequently contain levels of an important pollutant in excess of U.S. EPA environmental standards, and could be expected to contribute to asthma morbidity.

O_3 and PM have also been associated with exacerbations of asthma. Symptoms and medication use have been associated with ambient levels of both pollutants in reports from Mexico City (24), Seattle (5), and Atlanta (25). In a panel study of asthmatic patients, Delfino and colleagues (26) showed a close correlation between daily symptoms and exposure to O_3 , particulates, and fungal spores. In addition, exposure to O_3 (27) and residual oil fly ash [ROFA (Diesel exhaust)] (10) increases airway response to allergens in experimental airway challenges. Although it is not clear that inner city residents are exposed to unusual concentrations of these pollutants, O_3 equilibrates rapidly between indoor and outdoor air, and this pollutant is clearly related

to urban rather than suburban areas. In addition, particulates are much higher in indoor air from homes with smokers and higher ETS (28). In the absence of data from inner-city homes, we can only speculate that O_3 and PM pollutants interact with indoor allergen exposures to increase asthma morbidity.

Exposure to indoor allergens has recently been suggested as a source of respiratory morbidity. Between 70 and 90% of children and young adults with asthma have one or more positive skin tests to aeroallergen (22,29); the frequency is similar in asthmatic patients in urban clinics (30–33). The pattern of specific allergen sensitivity differs from that in the general population, with a higher frequency of sensitivity to cockroach and molds and less frequent sensitivity to cats, dogs, and house dust mites. In the NCICAS, children were skin tested using a Multitest (Lincoln Diagnostics, Inc. Decatur, IL) device for reaction to 15 allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *alternaria*, *helminthosporium*, *penicillium*, cat, dog, rat, mouse, German cockroach, American cockroach, oak, maple, grass, and ragweed pollen). At least one positive skin test was seen in 77% of the children; 47% had three or more positive tests. The most common positive skin test was *alternaria* (38%), followed by cockroach (36%) and house dust mite (35%). Allergy to rat (19%) and mouse (15%) was almost as common as allergy to cat (24%) and dog (16%). Most of the children were sensitive to several allergens (22).

The distinct pattern of skin test reactivity is mirrored by the pattern of allergen exposure found in inner-city homes. In an early study from Baltimore, fungal contamination was found in almost every sample of settled dust (34). Recently, an elegant epidemiologic study found that exposure to outdoor mold spore was closely correlated with symptom scores in a group of sensitized asthmatic patients (10). In addition, cockroach allergen has been implicated in several urban studies. Call et al. (35) and Gelber et al. (36) examined settled dust from inner-city homes and found high concentrations of cockroach allergen. In the NCICAS, settled dust samples were collected from the bedrooms, living rooms, and kitchens of over 600 homes. Cockroach allergen was detectable in 89% of the bedroom samples, whereas mite and cat allergens were found in only 49 and 86%, respectively (22). Therefore, it appears that exposure to fungal and cockroach allergens is characteristic of

inner-city homes, leading to more frequent sensitization to these allergens than to house dust mite and animal dander.

A strong association was found in the NCICAS between chronic morbidity from asthma and the combination of sensitization and exposure (Figure 2). Using questionnaire data from baseline, 3, 6, and 9 months, it was found that the sensitized and exposed children had greater asthma morbidity in a number of areas (11). For example, the rate of hospitalization in this group is almost three times higher (0.37 hospitalizations per child per year) and unscheduled visits are almost twice as frequent (2.56 visits per child per year) in these children compared to those who were either not sensitized or not exposed. These differences are significant ($p < 0.01$) even when adjusted for gender, family history and smoking exposure. Similar associations were not found for either house dust mite or cat allergen.

Access to Medical Care

Early in the 1980s a survey reported that nearly 50% of school-age children who had active asthma received their care for asthma only through the ER, and that 58% of these children had had at least 1 ER visit for asthma in the past 6 months (37). Almost all families in the NCICAS reported having a place for routine care, although 53.4% found it difficult to obtain follow-up care for acute attacks. Most (73.1%) paid for their care through Medicaid. Routine care was much more likely to be delivered in a neighborhood health clinic or university pediatric clinic, and acute care was delivered predominantly in the ER (22,26). This pattern was the same reported in a nationwide cross-sectional survey, the National Health Interview Survey, which included comparative data for more affluent families (38). In that survey, poor families were more likely to attend a neighborhood health clinic (15.1 vs 1.6%) or a hospital-based clinic (11.1 vs 2.8%) and were four times more likely to go to an ER for their acute asthma care. Although care at these sites is not necessarily bad, this pattern is likely to lead to more fragmented care. In addition, it creates the need to travel to several sites and makes telephone advice more difficult, especially since 25–30% of inner-city families do not have a telephone in the home (39).

