

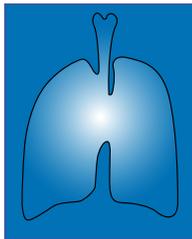
### 3. Coal's Effects on the Respiratory System



Virtually all airborne pollutants gain access to the body via the respiratory tract.

Thus, it is no surprise that this important system is affected significantly by pollutants discharged into the atmosphere by electrical utilities that burn coal. These effects fall into several classes: *de novo* production of a condition, such as asthma, that did not exist prior to an exposure; an exacerbation of a previously-existing illness, again, such as asthma; and the development or progression of a chronic illness such as asthma, lung cancer, chronic obstructive pulmonary disease (COPD), and emphysema.

Data from the California Children's Health study have shown that air pollutants have clinically and statistically significant adverse effects on lung development.<sup>1</sup> In this prospective study, 1759 children were enrolled when they were in the fourth grade, when they were approximately 10 years old, and followed until age 18. Various measures of lung function were made periodically and correlated with their exposure to various pollutants. During normal development, the amount of air that can be forcibly exhaled in one second ( $FEV_1$ ) increases with age. After controlling for various factors that could potentially confound the results, the investigators found that the  $FEV_1$  failed to increase as predicted among children exposed to  $NO_2$ , acid vapor, and  $PM_{2.5}$ . Using a reduction of  $FEV_1$  to 80%



or less of the predicted value, children exposed to the highest levels of particulates were almost five times more likely to fall into the abnormal range than those with the lowest exposures. This impact on lung development is likely to be an additional risk factor for the subsequent development of other pulmonary diseases, such as asthma and chronic obstructive pulmonary disease.

#### ASTHMA

Asthma is a chronic disease of the lungs characterized by inflammation and narrowing of the airways. Patients with asthma experience recurrent episodes of dyspnea (shortness of breath), a sensation of tightness in the chest, wheezing, and coughing that typically occurs at night or early in the morning. Airway inflammation in asthmatics



