AIR AND WATER POLLUTION

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CLEAN AND DIRTY LUNGS

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Introduction

I shall discuss only three of the many areas of research into the effects of air pollution on the lung. Dr. Williams told me there would be few biological scientists in the audience. For this reason, I shall devote a good portion of the talk to describing the functional anatomy of the lung. The purpose is to provide you with a background for understanding how pollutants may cause harm.

The respiratory system of a seated healthy adult male at the end of quiet expiration contains about 3-4 liters of gas. This gas is distributed between the airways and alveoli, the latter being the site of gas exchange with the blood. (About 95% of the total gas volume is in the alveoli.) The airways may be further subdivided into upper and lower portions. The upper airways comprise the nose, paranasal sinuses, mouth, pharynx, and larynx. They perform three important functions: 1) Bring inspired air close to body temperature (37° C) by heating or cooling (1), 2) Bring the relative humidity of inspired air close to saturation (at complete saturation, 37° C, P_{H_2O} = 47 mm Hg) (1), and 3) Remove some of the suspended particles and contaminant gases from inspired air.

The effectiveness of this last function is indicated by the following: During quiet breathing, about 98% of the sulfur dioxide (SO_2) in inspired air may be removed by the nasal mucosa (2); the removal of uniform spherical particles of methylene blue from air by the human nose, for a flow rate of 20 liters/minute, has been reported by Pattle (3) to be:

Diameter (u)	% Removal
9.0	98.7
8.4	88.0
3.5	60.0
2.0	37.0

The design of the lower airways permits inspired air to be distributed to the alveoli evenly and at a low cost in energy. Starting at the bifurcation of the trachea, these airways subdivide dichotomously. The human lung may contain up to 17 generations of purely conductive airways, the smallest of which are known as terminal bronchioles (Figure 1). Beyond the terminal bronchioles are several generations of transitional airways[1], that is, airways whose walls contain alveoli.

It is estimated that there are several hundred million alveoli in the adult lung which provide a total diffusing surface about 70 m^2 in area. The pathway across which oxygen and carbon dioxide diffuse is remarkable short: from the alveolar gas phase to the hemoglobin molecule, the distance varies from a fraction of a micron to about 4 microns[2]. Ordinarily this distance is traversed in about 0.3 seconds.

The portion of the respiratory system that may be affected by pollutant gases or particles will be determined by a number of factors: the concentration, physical, and chemical properties of the pollutant, the pattern of breathing (fast or slow, by nose or mouth, large of shallow breaths), and even the presence or absence of pulmonary disease. Within a diseased lung the structural and functional abnormalities tend to be unevenly distributed. Consequently, the exposure of such a lung to pollutants is also likely to be uneven.

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[1] The transitional airways are called 'respiratory bronchioles'.

[2] One experimental effect of photochemical oxidants is edema of the lung. Edema increases the length of this pathway and impedes the diffusion of oxygen.

Effects of Gas-Aerosol Combinations

A number of epidemiologic studies show that elevations in the concentration of SO_2 in urban communities may be associated with a rise in the morbidity rate, and occasionally the mortality rate, of chronic respiratory disease (5). In laboratory experiments, the exposure of volunteers or laboratory animals to levels of SO_2 (alone) that are an order of magnitude higher than those encountered in urban air generally results in only slight and transient functional changes (6,7). If it is assumed that the rise in urban SO_2 is not fortuitous, i.e., that the gas does affect patients with respiratory disease, how are these discrepant findings reconciled? While there is no satisfactory explanation, a promising clue has been provided by the cumulative work of Amdur (8) which began about 15 years ago. She measured pulmonary flow resistance in unanesthetized guinea pigs before and during exposure to a variety of pollutants. This measurement is a sensitive index of changes in airway caliber, expecially of the larger airways. Some of her findings are summarized in Figure 2. First, SO_2 alone caused an increase in flow resistance proportional to the concentration of the gas. Second, an aerosol produced from a 1% solution of NaCl caused no change in flow resistance; The geometric mean diameter of the crystalline particles was found to range from about 0.04 to 0.12 microns over a succession of studies. Third, if the gas and aerosol were administered in combination, the increase in flow resistance for a particular concentration of SO_2 always exceeded the response to the gas alone. A term used to characterize the effect of a combination of agents which exceeds the sum of the individual effects is Synergism.

Two hypotheses have been offered to explain this synergism. One is that the aerosol acts as a vehicle for the SO_2 thereby increasing the amount of gas that penetrates the upper airways. The second perhaps more attractive hypothesis is that the gas following absorption by the aerosol is converted to sulfuric acid or some other irritant sulfate[3]. No attempt was made in these studies to test

[3] See reference 9 for a comparison of the effects of three different sulfate aerosols on the pulmonary flow resistance of guinea pigs.

these hypotheses either in the dynamic mixing chamber in which the guinea pigs were exposed or in the non-equilibrium state that characterizes the upper airways where temperature and humidity change rapidly.

The oxidation of SO_2 to sulfuric acid is promoted by catalysts like manganese and ferrous salts (10). While such catalysts may be found in polluted air, they are not known to have been present in Amdur's experiments.

Studies on human volunteers utilizing similar combinations of SO_2 and saline aerosols have yielded conflicting results; some investigators have demonstrated synergism (6,11), others have not (7,12).