Patterns of Medication

Medication recommendations for the treatment of chronic asthma have changed a great deal in the last decade. Current

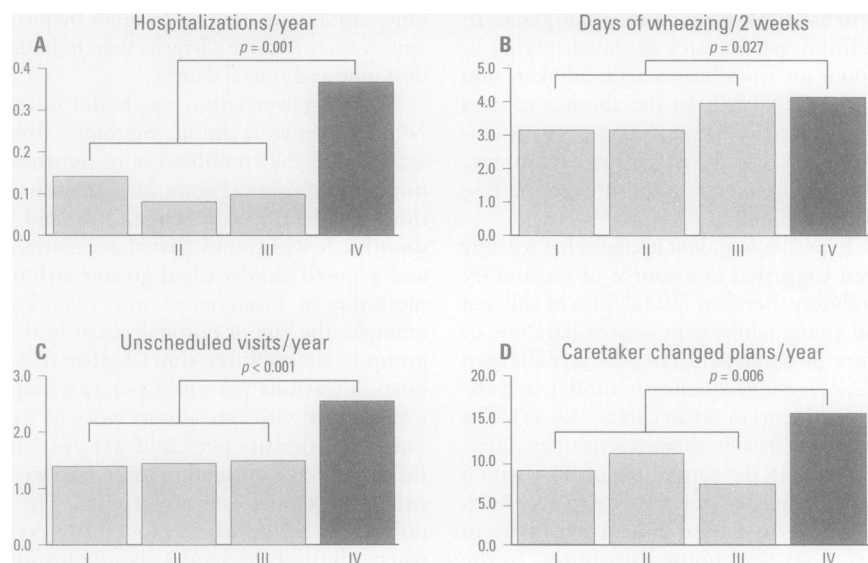


Figure 2. Asthma morbidity among children with IgE-mediated sensitivity to cockroach allergen and with exposure to cockroach allergen Bla g 1 in bedroom dust. Results represent the mean of each morbidity measure expressed as a rate. Group I = not allergic to cockroach and not exposed; group II = not allergic to cockroach but high exposure; group III = allergic to cockroach but not exposed; group IV = allergic to cockroach and high exposure. Statistical comparisons are between group IV and the mean of groups I–III combined. Outcome measures were analyzed using ANCOVA models including the covariates (gender, psychosocial scores, family history of asthma) selected as strongest predictors of outcome (11).

therapeutic guidelines (12,40) include daily anti-inflammatory medications such as cromolyn, nedocromil, and inhaled steroids for all patients with moderate to severe asthma and for any patient who requires daily treatment with a beta adrenergic agonist for asthma symptoms. Medications used by children in the inner city are similar to those used in the general population (22,27,41,42). In the NCICAS, 51% of families reported that their child relied only on beta adrenergic agonists for asthma and that 66% included beta agonists in treatment (22). Daily theophylline use was reported by 19% of the NCICAS schoolchildren, and 28% reported using inhaled steroids and cromolyn. These figures compare to national asthma prescription figures for children in 1993 of 71% beta adrenergic agonists, 7% theophylline, and 22% cromolyn, nedocromil, or inhaled steroids (43). This pattern of reliance on beta adrenergic agonists alone could lead to more unstable asthma (41). Both the NCICAS and a Baltimore/Washington survey (44) found that many children with asthma in the inner city took no medication for their asthma, despite frequent symptoms, ER visits, and absences from school.

Psychosocial Stress

Poverty creates a number of specific stresses that could impact on asthma. The NCICAS

data provided the most comprehensive examination of these factors and their relationship to asthma severity. The vast majority of caretakers (96%) were women, usually single (54%) and unemployed (49%). In keeping with previous data from young inner-city mothers, 18% of the children were reported to have low birth weight, 25% were in an intensive care unit at birth, and 10% were on a respirator (22). In describing their own psychological status, caretakers reported high levels of psychological symptoms. Using a standardized questionnaire, the Brief Symptom Inventory, the mean score was 56; 50% of the caretakers met the test criteria for referral. The children were given a similar screening questionnaire, the Child Behavior Checklist, and 35% met the criteria for referral. Maternal and child symptom scores were closely correlated and both related to asthma morbidity (45). From the CAGE (mnemonic for cut-down, annoyed, guilty, and eye-opener) questionnaire, 9.5% were identified as having a potential drinking problem, but this compares to 10.6% in the general population (46). The family's asthma knowledge was excellent, and they scored an average of 85% on asthma knowledge exams. However, the use of this information was inconsistent. When they were asked to respond to hypothetical vignettes, such as a child with acute asthma on a family

activity away from home, families were able to generate less than one solution and frequently provided an undesirable response.

The Impact of Changing Environmental Exposures

The finding of a strong association between cockroach allergen exposure and asthma in the inner city has important public health implications. If it can be shown that disease can be improved by changing environmental exposures, this would support programs to improve housing conditions in the inner city. In addition, if it is possible to provide practical measures for avoiding exposure to pollutants such as ETS, particles, O₃, or NO₂, or allergens, we may change the current epidemiology of asthma.

We currently have practical measures that are effective in clinical trials for house dust mite. We now need to develop interventions for cockroach allergens. Because the sources of cockroach allergens include the insect's gastrointestinal tract, saliva, feces, and body parts, it will be necessary to clean environments after reducing cockroach numbers through pesticides. A number of effective pesticides are now available (diazinon, chlorpyrifos, carbaryl, avermectin) that are capable of reducing populations in single- or multi-family housing by over 90% for as long as 3 months (47–49). Effective procedures to remove the allergen are not as well tested, although vacuum cleaning (25) and application of 3% tannic acid (50) have been effective in institutional settings.