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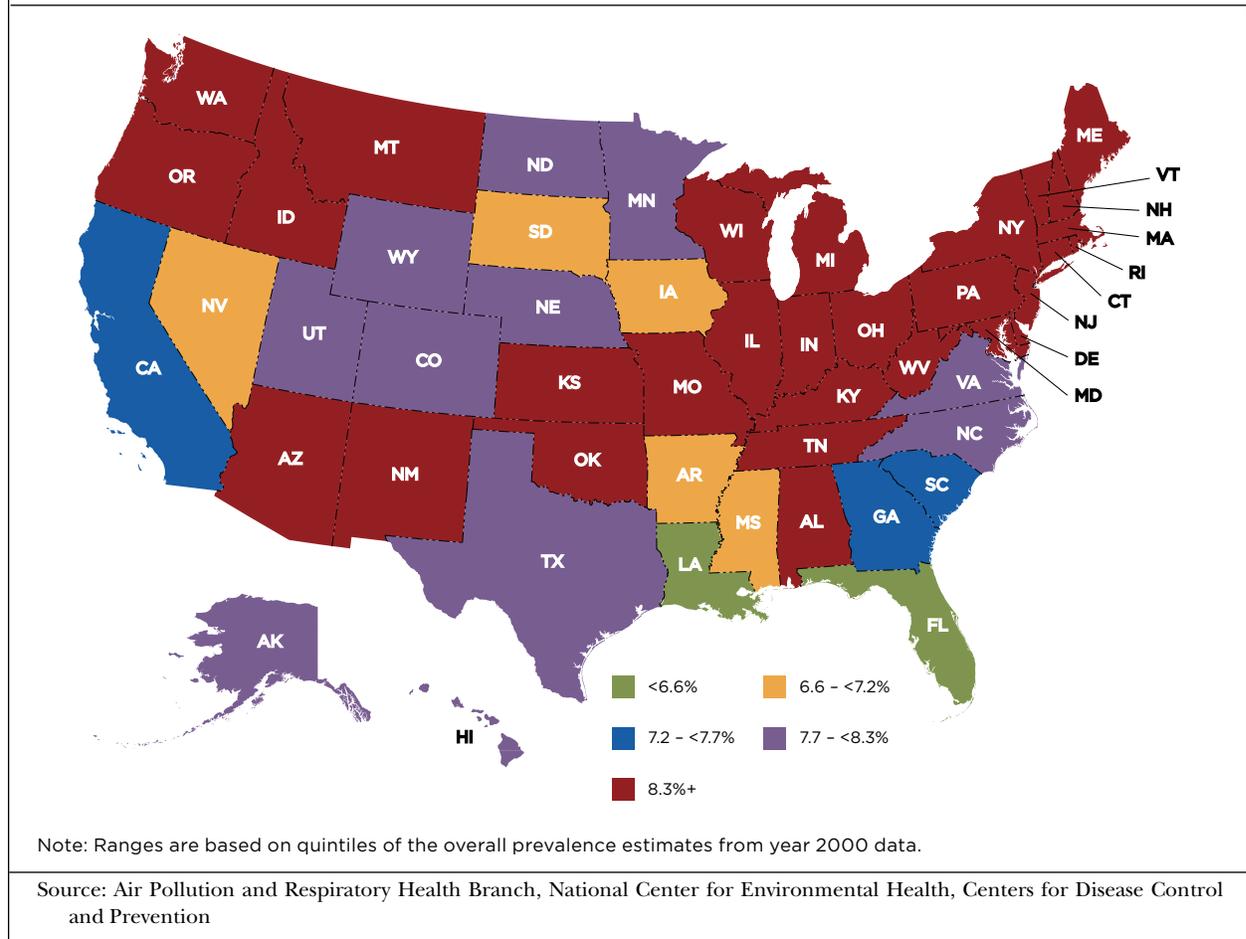
causes swelling that narrows a bronchial tree that has been previously sensitized to inhaled irritants, including many air pollutants. Exposure to an inhaled irritant causes further narrowing of the airways and the production of mucus that makes airways even narrower. During severe attacks, the lungs fail to perform their task of exchanging carbon dioxide, produced by metabolic processes in the body, for oxygen. This can lead to hypoxia (low blood oxygen level), hypercarbia (high blood carbon dioxide level), and respiratory acidosis (acidification of the blood caused by carbon dioxide retention) that may, in turn, cause cardiac arrhythmias and death. There are about 22 million asthmatics in the U.S., including 6 million children.<sup>2</sup> The Centers for Disease Control and Prevention

report that the number of persons with asthma increased by 84% from 1980 to 2004. As shown in Figure 3.1, more than half of the states report that 8.6% or more of its inhabitants have asthma. These high-asthma states are clustered in the northeast and Midwest.

During an asthma attack, the airway is constricted due to inflammation and contraction or spasm of the muscles that surround the airway. This is associated with swelling of the tissues of the airway caused by triggers, or stimuli, which in turn cause an immune response. Asthmatics are more sensitive to these triggers than non-asthmatics, a condition known as hypersensitivity. There are many triggers, including dust, smoke, pollen, and volatile organic compounds. Some of the

**Figure 3.1: CDC asthma prevalence by state**

Adult self-reported current asthma prevalence rate by state, Behavioral Risk Factor Surveillance System 2007



## OXIDATIVE STRESS

The possibility that oxygen, or reactive forms of oxygen, might be toxic to certain cellular functions emerged in the 1950s. Subsequent research has focused on the importance of highly reactive forms of oxygen, known as oxygen free radicals, in biological systems. We now know that some of these free radicals exert critical controls over normal cellular metabolic process and cellular signaling. "Oxidative stress" is the term used to describe the physiological state characterized by an excessive concentration of these oxidizing free radical molecules.

Oxidative stress is one of several mechanisms implicated in the pathogenesis of diseases caused or made worse by pollutants formed by burning coal.

