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EMPHYSEMA AND FIBROSIS: RISK FACTORS IN RESPONSIVENESS TO AIR POLLUTION

Daniel L. Costa, Sc.D. and James R. Lehmann, M.S.

Medical Department
Brookhaven National Laboratory
Upton, New York 11973

In his essay on why only certain individuals contract infectious disease when exposed to a pathogen, Professor Evans of Yale (1982) refers to a short story by O. Henry entitled "The Third Ingredient." In the story a poor young woman with but a piece of beef and a young, fledgling artist with only a potato combine their assets in an attempt to make beef stew. However, they soon realize that the simple combination of those two ingredients is not palatable. As any Irishman knows, a "third ingredient", an onion, is necessary to bring forth these basic components into a tasty meal. Evans relates that just as beef stew requires this "third ingredient", the initiation of infectious disease is critically dependent on factors intrinsic to the host. Similarly, the single interaction of "host" and "toxicant", particularly at present-day environmental concentrations, does not inevitably result in an "adverse response." While there is little argument that exposure concentration or dose is the primary determinant of response, other factors, often unique to the individual exposed, play a major role in determining at what dose that individual will experience the toxic adversity and, on occasion, even the type of response.

The Clean Air Act of 1970 specifically states that the primary air standards protect public health in its entirety by incorporating safety margins adequate to avoid adverse responses even in susceptible subgroups of the population. Therefore, the Act assumes the existence of "no-effect" levels for each regulated pollutant; i.e., there exists a threshold below which no adverse response is expected anywhere in the public domain (Finklea, 1973). By the application of "adequate" margins of safety to no-effect levels for the large majority of the "normal" population, the health of susceptible or high-risk groups is thought to be ensured indirectly in spite of the lack of quantitative knowledge of their responsiveness to any of the regulated pollutants.

With a highly heterogeneous population, the assumption of a single threshold is, of course, a statistical illusion. A threshold is most relevant for use with well-defined homogeneous populations or for cost-benefit analyses. If desired, however, thresholds can be derived for each risk segment of the population and, ultimately, even for individual persons (Calabrese, 1978). Thus, when legislation is enacted which philosophically endeavors to protect those who reside at the sensitive tail of the dose-response distribution curve, categorical identification and characterization of hyperresponsive individuals can greatly enhance the effectiveness and legitimacy of imposed standards while minimizing health and economic calamity.

The catastrophic incidents of high air pollution in the Meuse Valley, Donora, London, Pittsburgh, and elsewhere, provide the clearest evidence of the impact of air pollution on health, particularly among the very young, the old, and those with impaired cardiopulmonary health (Table 1). Mortality was highest in this latter group in each episode. Overall, the impact of the first day or two of pollution seemed to most heavily bear on those with cardiovascular disease. Pulmonary-based deaths generally increased during day two and three and persisted throughout the high pollution period (Calabrese, 1978).

TABLE 1. CLASSIC EPISODES[a] OF AIR POLLUTION AND MORTALITY

Event	Effect and Number	Estimated Pollutant Concentrations
Meuse Valley Belgium, 1930	60 deaths; breathlessness, chest pain, irritation	> 10 ppm SO_x 12.5 mg/m^3 particles
Donora, PA 1948	17 deaths, irritation respiratory symptoms 6000/14000 ill	0.5-2.0 ppm SO_x 200 µg/m^3 Zn and SO_4 = particles
London England, 1952	4000 deaths; hospitalization for bronchitis, bronchopneumonia and heart disease	1.4 ppm SO_x 4.5 mg/m^3 smoke
New York, New York[b], 1963	24% excess deaths, upper respiratory discomfort, cardiac and asthma related deaths	0.44 ppm SO_x 800 µg/m^3 smoke
Pittsburgh, PA[b] 1975	9% excess deaths and discomfort among those with cardiopulmonary disease	0.07 ppm SO_x 900 µg/m^3 smoke

[a] Calabrese (1978).
[b] Lipfert (1980).

In London, the excess mortality was attributed mainly to bronchitis and pneumonia, while in New York City, upper respiratory and cardiac disorders and asthma-originated deaths prevailed (Higgins and Ferris, 1973). In Donora, in 1948, 80% of those individuals with previously documented histories of heart disease or chronic bronchitis became ill during the four days of high pollution (Schrenk et al., 1949). Moreover, when these affected pulmonary patients were monitored over the following 10 year period, their mortality and morbidity rates were significantly higher than was predicted (Ciocco and Thompson, 1961). Thus, acute air pollution stress appears to have both immediate and long-term, progressive health implications for the pulmonary-compromised public.

