

Inhaled Environmental/Occupational Irritants and Allergens: Mechanisms of Cardiovascular and Systemic Responses

Donovan B. Yeates¹ and Joe L. Mauderly²

¹Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; ²Lovelace Respiratory Institute, Albuquerque, New Mexico, USA

<http://ehpnet1.niehs.nih.gov/docs/2001/suppl-4/479-481/yeates/abstract.html>

The articles in this monograph focus on the mechanisms whereby ambient particulate matter (PM) and co-pollutants deposited in the respiratory tract cause cardiovascular and systemic effects, especially in persons with preexisting conditions such as allergic hyper-responsiveness and pulmonary, cardiac, and vascular diseases. During the past few years, it has become clear that inhaled pollutants cause adverse effects outside the respiratory tract and that these effects may in some cases be more important than respiratory effects. Investigators pursuing traditional approaches to understanding mechanisms of air pollution effects need to be brought together with those outside that community who have expertise in pathogenetic mechanisms by which deposited air pollutants might affect nonrespiratory organs. To this end, a workshop was held and papers were developed from a broad range of scientists having specialized expertise in allergic and cardiovascular physiology. The overall goal of this monograph is to benchmark current thinking and enhance progress toward identifying and understanding the mechanisms by which nonrespiratory health effects occur and, by extension, to facilitate the appropriate management of relationships between air quality and health. This monograph contains a compilation of multidisciplinary research that forms a framework for generating and testing plausible new research hypotheses. Not only will this information stimulate the thinking of researchers, but it will also provide an improved foundation for funding agencies and advisory groups to frame research strategies, programs, and priorities.

Epidemiologic studies continue to confirm links between inhaled materials and nonrespiratory effects. The associations between adverse health outcomes and inhalation of airborne particles and co-pollutants are summarized by Dockery (1). He notes that although the relative risks for effects of particles are greater for respiratory than for cardiovascular deaths, the actual numbers of deaths are greater for cardiovascular than for respiratory causes. Increased air pollution can decrease heart rate variability as well as increase cardiac arrhythmias, especially in the elderly (1). The effects can occur quickly. Dockery found an increased risk of myocardial infarction 1–2 hr

as well as 1–2 days following elevations in particulate matter with a mass median aerodynamic diameter less than 2.5 μm ($\text{PM}_{2.5}$). These results are separable and additive, suggesting that particles affect cardiovascular function by more than one mechanism. Goldberg et al. (2) show that daily mortality increases linearly as concentrations of particles increase for individuals who had acute lower respiratory diseases, chronic coronary artery disease (especially the elderly), and congestive heart failure.

A critical analysis of selected epidemiologic evidence linking inhalation of airborne particles and co-pollutants to cardiovascular disease is presented by Morris (3). He points out that classifying disease too broadly may reduce the magnitude of the adverse health effects of inhaled particles and that estimates of both the magnitude and time of these effects are very susceptible to the model employed. Both Goldberg et al. (2) and Morris (3) note that the inclusion of co-pollutants in models generally reduces the apparent effects of particles—an important but not surprising result. Gwynn and Thurston (4) report that, for multiple reasons, the socially disadvantaged and minorities have a higher relative risk for the adverse effects of air pollution. Walker et al. (5) note that air pollutants can cause nose and eye irritation, headache, and difficulty in concentration. They suggest that these effects may be widespread and could have a large economic impact. Clearly, more research is needed on these quality of life issues and the impact on human health and productivity.

Laboratory and clinical studies further demonstrate that inhaled pollutants deposited in the respiratory tract can cause significant cardiovascular and systemic responses. Yeates et al. (6) show that histamine, a mediator released during allergen and ozone challenges to the bronchial or alveolar regions of the lungs, can cause decreases in blood pressure and deterioration of blood gases. They also demonstrate that even as little as microgram quantities of ragweed allergen deposited in the bronchi or alveoli of ragweed-sensitized dogs can precipitate anaphylactic reactions, leading to profound decreases in heart rate and blood pressure. Watkinson et al. (7) demonstrate that exposure of rats to a variety of inhaled

pollutants can result in significant decreases in heart rate and core temperature, along with secondary decreases in related parameters such as cardiac output, blood pressure, and ventilation. They suggest that these responses may be mediated via either humoral or neural pathways. Although the time courses of the observed responses are consistent with epidemiologic findings of pollution-induced increases in mortality in humans, the relevance of these responses and their mechanisms to humans has yet to be established.