Free radicals are defined as atoms or molecules that contain at least one unpaired electron in an atomic or molecular orbit and are therefore unstable and highly reactive. Examples of reactive oxygen species (ROS) include the superoxide anion radical, formed by the addition of an electron to molecular oxygen ( $O_2$ ); the hydroxyl radical, the neutral form of the hydroxyl ion; and peroxy radicals, the simplest of which is the hydroperoxyl radical, composed of one molecule of hydrogen and two molecules of oxygen. More complex peroxy radicals

have an organic group (abbreviated by an R) substituted for the hydrogen molecule.

ROS are a normal cellular constituent and play critical roles in the control of many cellular functions. However, the concentration of ROS can be increased through exposure to environmental substances such as air pollution, tobacco smoke, pesticides, and solvents. When the ROS concentration is excessive, these highly reactive molecules damage lipids, proteins, DNA, cell membranes, and other cellular components, producing oxidative stress, an important contributing factor in a variety of diseases.

In a contemporary review Valko, et al., summarize the current state of knowledge of oxygen free radicals and their importance in the production of a variety of diseases including cardiovascular and pulmonary disease, as well as other conditions including atherosclerosis, hypertension, rheumatoid arthritis, diabetes mellitus, neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, and normal aging.

Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem and Cell Biology* 2007;39:44–84.

pollutants discharged by coal fired power plants may act as triggers and produce an asthma attack. These pollutants include sulfur dioxide, nitrogen oxides, and particulate matter. In addition, the carbon dioxide emissions from coal accelerate global warming, which is likely to increase the concentration in air of pollen from some plants, such as ragweed, and thereby contribute to the development of additional asthma attacks.

Genetic variability accounts for some of the differences in the sensitivity of individuals to asthma triggers.<sup>3</sup> Genetic studies have shown differences in the susceptibility to ozone that are due to polymorphisms (subtle differences in genes that control the expression of a trait) in the genes responsible

for dealing with oxidative stress. Oxidative stress is created when oxygen ions, free radicals, or other reactive species are produced in excess of the body's ability to remove these molecules. Oxidative stress may be an important mechanism for the production of a variety of diseases (see text box). Genetic polymorphisms responsible for controlling the inflammatory response also increase an individual's susceptibility to the respiratory effects of ozone. Thus, the probability that an individual will develop asthma depends on exposure to a trigger, such as ozone, and the individual's susceptibility to that trigger, i.e., a complex combination and interaction between genetic and environmental factors. For a review of the genetic susceptibility

to the effects of air pollutants, such as ozone, particulates, nitrogen dioxide, and sulfur dioxide, on respiratory function see Yang, et al.<sup>4</sup>

Children appear to be more susceptible to the development of pollution-related asthma attacks than adults. There are several explanations for this increase in susceptibility. According to a review by Bateson and Schwartz, the susceptibility of children to the effects of air pollution is multifactorial and includes the following.<sup>5</sup> 1) Children have different rhythmic patterns of breathing than adults. 2) They are predominantly mouth-breathers, thereby bypassing the filtering effects of the nasal passages. This allows pollutants to travel deeper into the lungs. 3) They have a larger lung surface area per unit weight than adults. 4) They spend more time out of doors, particularly in the afternoons and during the summer months when ozone and other pollutant levels are the highest. 5) Children also have higher ventilation rates. i.e., volume of air per minute per unit body weight compared to adults. 6) When active, children may ignore early symptoms of an asthma exacerbation and fail to seek treatment, leading to attacks of increased severity. There are other factors that are important. The diameter of the airways in children is smaller than in adults and therefore airways may be more susceptible to the effects of the airway narrowing that is characteristic of asthmatic attacks. These factors, combined with the possible adverse impact of pollutants on lung development and the immaturity of enzyme and immune systems that detoxify pollutants, may all contribute to an increase in the sensitivity of children to pollutants produced by burning coal.<sup>6</sup>

### **CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), CHRONIC BRONCHITIS AND EMPHYSEMA**

Asthma is a reversible condition. When permanent damage to the airway occurs, a chronic obstructive airway condition is present.

COPD is a condition characterized by narrowing of the airway passages. Unlike asthma, these changes are permanent rather than reversible.

