Enhanced Sensitivity of the Postnatal Lung to Environmental Insults and Oxidant Stress

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ABSTRACT. Examination of the current state of health in the United States suggests that childhood lung diseases are increasing at an alarming rate. Looking more closely at the data, it can be seen that this increase is especially true for chronic respiratory diseases such as allergic asthma. This is a disease that is thought to have its roots in childhood insults. The demographics of the current wave of asthma and other chronic lung diseases reveal that the incidence is highest among children in polluted inner cities, where it seems to have reached epidemic proportions. This gives rise to a number of serious questions as to causality. Has the nature of the urban environment changed to such an extent as to lead to increased disease? Are current populations more sensitive to existing environmental insults? Is the increase real, or has our ability to detect it improved? This article addresses the possibility that factors intrinsic to the lung and its development have combined with specific environmental risk factors to have an adverse impact on children's health. Pediatrics 2004;113:1092–1096; postnatal lung development, environmental pollutants, inflammation, respiratory epithelium.

ABBREVIATIONS. LPS, lipopolysaccharide; ETS, environmental tobacco smoke.

A n editorial by Plopper and Fanucchi¹ suggests that the recent marked increase in the incidence of childhood asthma results from a combination of factors that they suggest are characteristics of lung biology and others related to changing environmental factors. In the context of their discussion, neither of these alone would be sufficient to compromise the respiratory health of children. For the purposes of our current discussion, we focus on the issues intrinsic to the biology of the system and then identify a number of potential environmental concerns.

In experimental animals, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses well below the no-effect levels for adults.² This exists despite what would be expected on the basis of the lowered levels of xenobiotic-activating enzyme systems and the elevated phase II detoxification mechanisms found in neonatal lungs when compared with those of adults of the same species. Arguably, this suggests that metabolic differences are not a critical factor in these circumstances. In addition, data from a number of laboratories can be interpreted to show that acute injury to the lung during early postnatal development results in a failure of normal repair processes. Among these would be downregulation of cellular proliferation at injury sites and inhibition of the normal processes of differentiation of cell populations surviving at the site of injury.³ Both the heightened susceptibility and the failure of the repair process occur in limited windows of time during postnatal lung development.

BIOLOGICAL FACTORS THAT INFLUENCE SUSCEPTIBILITY

A critical biological factor that plays a role in childhood pulmonary susceptibility is that a significant portion of lung development takes place postnatally. During this period, the lung may be exposed to a vast array of materials of undefined toxicity. In humans, this period involves the first 6 to 8 years of childhood.⁴ During this period, the lung undergoes alveolarization and continued morphogenesis, including differentiation of critical cell types and systems. Among the most important of these are the respiratory epithelium and critical immune effector cell populations. It has also been suggested by Evans et al⁵ that this period is one in which specific cell–cell interactions that influence the response of the system are established. Factors that disrupt these “developmental” events may have drastic long-term consequences. We know from a number of animal studies that many of these postnatal developmental processes exhibit critical windows.

Studies using oxidant gases have shown that mature and old animals are more sensitive to oxidant stress injury than are young animals.⁶–¹¹ Lethality from continuous exposure to hyperoxia is dramatically reduced in newborn rats and mice. Exposure to >99% oxygen for 70 to 80 hours resulted in 100% mortality in adult animals. In contrast, a similar time course in neonatal animals results in only a 10% to 15% mortality.⁹,¹² Age-dependent responses to photochemical smog and nitrogen dioxide have also been noted.⁶,¹³