We have not yet demonstrated that the current abatement measures are able to change asthma morbidity. Until this is done, we are not in a position to recommend changes in public policy to reduce this important risk factor. These measures were included in an intervention trial in the NCICAS, but because the intervention used was global, we were not able to isolate the effect of environmental abatement measures themselves. At this time, cockroach allergen abatement trials are under way that will address the question and determine the usefulness of this approach with the asthmatic child in the inner city.

Exposure Assessment and the Study of Childhood Asthma

The prevailing epidemiologic evidence of an association between asthma exacerbation and air pollution is based on central site ambient air measurements (46,51–56). Although these studies have to various

degrees identified an association, misclassification of nondifferential exposure, confounding, and model specification limit causal inference to the individual (57). It has been shown that the more accurate the exposure measure (progressing from central site ambient monitoring to microenvironmental measurements to personal exposure monitoring), the larger is the effect that can be detected (58). The need for epidemiologic studies that rely on more direct exposure surrogates has been highlighted by Phalen and McClellan (59).

The goal of the exposure assessment as a part of an epidemiologic study is to estimate and properly classify exposure with respect to environmental agents suspected of causing asthma. This can be achieved through direct and/or indirect assessment (60,61). A direct assessment entails monitoring the individual, using samplers that can be attached or worn by the individual. The advantage of the assessment is that it provides the single best measurement of individual exposure (62). The disadvantage of personal monitoring is that it can be costly and presents a burden to the subject that can adversely affect response rate. Indirect assessment relies on measurements in one or more microenvironments combined with time/activity data in a model that weighs the microenvironmental concentration by the time the individual spent in that microenvironment (61–63). This approach has been successfully employed in a number of air pollution studies (64–66). The major advantage to this approach is that the subject is not required to carry a personal monitor. This advantage comes at the cost of decreased accuracy of the exposure estimate. Because it includes indoor air where children spend most of their time, it is believed that the approach will capture most of the variability of individual exposures.

Efficiency in design can be achieved by combining indirect and direct assessment and nesting personal monitoring within the microenvironmental assessment. This combined approach is advocated and conceptually described by Duan and Mage (67) and applied to NO₂ by Leaderer et al. (65). This approach addresses the practical limitations (e.g., cost and burden) of measuring exposure in a large-scale epidemiologic study in a scientifically defensible fashion. The concentration of pollutants in microenvironments not measured (i.e., school and other) can be estimated from indoor/outdoor data from nonsource homes. If source activity (e.g., smoking, cooking, burning) is reported for a nonmeasured microenvironment, the

concentration can be estimated based on published source models (60,68).

The home is the single most important environment for assessing exposure, as people spend most of their time there, there are large and unique indoor sources (e.g., cooking, animals, mites, smoking, dust resuspension), and ventilation with outdoor air is limited. A recent report on human activity patterns show that school-age children spend most of their time indoors at home (68%). School is the next most important microenvironment, occupying 15% of their time on average (69). Central site ambient monitoring by itself provides a very poor surrogate for individual exposure for most air pollutants (23,64,69,70,71). This is particularly true for the pollutants of greatest concern for asthma, including bioaerosols, airborne particles, NO₂, O₃, and ETS.

Particle exposure is especially complex because of large spatial and temporal variability in air concentrations, numerous and varied sources, and an observed phenomena of an increasing concentration gradient in the immediate proximity of the individual ("personal cloud") (72). In addition, particles are highly variable in shape, size, density, and chemistry. Airborne particles are formed through mechanical and combustion processes for which there are myriad sources indoors and out (73,74). There is consistent and convincing evidence that smoking is the single largest indoor source of fine particles in homes with smokers (72). Smoking adds 25–45 µg/m³ to the indoor PM_{2.5}, with 1–2 µg/m³ coming from each cigarette when averaged over a 24-hr period. Source strength for smoking is estimated at 12.7 ± 0.8 (SE) mg/cigarette (75). Cooking is the second largest identifiable indoor source contributing 10–20 µg/m³. The particle TEAM (total exposure assessment methodology) study in Riverside, California, showed that, on average, across all homes (smoking and nonsmoking), 76% of the measured indoor air particulate (PM₁₀) was from outdoor sources (76).

A strategy of relying on indoor air as an exposure surrogate is justified based on the recognition that human contact with air contaminants is more a function of sources and activities in homes and neighborhoods and less a function of large sources, their releases to the ambient environment, and resulting ambient air contamination (72). This perspective is substantiated by exposure studies that show that individual exposure is poorly predicted by the concentration of particles outdoors, whereas a

much stronger correlation occurs with indoor air measurements. For a population-based sample ($n = 178$) in Riverside, California, Ozkaynak et al. (76) reported R^2 values of 0.40 and 0.65 for the regression of indoor or personal PM₁₀ for day and night, respectively. Dockery and Spengler (77) reported an R^2 value of 0.51 for the same regression for PM_{3.5} measured on 37 subjects in Watertown, Massachusetts, and Steubenville, Ohio. The R^2 value increased to 0.57 when indoor and outdoor concentrations were included in a model that weighted these concentrations by the time spent in each microenvironment. Using a similar model for measurements of PM₁₀, Buckley et al. (78) reported a median correlation of 0.55 for 13 individuals monitored over 14 days. In general, these assessments of microenvironmental measurements as surrogates for estimating exposure are based on adults. There are only emerging data on these relationships in children (79) and no data on children with asthma living in the urban environment.