Like asthma, exposures to pollutants that produce an immunological response are critical in the pathogenesis of the condition. The response in larger airways is referred to as chronic bronchitis. A cough that produces sputum is characteristic of chronic bronchitis. In the alveoli, the inflammatory response leads to a destruction of tissue, or emphysema. These two conditions usually co-exist. Exacerbations of COPD may be triggered by pollutants or infections. Although current and ex-smokers account for 80–85% of all patients with COPD, exposure to air pollutants, including those that are produced by burning coal, plays an important role in the pathogenesis of acute exacerbations and the development of COPD.

### **PULMONARY INFLAMMATION AND AIR POLLUTANTS**

Inflammation of pulmonary tissues is a critical element in the pathophysiology of illness caused by air pollution. Reactive oxygen species, such as free radicals and oxygen ions, appear to be central to this process. To avoid some of the difficulties associated with in vitro studies, several investigators have studied the response to particulate pollution in experimental animals. Roberts, et al., instilled particles into the lungs of rats treated with a compound (dimethylthiourea) that is believed to blunt the response to reactive oxygen species.<sup>7</sup> After treatment, the lungs of the animals were lavaged (rinsed with saline) and biomarkers of pulmonary injury were measured. Treated animals exhibited less evidence of damage to their lungs such as toxicity to cells, cytokine gene expression (genes that control cellular communications), pulmonary inflammation and other markers of pulmonary injury. In a subsequent study, Rhoden, et al., instilled standardized urban air particles (active agent) or saline (placebo control) into the lungs of rats.<sup>8</sup> Half of the animals in each group were treated with a reactive oxygen species inhibitor. Pretreatment with the inhibitor blocked the deleterious effects of the particles, as shown by reductions in several markers of pulmonary inflammation. These studies show that common

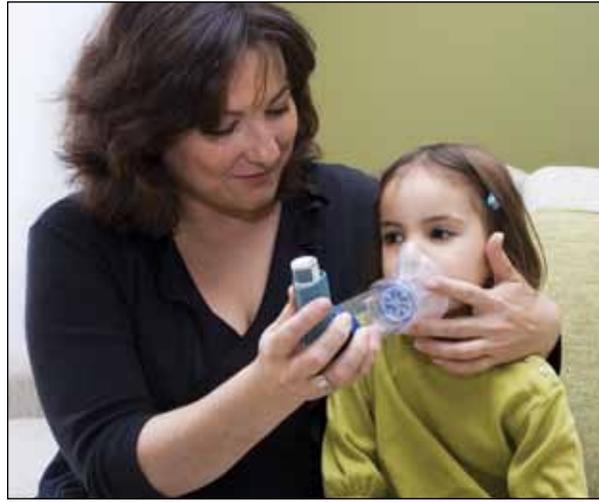
air pollutants such as particulates interfere with a variety of basic cellular mechanisms and dispose to the development of inflammation, a process that leads to diseases such as asthma, COPD, and emphysema.

These two studies are representative of many that have been performed using a variety of agents and techniques. Although performed in animals and not humans, they are consistent with a larger body of scientific evidence that helps establish a cause-and-effect relationship between particulates and pulmonary disease. As noted above, inflammation is a critical element in the pathogenesis of attacks of asthma and exacerbations of COPD. It matters little whether the inflammation is caused by particulates or other pollutants.

Additional evidence to support the hypothesis that air pollutants produce oxidative stress is derived from many studies. Recently, Fitzpatrick, et al., studied 65 children with severe asthma, including 35 with a reduction in baseline airway function as shown by a forced expiratory volume of less than 80% of that predicted, i.e., their ability to move air rapidly out of the lung was impaired.<sup>9</sup> Bronchoalveolar lavage (rinsing the airway with saline) was performed and metabolites and enzymes related to oxidative stress were measured. In the asthmatics, the concentration of glutathione, an antioxidant that protects cells from free radicals, was reduced and the concentration of the oxidized form (glutathione disulfide) was increased. This made the children less able to withstand oxidative stress and more susceptible to the development of an asthmatic attack.