Our own work demonstrates that ozone exposure, which leads to more extensive epithelial cell injury in adult mice, resulted in differential chemokine, cyto-
kin, and antioxidant induction between newborn and adult mice. The results of the studies also showed that although differences in acute sensitivity to ozone exist between newborn and adult mice, once initiated, the acute chemokine and cytokine changes follow a common response pattern. Other ozone studies observed altered injury and biochemical parameters after exposure to 0.85 ppm of ozone for 24 to 72 hours in rats. The apparent resistance of newborns to oxidant exposure was suggested to be a consequence of the ability to induce antioxidant enzymes during exposure, whereas adults did not induce antioxidant enzymes. Endotoxin exposures, an inflammatory agent not injurious to the epithelium, have been shown to induce a similar acute inflammatory response after inhalation in newborn and 8-week-old mice. Martin et al showed that neonatal and adult alveolar macrophage released similar amounts of neutrophil chemotactic activity and tumor necrosis factor in response to incubation with lipopolysaccharide (LPS) in vitro. Support for the hypothesis of differential sensitivity and differential response of the “differentiating” respiratory epithelium can be seen in studies comparing the initiation of inflammation after endotoxin exposure in comparison with the response to oxidant pollutants such as ozone. The endotoxin response seems fully developed early in life, whereas the oxidant response is a developmental process. Although these differences seem to suggest resistance in the early postnatal lung, it is equally likely that the converse is true. The lack of antioxidant induction in early life could subject the tissue to a greater oxidant burden, resulting in long-term alterations in structure and function. Alterations in function or exposure to mild irritants or toxicants are likely to modify developmental processes. The timing and interaction between these developmental events seem to play a role as susceptible targets for environmental perturbation. In other words, age seems to be a critical variable in the ability of the lung to cope with external stress.

A second aspect of lung biology that seems to play a role is the wide genetic variability that modulates predisposition to enhanced perturbation by environmental contaminants. Many of these disease processes are controlled by specific genes. Studies of these critical genes and the information uncovered as part of the genome project have defined a large variety of genetic polymorphisms in these genes. These polymorphisms are closely associated with susceptibility to environmental contaminants.

Experimental studies have shown that individuals differ in their sensitivity to oxidants, among other agents. Animal studies have also shown that the toxicity induced by ozone is species-specific and strain-specific and most probably is genetically determined. Such genetic differences may make it difficult to extrapolate from animal experiments to human susceptibility, but they are illustrative of the type of issues that can be addressed.

When the 2 biological factors of developmental regulation of defense mechanisms and genetic variability are subjected to our declining environmental quality, coexposure to a combination of environmental contaminants may have a decidedly negative impact. One of the environmental factors relevant to childhood lung disease is the recent increase in complexity and distribution, if not the levels, of airborne pollutants, including environmental tobacco smoke (ETS), diesel exhaust, respirable particulate matter (ultrafine, fine, and coarse modes [<0.1, 2.5, and 10 μm in aerodynamic diameter, respectively]), and irritant gases (ozone, sulfur dioxide, and nitrogen dioxide).

Ozone

Ozone is 1 of the most important outdoor and indoor airborne pollutants. The toxic effects are a function of the gas concentration and exposure duration. Acute exposure to ozone at concentrations near the National Ambient Air Quality Standard causes respiratory symptoms, decrements in lung function, and upper and lower respiratory tract inflammation. Studies in humans using bronchoalveolar and nasal lavages have shown ozone-induced increases in inflammatory cells, soluble markers of inflammation and repair, and markers of epithelial permeability. The main health effect to humans after short-term exposures to nitrogen dioxide is an increased susceptibility to respiratory infection.

Morphologic changes are known to occur in the lungs of animals that are exposed to ozone, most especially cells at the air/tissue interface that are undergoing the most significant changes during alveolarization and postnatal morphogenesis. These include degeneration of type I alveolar pneumocytes and loss of ciliated epithelium from the upper airway. Pulmonary surfactant producing type II epithelial cells proliferate and differentiate into type I cells to repair the damaged epithelium. Nonciliated secretory (Clara) cells are relatively resistant to injury; however, they lose secretory granules during the period of injury. The lung inflammatory response to ozone places the cells at the air/tissue border under additional oxidative stress from reactive oxygen species formed by the oxidative burst of the activated macrophages.

