



Progress Sometimes Leads to Problems

Interactions May Be More Important Than Direct Effects

Dr. Peden suggested that the interaction between environmental air pollutants and allergic respiratory diseases may be complex and bidirectional. Independently, each has the potential to activate parts of the inflammatory cascade in tissues. Data suggest that pre-existing allergic inflammation may make patients more sensitive to inhaled pollutants, and exposure to pollutants may modify the allergic response. Although investigators are examining a number of potential environmental toxins, most of the evidence suggesting an

important association with asthma comes from studies of ozone and diesel exhaust particles.

Ozone Is a Potent Inflammatory Stimulus

Ozone is a major component of heavy smog. According to the US Environmental Protection Agency, more than 50% of the United States population lives in counties where levels of ozone exceed the primary National Ambient Air Quality Standards. John R. Balmes, MD,[2] Professor of Medicine, University of California San Francisco, reviewed some of the important biologic effects of ozone. Ozone is a nonspecific stimulus to inflammation, and, if given in sufficiently high concentrations, it will produce airway inflammation in all subjects. In nonatopic, nonasthmatic subjects, the airway response is mostly neutrophilic; in asthmatics, the response is exaggerated and may also include eosinophils.[3]

Allergen Exposure Is Worse After Ozone

When an allergen is delivered into the nose or lower airways following exposure to ozone, the response is greater than when the allergen is given alone. After ozone, less allergen is required to produce a predetermined degree of bronchoconstriction, and eosinophil influx is greater.[4] These observations may explain why hospital and emergency department admissions for asthma and medication use increase after exposure to ozone. Of interest, when traffic in Atlanta was rerouted because of the 1996 Summer Olympics, peak ozone levels decreased by approximately 25% and asthma care decreased by 20% to 40%.[5]

Chronic Ozone Exposure May Produce Chronic Disease

Little is known about the effects of chronic exposure to ozone. Although the bronchoconstrictor and inflammatory response to repeated (multiday) exposures in the laboratory diminishes over time, epidemiologic data suggest that chronic exposure may lead to airway remodeling. Kunzli and colleagues[6] found that freshman at the University of California at Berkeley who grew up in Southern California, where ozone levels were frequently high, had evidence of "small airways dysfunction" (ie, decreased airflow rates at mid and low lung volumes) that was not found in students who grew up in Northern California.

Similar results were obtained in a study at Yale.[7] Finally, there are provocative new data suggesting that ozone exposure may be linked to the

development of asthma. McConnell and associates[8] reported a higher risk for new-onset asthma in children who lived in a community where ozone levels were frequently elevated and who played 3 or more sports. Outdoor exercise, because it results in increased minute ventilation, will increase deposition of environmental pollutants in the lower airways and may increase the effect of a given level of ozone.

Diesel Exhaust May Have Unique Properties

Dr. Peden and David Diaz-Sanchez, PhD,[9] Assistant Professor of Medicine, University of California Los Angeles, reviewed the evidence suggesting that diesel exhaust may be important for the development of asthma. Perhaps the association is only coincidental, but the increase in the prevalence of asthma and allergy over the last 30 years is paralleled by an increase in the use of diesel trucks. Epidemiologic studies describe a greater prevalence of hay fever in residential areas with heavy truck traffic. [10] Diesel exhaust particles increase cellular influx and inflammatory mediators (especially the "proatopic" TH2 cytokine products) in nasal tissues and potentiate the immunoglobulin (Ig)E response[11] --effects that may exacerbate pre-existing allergy. Perhaps of more importance, diesel exhaust particles appear to affect the primary immune response. Thus, humans immunized with keyhole limpet hemocyanin (KLH) alone produced IgG and IgA responses and had no allergic symptoms. Those immunized with diesel exhaust particles and KLH together produced IgE and developed allergic symptoms.[12] Taken together, these data suggest that diesel exhaust may sensitize individuals to develop allergic disease and also has the potential to make that disease worse.

Are There Genetic Factors That Determine Susceptibility?

One of the most fascinating aspects of the studies of airway effects of air pollutants is the variability of response between individuals. Even in carefully controlled laboratory studies, there is a wide distribution of responses that includes some nonresponders and some subjects with huge responses.[13] When individuals are retested, their individual response is reproducible (ie, sensitive individuals remain sensitive; resistant individuals remain resistant). Although the etiology of these differences is not known, Steven R. Kleeberger,

PhD,[14] of the Bloomberg School of Public Health at Johns Hopkins University, Baltimore, Maryland, reviewed recent data searching for a genetic basis for this susceptibility. Using positional cloning and candidate gene approaches, investigators have found loci on chromosomes 4, 11, and 17 that may determine susceptibility to inhaled ozone. If confirmed, this will provide important clues regarding the effects of ozone. It may also be useful in counseling patients regarding the risks of specific occupations and geographic areas.