### OZONE, AIR POLLUTION, AND ASTHMA

Ozone, a highly reactive gas that consists of three atoms of oxygen ( $O_3$ ), is formed by the reaction of volatile organic compounds (VOCs) with oxides of nitrogen ( $NO_x$ ) in the presence of sunlight. Coal combustion does not produce ozone directly, but both the  $NO_x$  and the VOCs released by coal plants are essential contributors to the formation of ground-level ozone, the primary ingredient in urban smog. Ozone is a powerful oxidizing agent



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that irritates the lungs at concentrations typically encountered in urban settings, particularly in summer months. There are many studies linking increases in ozone to asthma and other pulmonary diseases (see Trasande and Thurston for review<sup>10</sup>).

One of the most compelling studies linking ozone with asthma exacerbations was performed by Gent, et al.,<sup>11</sup> who examined the effects of relatively low ozone levels on asthmatic children. Those authors conducted a prospective cohort study of 271 children younger than 12 who had physician-diagnosed asthma. The children were divided almost equally into groups who did or did not use daily maintenance medications. Rigorous statistical techniques were used to examine the relationship between ozone levels below EPA standards, respiratory symptoms, and the use of rescue medications as charted by the children's mothers on daily calendars. The authors found a significant association between ozone levels and symptoms, as well as the use of rescue medications in the children who used daily maintenance medications. No significant relationships were found between ozone levels and symptoms or medication use in the children who did not take daily maintenance medications. Thus, it appears that the threat to children posed by ozone is greatest among those with severe asthma, even when ambient ozone levels fall within the limits set by the EPA to protect public health.

Peel, et al., studied the relationship between a one standard deviation increase in ambient air pollutant levels and emergency room visits for various respiratory problems, including asthma.<sup>12</sup> They found the strongest association between increases in 24-hour PM<sub>10</sub> levels, 24-hour increases in 10–100 nm particle concentrations, and 1-hour NO<sub>2</sub> concentrations and asthma attacks that occurred six to eight days after the peak. There were shorter delays between peaks of PM<sub>10</sub>, ozone, NO<sub>2</sub>, and carbon monoxide and emergency room visits for upper respiratory infections. During warm months, there was a 2.6% increase in asthma admissions after a 25 ppb increase in the ozone concentration. To give the 25 ppb increase perspective, the EPA eight-hour exposure standard in 2008 was set at 75 ppb. This study is one of many that establish a statistically rigorous link between a peak in the concentration of an air pollutant and the onset of a disease or disease symptom.

The evidence linking ozone levels to the development of asthma is less compelling than that linking ozone to asthma exacerbations. Gilmour, et al., reviewed five studies that address this issue.<sup>13</sup> A Dutch study of over 4,000 children enrolled at birth and followed for two years, focused on NO<sub>2</sub> and PM<sub>2.5</sub> attributed to traffic, found small but statistically significant associations between pollutant peaks and the development of symptoms of asthma.<sup>14,15</sup> Although this study focused on traffic as the source of the pollutants, burning coal can't be ignored as a source of NO<sub>2</sub> and PM<sub>2.5</sub>. There were similar results from a second study of children in that age group from the Netherlands, Germany, and Sweden. The Children's Health Study of more than 6,000 children from southern California evaluated a wide range of ozone, particulates, oxides of nitrogen, and acids.<sup>16</sup> A significant association between ozone and asthma was confined to those children who participated in three or more sports. This result may be the consequence of the increases in the amount of air breathed per unit of time associated with exercise and the consequent

increases in exposure to pollutants. Gilmour, et al., conclude that the results of all five of the studies they reviewed "support a modest increase in the risk for air pollution in relation...to asthma."<sup>17</sup>

The increase in susceptibility to pollutants

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*Increases in the risk of death from respiratory causes, including sudden infant death, were correlated with the concentration of PM<sub>10</sub> and NO<sub>2</sub>.*