ETS

ETS, a common indoor air pollutant, has been implicated as a significant risk factor for disease and increased morbidity and mortality among nonsmokers. ETS has been a focus because exposure in children increases the risk for respiratory infections such as bronchitis and pneumonia, upper respiratory tract irritation, reduced lung function, and asthma. Also of concern is the extent to which ETS might influence pulmonary responses to other inhaled toxic materials. Cigarette smoke has been reported to delay pulmonary clearance of inhaled, insoluble particles in humans and laboratory animals, and the magnitude of effect is related to exposure and concentration of cigarette smoke.
also an increase in exposure to complex and possibly even more toxic pollutant mixtures. Combined exposures to multiple toxicants may result in injuries/responses not predicted by evaluating exposures to an individual toxicant. At particular risk may be the developing organism or individuals with preexisting lung disease. This may indicate that the lung is damaged or primed by earlier events, so exposure to a nontoxic dose of an environmental pollutant may be sufficient to trigger morphologic changes, including increased inflammatory cell recruitment and epithelial cell damage and toxicity in the lung. A study by Fanucchi et al demonstrated that although bacterial endotoxin alone did not cause a phenotypic change in rat nasal transitional epithelium, it can augment the mucous cell metaplasia induced by a previous exposure to ozone. Adamson et al showed that inhalation of an urban dust at a level that causes few lung effects when inhaled alone can potentiate ozone toxicity and be an important factor in the development of subsequent pathologic changes. Elder et al also suggested that urban ultrafine carbonaceous particles are causally associated with lung inflammatory responses; however, other common pollutants such as ozone or existing stress in lung target cells (e.g., LPS priming) can significantly alter the response and function of pulmonary inflammatory cells. Studies from our laboratory have demonstrated that coexposure of the lung to ozone followed by endotoxin inhalation potentiates ozone-induced lung injury.

To date, very little work has focused on complex mixtures, especially as they affect postnatal lung development. The studies that are available suggest that exposure to individual chemicals alters postnatal lung development in experimental animals. Epidemiologic studies of the impact of maternal smoking on diseases of children and the increase in incidence of asthma in polluted inner cities suggest that pollutant exposure has a negative impact on postnatal lung development.

ENVIRONMENTAL ALLERGENS AND ENDOTOXINS

A second environmental factor that is relevant to lung disease is the increase of a variety of known human allergens, especially those derived from house dust mites and cockroaches. These allergens have well-documented modulatory impacts on the trophic interactions of conducting airway epithelial and interstitial wall components after both acute and chronic exposure. The third relevant environmental factor is the prevalence of bacterial wall–derived endotoxins in both the indoor and outdoor air. As with the allergens, endotoxins also have an impact on the trophic interaction of conducting airway epithelial and interstitial wall components.

Chronic exposure of endotoxin measured in the dust from occupational and domestic settings has been related to both the risk of developing chronic obstructive pulmonary diseases and the severity of domestic asthma. Thus, there is growing evidence that environmental endotoxin is related to lung diseases. Endotoxin (LPS) induces acute lung injury in sepsis and Gram-negative pneumonia, 2 conditions marked by the activation of alveolar macrophages and massive tissue infiltration of neutrophils, which may lead to adult respiratory distress syndrome. The symptoms of acute endotoxin exposure include fever, chills, dyspnea, chest tightness, coughing, and decreases in lung diffusion capacity. Airborne endotoxin concentration (0.006–0.779 μg/m³) correlated with decreased forced expiratory volume in 1 second in exposed humans. Results from animal models also indicate that endotoxin is a potent toxicant. Inhalation of endotoxin by guinea pigs resulted in a neutrophil influx into airways. In addition, 2 primary inflammatory cytokines, tumor necrosis factor and interleukin–1, were induced by inhalation of endotoxin.

It is not clear whether levels of endotoxin have been markedly elevated in the past 10 to 20 years; however, the presence of endotoxin in air contaminated by pollutants and by known human allergens suggests that the confluence of these 3 classes of airway inflammatory and allergic agents could markedly exacerbate the effects of each agent individually. Mutations in specific human genes are thought to be closely linked to the variation of sensitivity of individuals to these materials.

CONCLUSION

The limited experimental and epidemiologic studies that have been performed support the hypothesis that the early postnatal period of lung development is a window of high susceptibility for lung damage created by exposure to environmental toxicants. Whether these effects are irreversible, as has been suggested by some authors, requires additional investigation. From such investigation will come information about fundamental issues such as the mechanisms by which environmental contaminants initiate or exacerbate debilitating lung disease and their relationship to the cause of childhood lung disease. This would help in the development of effective therapeutic and preventive measures to reverse the seeming epidemic. The potential long-term fiscal impact on the health care system of reducing chronic lung disease in children and adults makes this effort appropriate and long overdue. The situation is made all the more urgent by the recent data from the group at Davis, which has indicated the generation of an asthmatic phenotype and significant lung remodeling in the distal conducting airways of young rhesus monkeys exposed since infancy to cyclic episodes of ozone and house dust mite aerosol.

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