Numerous particle exposure studies have recently been summarized to show that central site ambient measurements provide a poor surrogate for an individual's actual exposure, explaining only 0–25% of the variation in personal measurements (69,72,80). Outdoor air is an especially poor surrogate in cross-sectional evaluations where exposure variability is primarily driven by interpersonal differences. In contrast, in longitudinal studies where the influence of intrapersonal variability is lessened, outdoor central site measurements appear to provide a better surrogate (78–80). If the variation in outdoor PM is not predictive of the variations in personal exposures, then use of outdoor central site measurements will tend to misclassify exposures, resulting in an attenuation in the exposure–response relationship.

The use of a single central site ambient monitoring station for estimating the outdoor PM₁₀ concentration for a community or city is supported based on studies (76,81,82) demonstrating high correlations (PM₁₀: $r > 0.7$; PM_{2.5}: $r > 0.9$) in measurements across sites within a city (e.g., Philadelphia, Pennsylvania; Chicago, Illinois; Los Angeles, California). Because of vast differences in factors known to be important for exposure (e.g., time/activity patterns, socioeconomic status, and source use) between the populations for which these relationships have been defined, there is a clear need to define this relationship for the urban asthmatic population.

The epidemiologic evidence implicating particle exposure as a causative agent in children's asthma exacerbation is equivocal with respect to the responsible size, e.g., PM₁₀, PM_{3.5}, PM_{2.5}, or PM_{1.0}. This assessment is substantiated by a recent study where an association between visits to asthma physicians and increased levels of the coarse fraction of PM₁₀ has been reported (51). Size-selective sampling inlets are available for measuring personal and microenvironmental particle concentrations (e.g., Personal Environment Monitor, MSP Corporation, Minneapolis, MN) (83). These inlets are well characterized and validated and have been successfully used in other exposure studies (76,78). Compliance with personal monitoring is of concern, especially among population subgroups such as children. Investigators have employed motion sensors with logging capability bundled with the personal monitor to evaluate compliance by comparing the objective motion data with the time/activity questionnaire and expected activities such as school attendance, sleeping, etc.

In contrast to airborne particles, the determinants of exposure to NO₂ and O₃ are less complex, as these pollutants are specific chemicals with well-characterized physical and chemical properties. A major outdoor source for nitrogen oxides is the automobile (72). Indoor sources including kerosene heaters and gas stoves. Their impact on indoor air concentrations has been well characterized. A number of different studies have shown that much of the variability in NO₂ personal exposure can be explained by indirect assessment with indoor and outdoor measurements in a time-weighted model (23,64,65,71). A similar situation exists for O₃ that is formed outdoors as a secondary pollutant. Because there are no indoor residential sources, the exposure variability is driven by outdoor concentration gradients and building factors (e.g., air exchange, air conditioning) affecting the decay of O₃. Liu et al. (70) reported an indoor/outdoor ratio of 0.45 ± 0.23 and an R² value of 0.72 for a microenvironmental model relying on home indoor and outdoor, workplace, and central site measurements in a study conducted in State College, Pennsylvania.

ETS exposure can be effectively monitored by measuring cotinine in urine (84) or nicotine air concentrations. Urine cotinine is an effective biomarker for classifying children from homes with and without smokers (85). Urinary cotinine reportedly provides a stable marker of exposure.

Henderson et al. (85) showed that urinary cotinine levels were not affected by collection time of day; Over a 1-month period, sequential urine levels were highly correlated ($r > 0.88$).

Interactions of Pollutants and Allergens

The pathologic characteristics of allergic asthma are airway hyperresponsiveness, eosinophilic inflammation, elevations in serum IgE levels, and overproduction of mucus. It is now well accepted that asthmatic inflammation is driven by the expansion of allergen-specific T cells producing type-2 cytokines (i.e., interleukin (IL)-4 and IL-5). Under this paradigm, allergen presentation results in differentiation of CD4 T cells to a T helper cell (Th2) cytokine-2 producing phenotype in allergic individuals, whereas differentiation along a Th1 pathway is associated with normal responses. An immunopathogenic role for Th2 cytokines in asthma is suggested by the fact that IL-4 and IL-13 modulate the growth and differentiation of mast cells and regulates IgE synthesis (86,87), whereas IL-5 controls the differentiation (88), recruitment (89), and activation of eosinophils (90). Mast cells and eosinophils both elaborate a number of bronchoactive mediators that induce the airway obstruction characteristic of asthma.