With varying success, epidemiological studies performed since the early air pollution disasters have correlated patterns of public mortality and morbidity with variations in specific pollutant levels (Higgins and Ferris, 1973; Finklea et al., 1974; Lipfert, 1980). Although many studies generally are not designed to assess potentially sensitive subgroups of the study populations, re-analysis of data often reveals marked correlations between the responsiveness of specific subpopulations and pollutant levels (Carnow et al., 1969; Finklea et al., 1974; Zagraniski et al., 1979). Investigations purposely designed to evaluate purported susceptible groups (Table 2), such as bronchitics, asthmatics, and other chronic cardiorespiratory patients, have provided more direct evidence of subgroup sensitivities to atmospheric pollutants (Lawther et al., 1970; Burrows et al., 1968; Holland et al., 1979).

TABLE 2. EPIDEMIOLOGY OF PULMONARY PREDISPOSITION TO THE EFFECTS OF AIR POLLUTION

Investigators	Pollutant	Findings
Carnow et al. (1969)	SO_2	Elderly males with moderately severe bronchitis experienced exacerbated symptoms when [SO_2] neared 0.25 ppm
Lawther et al. (1970)	SO_2 and smoke	Bronchitics suffered in winter; complaints declined with improved air conditions
Finklea et al. (1974)	SO_x and particles	Pre-existing pulmonary disease pre-dispose to air pollutant response
Lipfert (1980)	SO_x and particles	Particulate matter had better association with mortality in impaired individuals

Unfortunately, even the best designed epidemiological studies often yield only relatively non-specific risk estimates. Variations in health frequently relate better to air pollution in general or other associated variables such as weather, and thus provide minimal evidence to implicate specific contaminants or contaminant groups. Thus, clinical studies have grown increasingly important in the study of susceptible groups, since they allow the controlled exposure of well-characterized patients to specific air pollutants or defined complex atmospheres. To date, clinical studies have emphasized hyper-reactive airway diseases, such as asthma, with the rationale that these individuals will have the greatest responsiveness to airway irritants (Gaudio, 1980; Abraham, 1982; Bethel et al., 1983; Holtzman et al., 1983). Other chronic pulmonary diseases have received less investigative attention in spite of several functional deficiencies which would suggest that these impaired lungs would be less able to accommodate air pollution stress. Ventilation, perfusion, and diffusion abnormalities, loss of functional reserve or compensatory capability, as well as mechanical (work) stress on the cardiopulmonary system could all contribute to enhanced susceptibility.

The few published clinical studies suggest only weakly that COPD patients suffer some degree of pulmonary adversity when exposed to single or complex oxidant atmospheres (Table 3). While improvement in the performance of pulmonary function tests (PFT's) upon prolonged removal from highly polluted smog atmospheres indirectly indicates pollutant-exacerbated cardiopulmonary stress (Motley et al., 1959; Balchum, 1973), the distinctiveness of these improvements is difficult to assess due to inherently weak statistical comparisons and the variable response of so-called "normal" control populations (Balchum, 1973). Even the best controlled patient studies with single oxidant exposures, which similarly show small changes in normal respiratory function yield evidence of stress of uncertain biological significance or distinction from normal response (von Nieding and Wagner, 1979; Solic et al., 1982).

Particles, on the other hand, when inhaled by the diseased or impaired lung will deposit preferentially in partially obstructed airways where airflow is most turbulent (Table 4). Thus, deposition of inhaled particles is altered both qualitatively and quantitatively, at least in specific regions of the lung, in apparent concert with airway dysfunction and disease. Though the data are absent in this regard, responsiveness of non-asthmatic COPD patients to particulate irritants may be expected to be acutely enhanced due to more central airway deposition similar to that reported for asthmatics (Cohen et al., 1972).

TABLE 3. RESPONSE OF THE IMPAIRED HUMAN LUNG TO ATMOSPHERIC CONTAMINANTS

Inhalation Challenge	Pulmonary Disability	Findings
Los Angeles Smog[a] (2-4 days)	COPD	- Improved PFT's after ~40 hrs in clean air
Los Angeles Smog[b]	COPD	- Marginal improvement in PFT's with low pollution
Los Angeles Smog[c] (alternate weeks with clean air)	COPD	- PaO_2 and R_{aw} improved during clean air periods
NO_2-air mixtures[d] (0.5 to 8.0 ppm, 15 to 60 min.)	Chronic non-specific lung disease (would include asthmatics)	- > 21.5 ppm, 5 min, ↑ R_{aw} - 4 ppm, 15 min, ↓ PaO_2
O_3-air mixtures[e] (0.2 ppm, 2 hrs)	COPD (non-reversible)	- 11/13 patients showed small decrement in Hb saturation

[a] Motley et al. (1959).
[b] Schoettlin (1962).
[c] Balchum (1973).
[d] von Nieding and Wagner (1979).
[e] Solic et al. (1982).