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among children appears to translate into pollution-related increases in infant mortality. Ritz, et al., reported increases in the risk of death from respiratory causes, including sudden infant death, with rises in the concentration of carbon monoxide, PM<sub>10</sub>, and NO<sub>2</sub>.<sup>18</sup> Bateson and Schwartz also cite a study reporting between 4 and 7 fewer infant deaths per 100,000 live births with a reduction in the concentration of total sus-

pending particles of 1 µg/m<sup>3</sup>.<sup>19</sup> To give this number perspective, Pope, et al., reported that there was a mean reduction in the PM<sub>2.5</sub> concentration of 6.52 ± 2.9 µg/m<sup>3</sup> in major U.S. metropolitan areas in the time interval between 1979–83 and 1999–2000.<sup>20</sup>

## AIR POLLUTION AND COPD

Smoking tobacco is the most important risk factor for the development of COPD. Most authors report that approximately 85% of all cases of COPD can be attributed to this single, preventable cause. Data that have emerged during the past several years have shown that there is a smaller but important link between air pollution, including pollutants produced by burning coal, and the subsequent development of COPD exacerbations.

In a study of the residents of Helsinki, Finland, where coal-derived air pollutants account for a relatively small portion of total pollutant levels, pooled asthma and COPD emergency room visits increased on those days when there were increases in PM<sub>2.5</sub>, coarse particles, and gaseous pollutants.<sup>21</sup> The Atlanta, Georgia, study of Peel, et al., found that when NO<sub>2</sub> or carbon monoxide increased by one standard deviation, emergency room visits for COPD increased by 2–3%.<sup>22</sup> Finally, in a study of hospitalization rates among Medicare enrollees, a 10 µg/m<sup>3</sup> increase in the concentration of PM<sub>2.5</sub>

particles was associated with a same-day increase in COPD admissions of 2.5% (95% confidence interval (CI) = 2.1–3.2%).<sup>23</sup> These three studies of three different populations using different criteria all link increases in air pollutants to increases in exacerbations of COPD. Although they did not focus on pollutants derived exclusively from the combustion of coal, the pollutants they studied included those produced by coal burned by electrical utilities as well other sources.

## LUNG CANCER

The National Cancer Institute estimates that in 2008 there were 215,020 new cases of lung cancer, the leading U.S. cancer killer in both men and women, with 161,840 deaths. While smoking tobacco, radon and other radioactive gases, second-hand smoke, asbestos, arsenic, nickel compounds, and other airborne organic compounds have been identified as risk factors for developing lung cancer, data from three large epidemiological studies show that air pollution may also be a risk factor.

First among these was a study of Seventh Day Adventists who lived in California.<sup>24</sup> This cohort of over 6,300 non-smoking white adults was followed from 1977 to 1992 and monitored for the development of lung cancer. These data were combined with monthly ambient air pollution data in various zip codes. For men, the interquartile range (the middle 50% of the range) increase for ozone of 100 ppb was associated with an increase in the relative risk (RR) for lung cancer of 3.56 (95% CI = 1.35–9.42). Lung cancer increases were also associated with significant increases in PM<sub>10</sub> (RR = 5.21, 95% CI = 1.94–13.99) and for SO<sub>2</sub> (RR = 2.66, 95% CI = 1.62–4.39). Smaller increases among women were also found, however only the association with SO<sub>2</sub> was statistically significant. The difference between men and women was thought to be due to greater exposures among men.

In the Harvard Six Cities study, lung cancer death was positively associated with air pollution. The adjusted mortality rate ratio due to lung cancer for the most to least polluted cities was 1.26 (95% CI = 1.08–1.47).<sup>25,26</sup>

Complementary data were found in the American Cancer Society study.<sup>27</sup> This epidemiological study began with 1.3 million adults in 1982. From that set, approximately 500,000 adults were matched with air pollution data for their appropriate metropolitan area and vital statistics data through the end of 1998. Fine particulate increases of 10 µg/m<sup>3</sup> were associated with an 8% increase in lung cancer mortality. Increases in the concentration of oxides of sulfur were also associated with increases in lung cancer mortality.

These three large prospective epidemiological studies provide evidence that air pollution, particularly that due to particulates and ozone, may affect mortality due to lung cancer. Since some of the pollutants studied are formed directly or indirectly as the consequence of burning coal, it is possible that burning coal places those exposed to coal-related pollutants at greater risk for developing lung cancer.

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