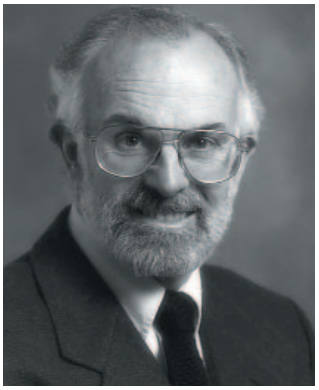
Epidemiologic studies… suggest that pollutant exposure has a negative impact on postnatal lung development.



Do Urban Environmental Pollutants Exacerbate Childhood Lung Diseases?

Childhood lung diseases in the United States are on the rise. This is especially true for chronic respiratory diseases such as allergic asthma, where the incidence among children in polluted inner cities has reached epidemic proportions. We believe that the recent marked increase in the incidence of childhood asthma results from the convergence of six separate factors (three of which are characteristics of lung biology and three of which are environmental factors) that individually would not be sufficient to compromise the respiratory health of children.

The first of the biologic factors is the extended period of postnatal life required for complete development of the human lung. For long-lived mammalian species such as humans, this period involves the first 6–8 years of childhood (*1*). The developmental events occurring during this postnatal period are the same events that begin before birth and include cytodifferentiation of epithelial and interstitial cell populations, morphogenesis and reorganization of the gas exchange area, and the development of the respiratory mucosal immune system. Further, the complex trophic interrelationships between various cellular and acellular components of the conducting airway wall are established during this extended postnatal period (*2*). As with prenatal development, many postnatal developmental processes exhibit critical windows in which minor alterations in function or exposure to mild irritants or toxicants can markedly modify developmental processes. The timing and interaction between these developmental events appear to play a role as susceptible targets for environmental perturbation.

The second aspect of human lung biology which appears to play a role is the wide genetic variability that modulates predisposition to enhanced perturbation by allergic and other environmental contaminants. As the complexities of the human genome have been defined, a large variety of genetic polymorphisms are being identified. These polymorphisms are closely associated with susceptibility to a wide variety of environmental contaminants, including allergens (*3,4*). Both of these characteristics of human biology (postnatal development and genetic variability) provide the platform on which perturbations by environmental contaminants could alter respiratory health. These differences in genetic composition of even closely related individuals could predispose some of them to disease processes produced by environmental contaminants.

When these two biologic factors 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, diesel exhaust, respirable particulate matter ($PM_{2.5}$ and PM_{10}, ≤ 2.5 and ≤ 10 µm in aerodynamic diameter, respectively), and irritant gases (ozone, sulfur dioxide, and nitrogen dioxide). This increase in air pollutants involves not only increases in exposure to individual chemicals but also an increase in exposure to complex, and possibly even more toxic, pollutant mixtures (*5*). To date, very little work has focused on complex mixtures, especially as they impact postnatal lung development. The studies which are available suggest that exposure to individual chemicals alters postnatal lung development in experimental animals (*6*). 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 (*7,8*). 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 impact the trophic interaction of conducting airway epithelial and interstitial wall components. It is not clear whether levels of endotoxin have been markedly elevated in the last 10–20 years; however, the presence of endotoxin in air contaminated by air pollutants and by known human allergens suggests that the confluence of these three 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.

The third biologic factor is the altered development of the respiratory system after neonatal exposure to environmental pollutants. In experimental animals, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses well below the no-effect levels for adults (*6*). This elevation is the inverse of what would be expected based on the lowered levels of xenobiotic-activating enzyme systems and the elevated Phase II detoxification mechanisms found in neonatal lungs when compared to those of adults of the same species. In addition, acute injury to the lung during early postnatal development results in a failure of normal repair processes including down-regulation of cellular proliferation at injury sites and inhibition of the normal processes of cytodifferentiation of cell populations surviving at the site of injury (*9*). Both the heightened susceptibility and the failure of the repair process occur in limited windows of time during postnatal lung development.

The limited experimental and epidemiologic studies currently available identify the early postnatal period of lung development as a window of high susceptibility for irreversible lung damage created by exposure to environmental toxicants. The lack of information about fundamental issues such as the etiology of childhood lung disease and

the mechanisms by which environmental contaminants initiate or exacerbate debilitating lung disease in children have hampered the identification of effective therapeutic and preventative measures to reverse the seeming epidemic. Given the magnitude of childhood morbidity attributable to chronic lung diseases and the potential long-term fiscal impact on the healthcare system, mobilization of governmental resources to the level that has been devoted to acquired immunodeficiency syndrome and cardiovascular disease seems appropriate and long overdue. The recent discovery of profound remodeling in the distal conducting airways of young rhesus monkeys exposed since infancy to cyclic episodes of ozone and house dust mite aerosol (*10*) emphasizes the urgency of the situation. This observation provides a pathophysiologic basis for the decrement in small airways function recently observed by Tager (*8*) in college freshmen who have grown up in polluted areas of California's South Coast Air Basin.

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