Donaldson et al. (8) present a paradigm whereby ultrafine particles, especially those containing transition metals, may give rise to oxidative stress and through low density lipoprotein oxidation destabilize atheromatous plaques, which leads to an ischemic event. Alternatively, particle-induced activation of nuclear factor kappa B and the subsequent release of cytokines affect the liver to increase coagulation and thus gives rise to an ischemic event. They present sufficient evidence to support these hypotheses and to warrant further research on each of the steps involved. A framework for assessing the cardiovascular consequences of inhaled pollutants in humans is proposed by Frampton (9), and approaches to analyzing the electrocardiogram for changes in autonomic and myocardial functions are proposed by Zareba et al. (10).

In our attempt to understand how inhaled materials cause responses outside the respiratory tract, it is becoming clear that some materials deposited on respiratory tract epithelia can be transported directly to other tissues and organs. The transport of gases, molecules, allergens, and particles across the bronchial and alveolar epithelia may result directly in systemic effects in the heart and other organs. Higenbottam et al. (11) report that inhaled nitric oxide (NO) has a remarkably rapid uptake in the lungs and can increase the mismatch of ventilation and perfusion (V/Q). Conversely, however, they propose that

Address correspondence to D.B. Yeates, Respiratory and Critical Care Medicine (M/C 788), University of Chicago (214 BGRC), 840 South Wood St., Chicago, IL 60672-7323 USA. Telephone: (312) 996-6464. Fax: (312) 996-1286. E-mail: yeates-d@uic.edu

Received 25 June 2001; accepted 4 July 2001.

delivery of NO in bolus form may result in a therapeutic decrease in pulmonary artery pressure while limiting V/Q mismatch. Wagner and Foster (12) report that relatively low molecular weight ^{99m}Tc -diethylenetriamine pentaacetate (^{99m}Tc -DTPA) (364 Da) deposited in the bronchi is removed via both the bronchial circulation and mucociliary clearance, with an average retention time of about 10 min. They propose that the rates of both of these clearance mechanisms depend on bronchial blood flow. Takenaka et al. (13) show that ultrafine silver particles deposited in the lungs at relatively low particle concentrations are cleared more rapidly than when instilled as agglomerates. The agglomerates were phagocytosed primarily by macrophages, whereas they propose that the more rapid clearance of the ultrafine particles was due to transport of both solubilized and particulate silver into the capillaries. It is not yet clear what portion of the silver found in the liver, kidney, and heart was translocated in particulate or solubilized form. Despite our limited understanding of the kinetics, this work suggests the plausibility of inhaled ultrafine particles giving rise to systemic responses by direct transport. Mattoli (14) demonstrates that allergens are transported across epithelia via intra- and intercellular mechanisms, with the epithelia in individuals with asthma having increased transepithelial allergen transport and processing characteristics at low concentrations of allergens compared to nonasthmatics. This provides additional mechanisms whereby persons with asthma maybe at increased risk of allergen-induced cardiovascular and systemic reactions.

Several investigators present evidence supporting the plausibility of the mediation of pollutant-induced effects via neural pathways. Exposures of animals to viruses, allergens, and tobacco smoke cannot only activate neural pathways but can also enhance the sensitivity and reactivity of neural reflex arcs. Carr and Undem (15) and Bonham et al. (16) give evidence for such neuroplasticity by showing the transformation of some neurons such that they acquire chemosensitivity. Both groups demonstrate that exposures can also increase the sensitivity of the central processing function of neural reflexes, thus providing an additional mechanism for the amplification of respiratory and cardiovascular effects. This information suggests several potential mechanisms whereby prior exposure to viruses, irritants, and allergens may result in increased risk, which is consistent with epidemiologic findings. However, inhibitory nerves may also play a modulatory role, as suggested by the finding that individuals with heart-lung transplant often have airway hyperresponsiveness (17). Whereas irritation of the upper respiratory tract can produce reflex hypertension,

Widdicombe and Lee (17) report that irritation of the lower respiratory tract can produce profound hypotension. Lee and Widdicombe (18) show that interactions between the chemosensitive C fibers and rapidly adapting pulmonary receptors modulate the physiologic responses resulting from the activation of these fibers. The C-fiber-initiated reflex pathways in the lungs can be sensitized by ozone and inflammation, likely due to the release of inflammatory mediators such as histamine and prostaglandin E_2 (PGE_2) (18). The neural pathways have been delineated better in animals than in humans. There is a pressing need to delineate in humans the cardiovascular consequences of irritants inhaled via the mouth and nose separately and together and to evaluate how these are affected by disease and compromised gas exchange.