TABLE 4. PARTICLE DEPOSITION IN THE IMPAIRED HUMAN LUNG

Aerosol Challenge	Pulmonary Disability	Findings
Dioctyl sebacate (1 μm)[a]	Coal workers with pneumononiosis; asymptomatic coal workers	- Correlation between deposition and small airway dysfunction
^{99m}Tc-polystyrene (5 μm)[b]	COPD	- Penetration α FEV_1; Enhanced central deposition
^{99m}Tc-Fe_2O_3 (1-5 μm)[c]	Bronchitis Smokers	- Altered deposition /retention (bronchitis>> smokers>>non-smokers)
^{85}Sr-polystyrene (3 μm)[d]	COPD Smokers	- Altered particle clearance rates: (COPD << smokers<ex-smokers ≐ non-smokers)

[a] Love and Muir (1976).
[b] Pavia et al., (1977); Agnew et al., (1981).
[c] Lippman et al., (1971).
[d] Bohning et al., (1976).

Hotspots of deposited particles may also be important in the ultimate pathogenesis of other pulmonary diseases such as bronchogenic carcinoma, as well. Moreover, reductions in particle clearance from the diseased lung would only be expected to exacerbate these problems (Bohning et al., 1976).

Because of ethical limitations in human exposure regimes and the need to understand the significance of predisposition to subacute and chronic toxicant stress, experimental studies in animal models of disease provide a realistic approach to questions otherwise unanswerable in man. However, neither past nor present animal models of chronic lung disease has been adequately exploited in terms of its respective responsiveness to air pollutant exposure. Gross and co-workers (1968), in a complicated pathological study, were unable to demonstrate expected morphological degeneration of lung tissue, i.e. described as emphysema, in control or dust (SiO_2, coal, or blast furnace) treated rodents followed by a year of NO_2 exposure (Table 5). In fact, the positive-control papain-treated animals with dust-pneumoconiosis fared better, in terms of body weight gain, 5 weeks postexposure than did their respective controls. More recent investigations (Table 6) of oxidant imposition on silicotic rat models have similarly revealed no apparent interactions between the two agents except for the fact that conventionally housed (non-SPF) rats appeared to be more susceptible than their SPF cohorts to oxidant-induced depression of the pulmonary defenses against infection (Chiappino and Vigliani, 1982).

TABLE 5. EMPHYSEMA AND NO_2 IN PNEUMOCONIOTIC ANIMALS[a]

NO_2 Exposure[b]	Intratracheal Dust[c]	Incidence of Emphysema	
		Hamster	Guinea Pig
+	+	2/64	2/18
-	+	6/70	0/24
+	-	0/6	4/22
-	-	0/9	----

[a] Gross et al. (1968).
[b] 10-34 ppm, 2 h/d, 5 d/wk for 12 months with 44-74 ppm one hour peak every 4 weeks.
[c] SiO_2, coal, or blast furnace dust administered intratracheally 3 weeks prior to NO_2. 50 mg for guinea pigs, 25 mg for hamsters.

TABLE 6. INTERACTION OF OZONE AND SILICOSIS IN THE RAT

Intratracheal Dust	Ozone Challenge[c]	Pulmonary Findings
50 mg tridymite[a]	1 ppm (8 h/d, 5 d/wk to 25 mo)	(a) SPF rats: lesions were additive (b) non-SPF rats: ~50% mortality; pneumonia and purulent bronchitis indicating enhanced infectivity
50 mg minusil[b]	0.77 ppm (6 h/d, 5 d/wk for 7.5 wk)	No interaction in lysyl oxidase activity, collagen content, or pathology

[a] Chiappino and Vigliani (1982).
[b] Yermakoff et al. (1984).
[c] Ozone exposures initiated within two days of SiO_2 administration.