What Can We Do ?

Although there are many aspects of the interactions between these environmental pollutants and lung health that are still not fully understood, there is much that is known. Ozone and diesel exhaust particles can potentiate allergic responses and may play a direct role in initiating airway disease.

Minimizing exposure to these substances is the best approach, and enforcement of existing air quality standards is important. The United States Clean Air Act established National Ambient Air Quality Standards that are intended to protect all susceptible groups in the population. These standards are based mostly on acute effects. If studies suggesting that long-term exposure may be important in sensitizing individuals or contributing to remodeling are correct, these standards may have to be adjusted downward. Similarly, most standards do not take into account the increased burden of air pollutants delivered under conditions of increased ventilation (heavy work or exercise). The existing standards should be viewed as a minimum; more recent studies suggest the need for more stringent controls.

Until air quality standards are achieved, susceptible individuals should be cautioned to avoid exposure and exercise on bad air days, In those with underlying asthma and allergic diseases, therapy aimed at reducing underlying inflammation will minimize the effects of environmental exposures.

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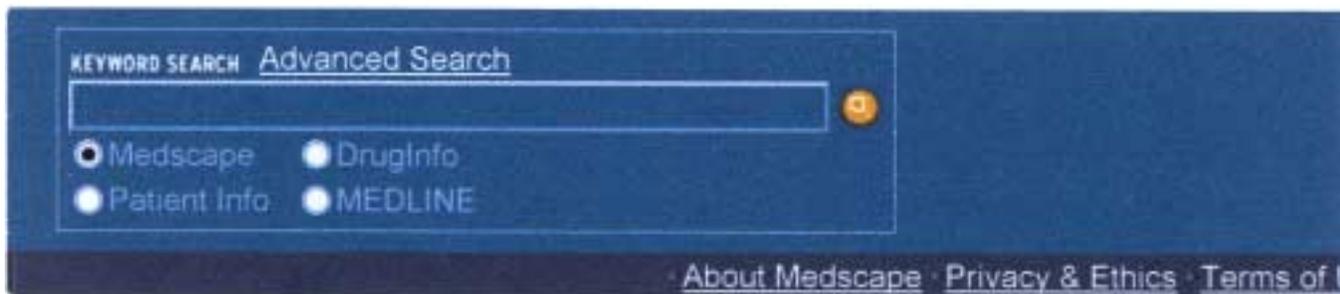
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The paradoxical mechanism by which ozone (a potent oxidant) can induce an antioxidant response, is currently demonstrated not only at a proteomic level, but also at a genomic one. Ozone at therapeutic dose modulates the nuclear factor Nrf2 and Nfĳ^ĳB and induces the re-equilibrium of the antioxidant environment.⁵³⁻⁵⁸ Oxidative stress and innate immunity have a key role in lung injury pathways that control the severity of acute lung injury during viral infections like SARS.⁵⁹ Although ozone is a weak inducer, the reinfused lymphocytes and monocytes, by migrating through the lymphoid system, can activate other cells that, in time, will lead to a stimulation of the immune system. Glucocorticoids limit acute lung inflammation in concert with inflammatory stimuli by induction of SphK1. Article. Full-text available. Jul 2015. Sabine Vettorazzi. Acute lung injury (ALI) is a severe inflammatory disease for which no specific treatment exists. As glucocorticoids have potent immunosuppressive effects, their application in ALI is currently being tested in clinical trials. However, the benefits of this type of regimen remain unclear. Here we identify a mechanism of glucocorticoid action that challenges the long-standing dogma of cytokine repression by the glucocorticoid receptor. Ozone is a gas found in the atmosphere in very trace amounts. Depending on where it is located, ozone can be beneficial ("good ozone") or detrimental ("bad ozone"). On average, every ten million air molecules contains only about three molecules of ozone. Indeed, if all the ozone in the atmosphere were collected in a layer at Earth's surface, that layer would only have the thickness of three dimes. But despite its scarcity, ozone plays very significant roles in the atmosphere. In fact, ozone frequently "makes headlines" in the newspapers because its roles are of importance to humans and other life on Earth.