With the recent understanding of the importance of CD4 T cells in the pathogenesis of asthma, much attention has been paid to the potential role of particulates in augmenting or initiating responses that may lead to activation of CD4 T cells. Although few controlled human or animal studies have examined the effects of real-world PM exposure on allergen-driven airway responses, recent studies using diesel exhaust particulates (DEP) or ROFA have shown enhancement of allergic responses in susceptible individuals. For example, Diaz-Sanchez and colleagues have shown that nasal challenge of human asthmatics with DEP markedly enhanced their IgE responses to ragweed challenge and skewed cytokine production to one of a Th2-type pattern (91). Similarly, studies in several animal models have confirmed these findings using a variety of sources of PM (i.e., ROFA, fly ash, DEP) (92,93). For example, Takano et al. (92) demonstrate that exposure to DEP enhances allergen-driven airway hyperresponsiveness and eosinophilic inflammation in mice sensitized with allergen. In this model, Th2 cytokine production in DEP-exposed animals was elevated over and

above that seen with allergen exposure alone. Gavett et al. (94) found similar results in mice exposed to ROFA. These studies suggest that PM may exacerbate asthma by enhancing production of Th2 cytokines in allergic individuals.

The mechanism(s) by which PM induces pulmonary inflammation and alters immune responses to allergens is currently unknown. Perhaps the simplest explanation is that PM serves as a carrier to transport allergens into the respiratory tract. However, studies in which allergens have been delivered by nonpulmonary routes show that the effects of PM on allergic responses are not solely due to its potential to serve as a carrier for allergens (95). On the other hand, exposure to PM or its components has a number of effects on macrophages and B cells that may augment their responsiveness to allergen exposure. Specifically, DEP induces expression of the costimulatory molecule CD80 in both human lavage cells and in the human macrophage cell line (THP-1) (96). CD80 binds with high affinity to its coreceptor CD28 on T cells and results in costimulation of T cells. Thus it is conceivable that PM could alter the response of the host to ubiquitous allergens by providing required co-stimulatory signals to enhance activation of T cells. A potential explanation for DEP effects on IgE production may be through its documented ability to directly enhance IgE production in normal human tonsillar B cells and peripheral blood B lymphocytes (92). The results of these studies suggest that perhaps the IgE-enhancing effects of DEP may result from direct effects on B lymphocytes.

Another potential mechanism by which PM may alter immune responses is via the induction of cytokine and chemokine production by the airway epithelium. For example, exposure to PM induces the production of several proinflammatory cytokines including IL-6, IL-8, and tumor necrosis factor alpha (TNF- α) by epithelial cells (97). Each of these cytokines has potent proinflammatory effects in the lung. IL-6, in particular, is a pleiotropic cytokine that elicits numerous biologic responses from a wide variety of tissues including differentiation of B cells into antibody-forming plasma cells, differentiation of T cells, and maturation of megakaryocytes and stimulation of the production of acute-phase proteins by hepatocytes. PM-induced IL-6 production can be mimicked by exposure of these cells to vanadium, one of the major components of ROFA (98).

As vanadium is a well-known tyrosine phosphate inhibitor, exposure of the epithelium or other lung cells to it could play an important role in the activation, responsiveness, and/or production of many immunologically active molecules (99).

Several studies have suggested that perhaps reactive oxygen species generated as a result of PM exposure may mediate the biologic effects of PM on the respiratory tract. For example, Kumagai and colleagues demonstrated that DEP extracts induce superoxide and hydroxyl radical generation in lung microsome preparations (100) and that the intratracheal effects of DEP could be prevented by pretreatment of animals with a polyethylene glycol-modified superoxide dismutase (101). As reactive oxygen species initiate intracellular signaling pathways and transcriptional activation of many genes [i.e., immediate early genes (*c-fos*, *c-jun*), cytokine genes, chemokine genes], they may play an important role in mediating the proinflammatory effects of PM in the respiratory tract. Collectively these studies suggest that PM may induce airway inflammation through a variety of mechanisms. As PM is a complex mixture of organic and inorganic components that varies from location to location, the challenge for investigators is to determine which components or mixtures of components in PM are responsible for the biologic effects.

Although most studies have been designed to determine whether particulate

exposure augments allergic symptoms in susceptible populations, there is accumulating evidence that perhaps acute particulate exposure can induce these responses in non-allergically prone individuals. Notably, DEP exposure of nonallergic individuals induces elevations in nasal IgE levels concomitant with increases in the number of T lymphocytes in nasal washes (10). In addition, a general increase in messenger RNA levels of both Th1 and Th2 cytokines in the nasal lavages has been noted. Studies in mice also support the conclusion that PM exposure in nonallergic individuals can induce airway inflammation. For example, Gavett et al. (102) demonstrated that exposure to ROFA results in pulmonary inflammation marked by increases in eosinophils, neutrophils, and T cells in nonsensitized rats. In addition, we have recently found that exposure of naive mice from several murine strains to particulate collected in urban Baltimore induces airway hyperresponsiveness and airway inflammation irrespective of their susceptibility to allergen exposure (unpublished data). Specifically, we have found that both A/J mice who display a natural susceptibility to the development of allergic airway responses when exposed to allergens, and C3H/HeJ mice who do not develop airway hyperresponsiveness and eosinophilic inflammation when exposed to ambient urban particulate. Taken together, these studies suggest that exposure to ambient particulates may play a role not only in exacerbation of existing

allergic disease, but may also contribute to the recent rise in the prevalence of asthma.