Inhaled biogenic particles, ozone, and airborne PM can induce changes in airway epithelial cell function and cause inflammatory cells to migrate into the airways. Wagner et al. (19) demonstrate that in the rat, ozone causes mucous cell metaplasia in the nasal passages and endotoxin causes mucous cell metaplasia in the bronchial airways, with each toxicant enhancing the metaplastic lesions induced by the other toxicant. Neutrophils are implicated for part, but not all, of these pathogenic processes. This reciprocal potentiation of epithelial cell alterations by ozone and endotoxin extends the toxicologic profiles of both agents. On the basis of this information, it is likely that both ozone and endotoxin may also exacerbate the respiratory responses to other air pollutants. Harder et al. (20) report that 2-hr exposures of healthy persons to concentrated PM produces only minor increases in airway neutrophils. This suggests that either longer exposures and/or impaired cardiopulmonary function may be prerequisite to a more substantial inflammatory response or that the parameters measured are not markers for the events leading to death. Mattoli (14) proposes that the allergen-induced release of mediators from the epithelium may have cardiovascular consequences. Hastie and Peters (21) show that human bronchial epithelial cells obtained by brush biopsy and immersed in a medium of pH 5 for 3 hr causes an inhibition of the active area of ciliary activity. The recovery of ciliary activity improved in individuals with more severe disease. After segmental allergen challenge, patients with mild injury were not susceptible to an allergen-induced inhibition of ciliary activity nor to the 3 hr of acid exposure. These findings indicate the possible induction of protective responses linked to a heat shock protein induced by mild injury. This protective effect appears to be lost following severe injury (21). These findings highlight the importance of evaluating

disease- or pollutant-induced protective mechanisms.

Inhaled air pollutants can also cause problems by impairing host defenses. Castranova et al. (22) present data consistent with the hypothesis that inhalation of diesel exhaust particles increases susceptibility of the lungs to infection by depressing the antimicrobial potential of alveolar macrophages. This inhibitory effect appears to be due to the adsorbed organic compounds rather than the elemental carbon core of the diesel particles. Ultrafine particles may be of special concern. Beck-Speier et al. (23) demonstrate that agglomerates of ultrafine particles cause the release of cyclooxygenase products of arachidonic acid metabolism from alveolar macrophages at lower particle surface areas than those required for the release of the 5-lipoxygenase products. The surface area of the particles rather than the mass appears to be the critical factor. Although release of PGE_2 may have an anti-inflammatory modulatory effect on the inflammatory reaction induced by ultrafine particles, PGE_2 also has proinflammatory actions. Gilmour and colleagues (24) show that exposure to residual oil fly ash may lead to an increase in pulmonary immune response as well as an increase in the severity of allergic lung disease. These findings are consistent with the increase in susceptibility of subjects with infections and those who are allergic to inhaled particles and allergens.

Although biomarkers were not a focus of the articles in this monograph, their importance is noted by Dockery and several other authors. Dr. Jaffe presented a paper in which troponin, a biomarker for myocardial injury, was used to illustrate the steps necessary to validate a biomarker in terms of mechanisms, the required specificity of biomarkers and their potential utility in evaluating at-risk populations (25–27). Such an assay may have use by epidemiologists in studies of the delineation of the effects of air pollution on cardiovascular disease. The participants agreed on the importance of identifying and developing additional biomarkers of respiratory and cardiovascular stress and the adverse health effects of air pollution.

The articles in this monograph are only a sampling of the possible pathways and mechanisms whereby inhaled particles and co-pollutants may cause increased morbidity and mortality. However, these reports expand our insight into how previously inexplicable links might occur. This information should facilitate a continued iterative interaction between epidemiology and laboratory studies. The description of immunologic, neural, and humoral mechanisms whereby irritants and antigens deposited in the lungs can affect other organs may assist epidemiologists to

design studies targeting specific diseases, pathogenic mechanisms, or increases in sensitivity. In turn, more focused epidemiologic studies may enable laboratory and clinical scientists to direct their investigations toward identifying key mechanisms. Further work to identify and validate biomarkers signaling the activation of specific mechanisms would facilitate both population and laboratory studies. Together, these articles will serve the purpose of bringing a greater knowledge of the pathways and mechanisms involved in the adverse health effects of air pollution to the attention of investigators. It is hoped that this communication will also bring a broader range of disciplines to bear on the problem of inhaled particulate matter.