Rodent models of papain or elastase induced emphysema have seen somewhat greater utility in these interaction studies (Table 7). Hartroft et al. (1976) found that continuous exposure of emphysematous hamsters to a complex atmosphere of several air pollutants had little impact on these animals save a slight rise in hematocrit. (Interestingly, hypertensive animals similarly exposed did not survive the same exposure regime). A somewhat different complex atmosphere continuously imposed on emphysematous and control hamsters for 4 weeks likewise had no overt pathological impact on either animal models, but did appear to detract from the diffusion compensation capability in the compromised animals, as indicated by a reduced elevation in DL_{CO} when compared to that of the controls (Raub et al., 1983). Toxic hyperoxic challenge to emphysematous rats also did not reveal unusual or different sensitivity to extreme oxidant stress in those animals when compared to the responses of the non-emphysematous cohorts (Harkema et al., 1982).

The particle deposition and clearance studies in lung-impaired rodents appear consistent with those of man (Table 8). Although total lung deposition of the tracer particles appears to be reduced in the diseased animals, the deposition pattern is more central (hilar) and tends to be more heterogeneous within the lung with the creations of hotspots. This pattern of deposition does not differ between the experimental emphysematous and fibrotic disease states (Hahn and Hobbs, 1979; Sweeney et al., 1983). Thus, the additional gas trapping reported in emphysematous guinea pigs exposed to H_2SO_4 mist (Loscutoff et al., 1980; Table 7) might be explained in part by foci of H_2SO_4 deposition

in the smaller airways resulting in their ultimate damage and obstruction. Moreover, the reduction in long-term clearance observed in symptomatic smokers (Bohning et al., 1976) is paralleled by that seen in the emphysematous hamsters (Hahn and Hobbs, 1979).

TABLE 7. EXPERIMENTAL EMPHYSEMA[a] AND RESPONSE TO TOXIC ATMOSPHERES

Atmosphere	Animal Model	Findings (Emphysema Model vs Normal)
Complex mixture[b] (24 h/d, to 18 mo)	Hamster	- No mortality - No change in mean linear intercept - Slight elevation in hematocrit
Complex mixture[c] (23 h/d, 4 wks)	Hamster	- Reduced compensatory $D_{L_{CO}}$ increase - No morphologic dissimilarities
H_2SO_4-10 mg/m^3[d] (6 h/d, 5 d/wk, 16 wks)	Guinea Pig	- Increased gas trapping - No changes in organ weights
Hyperoxia[e] (100% O_2 for 48 hrs)	Rat	- Similar survival rates - Similar lung function responses - Similar morphology/morphometry of challenged lung tissues

[a] Emphysema induced by intratracheal instillation of papain or elastase solutions.
[b] Hartroft et al. (1976). Atmosphere of SO_2 (1.25 ppm), NO_2 (1.00 ppm), CO (180 ppm), NO (1.25 ppm) and CH_4 (67.5 ppm).
[c] Raub et al. (1983). Atmosphere of dark reaction products of O_3 (0.08 ppm), SO_2 (0.76 ppm), SO_4=(400 µg/m^3), T-2-butene (2.05 ppm) and CH_3CHO (1.71 ppm).
[d] Loscutoff et al. (1980).
[e] Harkema et al. (1982).

Episodic and epidemiologic data appear to support the belief that chronic nonspecific lung disease imposes an additional risk to affected individuals when challenged by air pollution. While this concept has been implicitly enacted into law, little knowledge or understanding of the tenets of disease-based hypersusceptibility exists. The clinical and animal experimental data show trends, but in general have provided little substance to defend or challenge the legitimacy of the margins of safety incorporated into the standards of the EPA regulated pollutants. As more data on ~~so-called~~ normal individuals are being collected, many of these safety margins appear to be eroding, thus offering little encouragement that susceptible subgroups of the population are actually being protected. It seems imperative that more research be conducted in this area of differential susceptibility with the aim of identifying sensitive groups, reasons for their susceptibility, and perhaps biological markers for individualized screening.

TABLE 8. PARTICLE DEPOSITION IN EXPERIMENTAL LUNG DISEASE

Tracer Particle	Animal Models	Findings Diseased vs Matched Controls
TiO_2 (1.5 μm)[a]	Emphysematous Rats	- Variable deposition - Reduced clearance (25d)
^{137}Cs-alumina silicate (1.5 μm)[b]	Emphysematous Hamsters	- Reduced deposition - Accelerated short-term clearance (up to 30d) - Reduced long-term clearance (170d)
$^{59}Fe_2O_3$ (1.2 μm)[c]	Emphysematous Rats	- Reduced deposition - No effect on retention (30d)
^{99m}Tc-S Colloid (0.46 μm)[d]	Fibrotic Hamsters	- Reduced deposition - Less uniform deposition

[a] Ferin (1971).
[b] Hahn and Hobbs (1979).
[c] Damon et al. (1983).
[d] Sweeney et al. (1983).

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