Genetic Mechanisms of Ozone-Induced Inflammation

In many industrialized cities throughout the world, oxidant air pollutants have become an important public health concern. Among these agents, O₃ is the most potent. Over 150 million people live in communities where the concentrations of O₃ approach or exceed the national ambient air quality standards of 0.12 ppm (103).

In healthy human subjects, acute (2–6 hr) exposure to 0.08–0.75 ppm O₃ causes decrements in pulmonary function (104), elicits the release of bronchoactive chemical mediators (105,106), and induces airway inflammation in adults and children (106). Further, a number of epidemiologic studies have demonstrated an association between respiratory morbidity and mortality and O₃ exposure (107,108).

Asthmatics may represent a particularly susceptible subpopulation for the toxic effects of O₃ exposure. Recent studies have suggested that asthmatics may develop greater O₃-induced airway inflammation than normal subjects. Basha et al. (109) found statistically significant increases in bronchoalveolar lavage concentrations of IL-8, IL-6, and neutrophils in asthmatics but not in nonasthmatics after an acute exposure to 0.20 ppm O₃. Scannell et al. (110) also found greater O₃-induced inflammation and pulmonary function changes in asthmatics compared with normal, healthy subjects. Similarly, McBride et al. (111) exposed asthmatic and normal subjects to 0.24 ppm O₃ and demonstrated significant increases in neutrophils and epithelial cells in nasal lavage in asthmatics but not normal subjects. Association of asthma exacerbations with

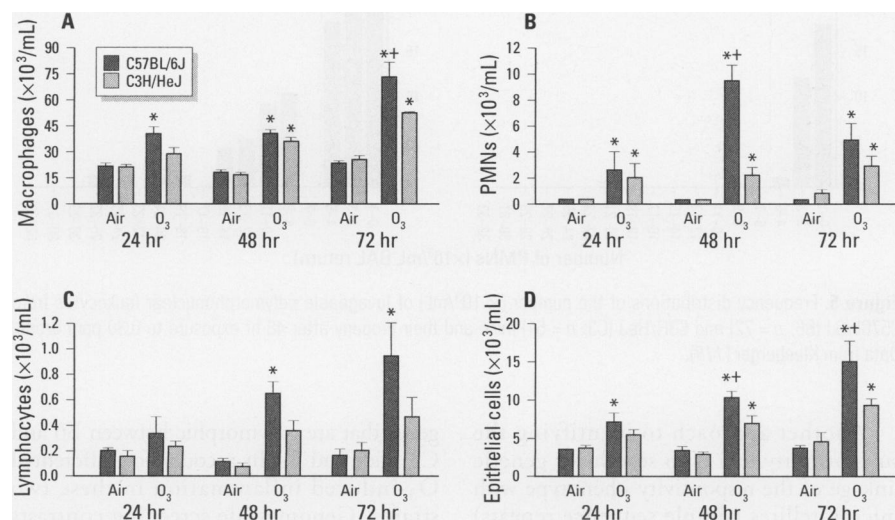


Figure 3. Number of macrophages (A), PMN (B), lymphocytes (C), and epithelial cells (D) recovered by bronchoalveolar lavage after 24-, 48-, and 72-hr exposure to 0.30 ppm O₃ or air in C57BL/6J and C3H/HeJ mice. Abbreviations: O₃, ozone; PMN, polymorphonuclear leukocytes. *n* = 6–8 mice/strain/time point. Statistical comparison of O₃-exposed animals with respective chamber (air) controls: **p* < 0.05. Statistical comparison of C3H/HeJ with C57BL/6J: ***p* < 0.05.

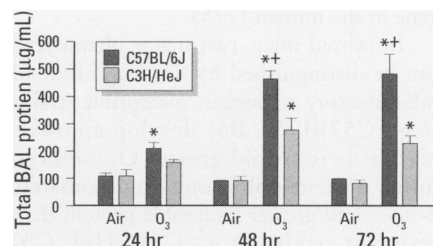


Figure 4. Total bronchoalveolar lavage protein concentration in C57BL/6J and C3H/HeJ strains of mice following 24-, 48-, and 72-hr continuous exposure to 0.12 ppm ozone (A), 0.30 ppm ozone (B), or filtered air. Symbols are as presented in Figure 3. Data from Kleberger et al. (116).

O₃ exposure have been demonstrated in a number of urban environments including Atlanta, Georgia (33), and Mexico City, Mexico (24). Other studies have demonstrated strong association between asthma and pollutant mixtures that include O₃ and particulates (112).