REFERENCES AND NOTES

- Dockery DW. Epidemiologic evidence of cardiovascular effects of particulate air pollution. *Environ Health Perspect* 109(suppl 4):483–486 (2001).
- Goldberg MS, Burnett RT, Bailar JC III, Tamblyn R, Ernst P, Flegel K, Brook J, Bonvalot Y, Singh R, Valois M-F, Vincent R. The identification of persons with cardio-respiratory conditions who are at risk of dying from the acute effects of ambient air particles. *Environ Health Perspect* 109(suppl 4):487–494 (2001).
- Morris RD. Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review of the evidence. *Environ Health Perspect* 109(suppl 4):495–500 (2001).
- Gwynn RC, Thurston GD. The burden of air pollution: impacts among racial minorities. *Environ Health Perspect* 109(suppl 4):501–506 (2001).
- Walker JC, Kendal-Reed M, Utell MJ, Cain WS. Human breathing and eye blink rate responses to airborne chemicals. *Environ Health Perspect* 109(suppl 4):507–512 (2001).
- Yeates DB, Mussatto DJ, Hameister WM, Daza A, Chandra T, Wong LB. Bronchial, alveolar, and vascular-induced anaphylaxis and irritant-induced cardiovascular and pulmonary responses. *Environ Health Perspect* 109(suppl 4):513–522 (2001).
- Watkinson WP, Campen MJ, Nolan JP, Costa DL. Cardiovascular and systemic responses to inhaled pollutants in rodents: effects of ozone and particulate matter. *Environ Health Perspect* 109(suppl 4):539–546 (2001).
- Donaldson K, Stone V, Seaton A, MacNee W. Ambient particle inhalation and the cardiovascular system: potential mechanisms. *Environ Health Perspect* 109(suppl 4):523–527 (2001).
- Frampton MW. Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. *Environ Health Perspect* 109(suppl 4):529–532 (2001).
- Zareba W, Nomura A, Couderc JP. Cardiovascular effects of air pollution: what to measure in ECG? *Environ Health Perspect* 109(suppl 4):533–538 (2001).
- Higenbottam T, Siddons T, Demoncheaux E. The direct and indirect action of inhaled agents on the lung and its circulation. Lessons for clinical science. *Environ Health Perspect* 109(suppl 4):559–5620 (2001).
- Wagner EM, Foster WM. The role of the bronchial vasculature in soluble particle clearance. *Environ Health Perspect* 109(suppl 4):563–565 (2001).
- Takenaka S, Karg E, Roth C, Schulz H, Ziesenis A, Heinzmann U, Schramel P, Heyder J. Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. *Environ Health Perspect* 109(suppl 4):547–551 (2001).
- Mattoli SW. Allergen-induced generation of mediators in the mucosa. *Environ Health Perspect* 109(suppl 4):553–557 (2001).
- Carr MJ, Udem BJ. Inflammation-induced plasticity of the afferent innervation of the airways. *Environ Health Perspect* 109(suppl 4):567–571 (2001).
- Bonham AC, Chen C-Y, Mutoh T, Joad JP. Lung C-fiber CNS reflex: role in the respiratory consequences of extended environmental tobacco smoke exposure in young guinea pigs. *Environ Health Perspect* 109(suppl 4):573–578 (2001).
- Widdicombe J, Lee L-Y. Airway reflexes, autonomic function, and cardiovascular responses. *Environ Health Perspect* 109(suppl 4):579–584 (2001).
- Lee L-Y, Widdicombe JG. Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators. *Environ Health Perspect* 109(suppl 4):585–589 (2001).
- Wagner JG, Hotchkiss JA, Harkema JR. Effects of ozone and endotoxin coexposure on rat airway epithelium: potentiation of toxicant-induced alterations. *Environ Health Perspect* 109(suppl 4):591–598 (2001).
- Harder SD, Soukup JM, Ghio AJ, Devlin RB, Becker S. Inhalation of PM_{2.5} does not modulate host defense or immune parameters in blood or lung of normal human subjects. *Environ Health Perspect* 109(suppl 4):599–604 (2001).
- Hastie AT, Peters SP. Interactions of allergens and irritants in susceptible populations in producing lung dysfunction: implications for future research. *Environ Health Perspect* 109(suppl 4):605–607 (2001).
- Castranova V, Ma JYC, Yang H-M, Antonini JM, Butterworth L, Barger MW, Roberts J, Ma JKH. Effect of exposure to diesel exhaust particles on the susceptibility of the lung to infection. *Environ Health Perspect* 109(suppl 4):609–612 (2001).
- Beck-Speier I, Dayal N, Karg E, Maier KL, Roth C, Ziesenis A, Heyder J. Agglomerates of ultrafine particles of elemental carbon and TiO₂ induce generation of lipid mediators in alveolar macrophages. *Environ Health Perspect* 109(suppl 4):613–618 (2001).
- Gilmour MI, Daniels M, McRillis RC, Winsett D, Selgrade MJK. Air pollutant-induced respiratory disease on experimental animals. *Environ Health Perspect* 109(suppl 4):619–622 (2001).
- Jaffe AS. 2001—a biomarker odyssey. *Clin Chim Acta* 284(2):197–211 (1999).
- Jaffe AS, Ravkilde J, Roberts R, Naslund U, Apple FS, Galvani M, Katus H. It's time for a change to a troponin standard. *Circulation* 102(11):1216–1220 (2000).
- Ottani F, Galvani M, Nicolini FA, Ferrini D, Pozzati A, Di Pasquale G, Jaffe AS. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. *Am Heart J* 140(6):917–927 (2000).