Extensive literature exists regarding O₃ damage at the organ and cellular level, although the mechanisms of O₃ toxicity are still not clear. A cascade mechanism has been proposed that suggests that O₃ reacts with unsaturated fatty acids at the air-tissue barrier and forms lipid ozonation products that include aldehydes, hydroperoxides, and Criegee ozonide (113). The lipid ozonation products in turn activate lipases that lead to production and release of cell signal transduction molecules and proinflammatory mediators such as platelet activating factor. Antioxidant enzymes (e.g., glutathione enzymes, superoxide dismutase, and catalase) and nonenzymatic factors (e.g., ascorbic acid, α -tocopherol) provide defense against oxidative damage of airway lipid membranes (114) by quenching O₃ either directly or through interaction with the reactive oxygen species by-products of O₃.

There are clearly a number of genetic steps that could lead to increased susceptibility to O₃ exposure. The inbred mouse is an important model to examine these steps, because controlled standardized inbreeding has led to genetic homogeneity that cannot be found or duplicated in human populations. Linkage relationships of homologous loci from human and mouse indicate that highly significant homology and gene order in chromosomal structure has been maintained since the divergence of the human and mouse. Therefore, the identification of chromosomal location(s) of the gene(s) for susceptibility to O₃-induced inflammation (or other airway response) provides the basis for potentially localizing a homologous gene in the human (115).

In inbred mice, two major phenotypes can be distinguished by the magnitude of inflammatory responses: susceptible strains (e.g., C57BL/6J, B6) develop approximately 4- to 6-fold greater O₃-induced influx of neutrophils and approximately 2- to 3-fold greater lavageable protein than resistant strains (e.g., C3H/HeJ, C3) (Figures 3, 4). Initial genetic analyses suggested that inflammation induced by subacute O₃ exposures in B6 and C3 strains of mice was a quantitative trait, but the analyses did not indicate the location of the susceptibility loci (116,117).

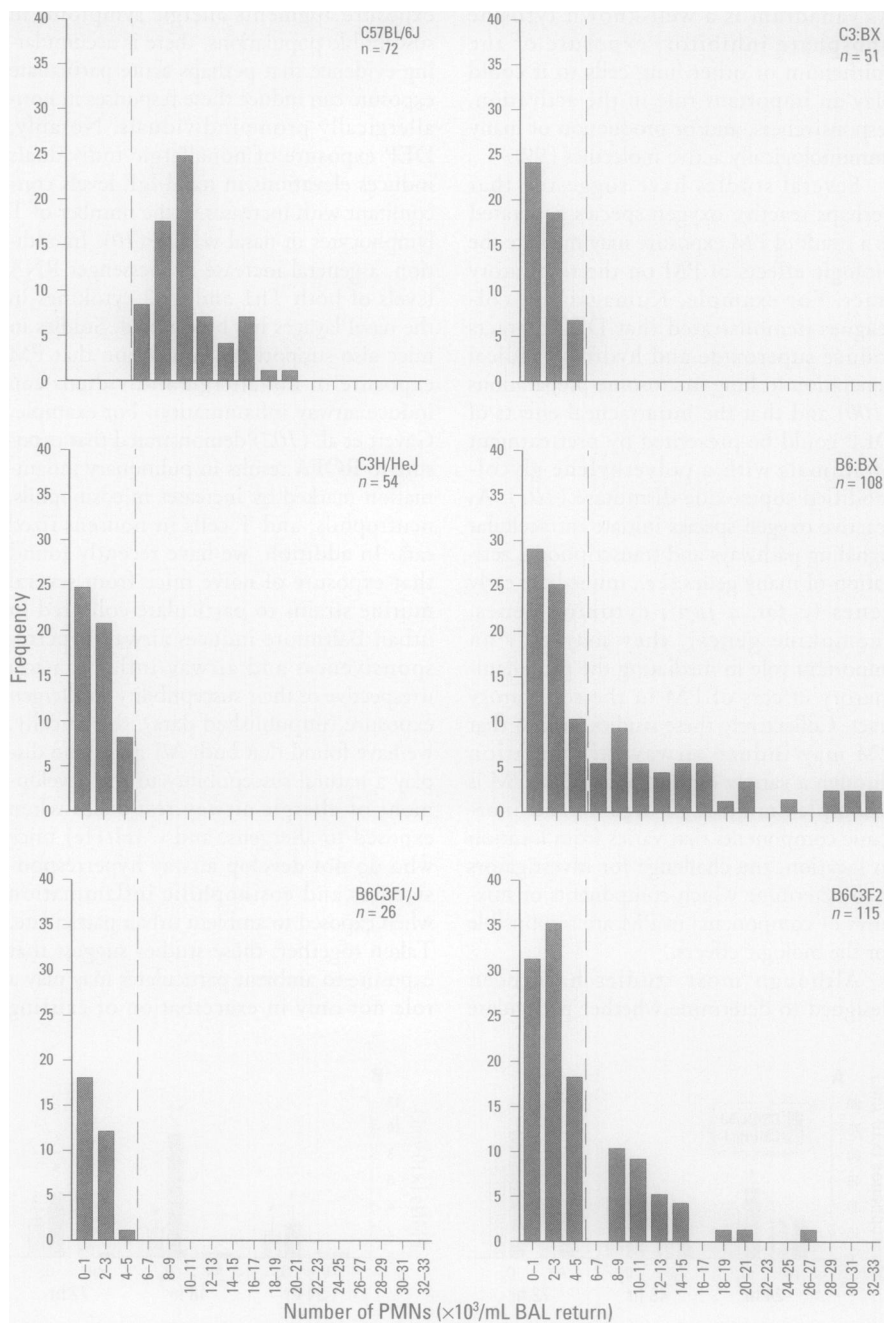


Figure 5. Frequency distributions of the number ($\times 10^3/\text{mL}$) of lavageable polymorphonuclear leukocytes from C57BL/6J (B6; $n = 72$) and C3H/HeJ (C3; $n = 51$) mice and their progeny after 48-hr exposure to 0.30 ppm ozone. Data from Kleeberger (118).

Another approach to identifying the susceptibility loci is to search for genetic linkage of the responsivity phenotype with microsatellites (simple sequence repeats) distributed throughout the mouse genome. It is important to emphasize that the genomewide screen was designed to identify linkage to any chromosomal intervals within the entire genome that might contain the

genes that are polymorphic between B6 and C3 mice and might account for differential O₃-induced inflammation in these two strains. Genomewide screening contrasts with the candidate gene approach in which loci are chosen a priori as likely mechanisms that determine differential susceptibility to O₃ in B6 and C3 mice. These might include genes for antioxidant enzymes and

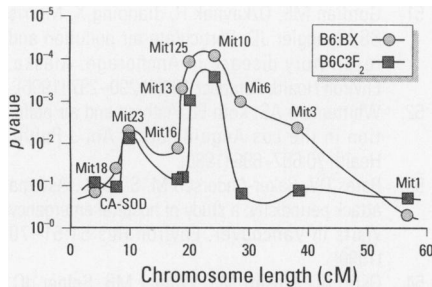


Figure 6. Graphic representation of *p* values for linkage (by χ^2 test) of ozone-susceptibility phenotype in B6:BX and B6C3F₂ animals, with microsatellite markers surrounding the quantitative trait locus on chromosome 17. The *p* values (*y* axis) are plotted against the markers studied in the correct order and genetic distance (*x* axis). Data from Kleeberger (118).

any other genes that may confer differential susceptibility to oxidant exposure. (e.g., antioxidant gene polymorphisms, differences in epithelial membrane polymorphisms, fatty acid content). With the candidate gene approach, linkage is then assessed between the phenotype of interest and markers flanking the candidate genes or the candidate genes themselves.

Using genome-screening procedures, we identified a statistically significant quantitative trait locus (QTL) on chromosome 17 in the interval between *D17-Mit125* and *D17Mit10* (Figures 5 and 6), and a suggestive QTL on chromosome 11 between *D11Mit20* and *D11Mit12* (118). Within the chromosome 17 QTL are a number of candidate genes: *Tnf* (TNF- α), *H2* (histocompatibility loci), and *Mcp6* and *Mcp7* (mast cell proteases 6 and 7). Interestingly, the chromosome 17 QTL is similar to a QTL for airways hyperreactivity (119), an important asthma subphenotype. Homologous loci with conserved synteny in the human genome are located on chromosome 6p21.3. There are also a number of candidate genes within the chromosome 11 QTL that may contribute to differential responsiveness to inflammatory effects of O₃ exposure. These include a cluster of CC chemokine genes including the genes for T-cell-specific RANTES (regulated on activation, normal T cell expressed and secreted) (*Scya5*), monocyte chemoattractant proteins 1 and 3 (*Scya2*, *Scya7*), and macrophage inflammatory protein 1 α and 1 β (*Scya3*, *Scya4*). Human homologs for these loci are located on 17q11.2 and this region has been implicated in the pathogenesis of asthma (120) and other inflammatory diseases.

Studies are currently being directed to utilize positional cloning and breeding

techniques to definitively identify the gene or genes that determine differential susceptibility to O₃-induced lung inflammation and injury in inbred strains of mice and to search for homologs in the human genome. Understanding the genetic basis of response to O₃-induced inflammation will lead to potential means for identification of susceptible individuals and, subsequently, methods for intervention to prevent injury.

Conclusion

Asthma is a classic example of a disease caused by gene-environment interaction. The need to understand this interaction has been intensified by our recognition that asthma is becoming increasingly common and severe in industrialized countries. Our understanding of environmental influences is still in its infancy, but we can say that indoor exposures are more important than ambient pollutants and that bioaerosols containing allergenic proteins are especially important. We understand that certain particulate aerosols and O₃, known to cause inflammation individually, may act synergistically to enhance acute and chronic IgE-mediated inflammation. As a consequence, environmental exposure assessment undertaken in epidemiologic studies must measure a variety of agents simultaneously if we are to understand the reality of environmental exposure. Finally, we understand that the environment to be studied must include not only important airborne pollutants and allergens but the psychosocial milieu in which the asthmatic patient lives. New genetic methods help us to dissect the genetic basis of the increased susceptibility in asthma to inflammation caused by either IgE-mediated mechanisms or those with no immunologic basis. Once identified in animal studies, individual genes can be confirmed in human populations and susceptible alleles sought, so that preventive strategies can be focused on susceptible individuals.

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