This is an area of critical research for it is generally believed that any adverse health effects of air pollution arise from combinations of the pollutants (perhaps abetted by other factors like weather) rather than the individual components. However, the evidence to support this belief is meager. I suspect that progress in this area will continue to be slow until collaboration improves between the physical scientists who can generate, control, and characterize gas-aerosol mixtures, and the biological scientists.

Altered Resistance to Respiratory Infection

The respiratory system has manifold equipment for ridding itself of relatively insoluble particles. Despite the pervasiveness of bacteria, most of the lower airways and alveoli of healthy lungs are therefore sterile. If the means of expelling particles are impaired, the susceptibility of the lungs to diseases that may be caused by infectious, radioactive, or chemically active particles becomes greater. A study of English infants, children and adolescents has shown an impressive association between the level of air pollution and the rate of lower respiratory infection (12). Laboratory studies have been complementary in showing that pollutants may impair one or another component of the clearance mechanism of the lung (13-15) while increasing the susceptibility to, and seriousness of, airborne infections (15).

A particle depositing within the lower airways or alveoli may be cleared in the direction of the pharynx in one of three ways: 1) cough, 2) muco-ciliary transport, and 3) phagocytosis (engulfment), usually by an alveolar macrophage; the cell then reaches the muco-ciliary layer.

Each method of removal operates over a circumscribed portion of the lungs. The first, coughing, is an explosive effort which generates particles from the liquid lining of the airways. Its effectiveness depends on the maximal air velocity that can be developed within the airway. As shown in Figure 3, there is a dramatic increase in the cumulative cross-sectional area of the bronchial tree beyond the 4th-5th generation. For any rate of flow measured at the mouth, the velocity at that instant at a particular level of the airways will vary inversely with the cumulative cross-sectional area at the same level. For this reason, coughing is effective in clearing only about the first 6-7 generations of airways (16).

The muco-ciliary system operates throughout the conductive zone (17 generations). The cilia are hair-like projections that arise from the cells lining the airways. They beat synchronously at a rate of about 1,300 per minute in rats (13) to propel the overlying thin layer of mucus (several microns thick) in the direction of the pharynx. The effectiveness of the cilia is influenced in turn by the volume and visco-elastic properties of the mucus. These mechanical properties of mucus are sensitive to changes in temperature, humidity, and the organism's state of hydration, and may be radically altered in pulmonary disease. The velocity of mucous flow appears to diminish from the trachea to the terminal bronchioles. The range is estimated to be from about 1.5 cm/min to 0.01 cm/min (17). Accordingly, the clearance rate of particles impinging on the airways may be expected to vary with the level at which the particles strike. The half-times for clearance are reported to be about 30 ± 10 minutes from the proximal airways, 2.5 ± 0.5 hours from the intermediate airways, and 6 hours (the least well defined value) from the peripheral airways (17).

The alveolar macrophage, a motile scavenger, cleanses the alveoli of insoluble particles. The cell appears to be derived mainly from a precursor found in the alveolar lining, but it may also have origin in the blood-forming tissues. The principle functions of the macrophage are: 1) to phagocytose foreign particles that land in the transitional and respiratory zones, 2) to neutralize or kill viable particles. The latter function is accomplished by means of a complex system of enzymes that are stored in membraneous capsules within the cytoplasm of the cell. The likelihood that a particle that lands in the alveoli will be cleared from the lungs in a relatively short time is enhanced once it is phagocytosed. For example, the half-time for removal of most particles that are phagocytosed has been estimated to be about 24 hours (18). For particles that penetrate the alveolar wall, the removal time is increased and becomes quite variable. A half-time of 90 days has been proposed for particles described as "moderately" retained, and of 360 days for those that are "avidly" retained (18). The persistence of particles in the lung may reflect their entrapment in inflammatory tissue (as with silica), or their clearance through the lympthatic and circulatory systems. Any persistence implies an increased hazard for the lungs.

A disquieting feature of the macrophagic system is its susceptibility to injury by a host of internal and external environmental stresses. Green and Kass (19) demonstrated that the rate of killing of staphylococcus aureus, administered as an aerosol to mice, was slowed if the animals were malnourished, intoxicated with ethanol, or breathed air that was low in oxygen. A similar effect has since been produced with ozone (20). Low concentrations of ozone may also reduce the number of alveolar macrophages available for phagocytosis (14). In mice, the death rate after airborne infection with Klebsiella pneumoniae rises if the infection follows a prolonged exposure to 0.5 ppm of nitrogen dioxide. Additional reports of this type could readily be assembled. They underscore the particular hazard that is posed by pollutants settling at the alveolar level.

Changes in Structural Proteins

There is evidence that oxidizing pollutants may interact with either the structural proteins of the lung or their surrounding matrix (21). Why should this be of concern to us? One reason is that changes in these proteins are implicit in both the aging of the lung and the degenerative processes that may culminate in diseases of the lung. Any agent which affects the structural proteins may therefore have implications for health.

The lung is an elastic, distensible structure. It has stress-strain or "applied pressure-resultant volume" relations which can be measured either in the intact animal or in vitro. Two factors contribute to this elastic behavior: 1) surface forces that operate at the air-liquid interface of alveoli, 2) tissue elastic forces due to the presence of three fibrous proteins: collagen, elastin, and reticulin, collagen being the most abundant. The contribution of each of the two factors can be distinguished by methods that will not be considered in this discussion (22).

Several years ago Buell and co-workers (21) reported that ozone could denature the proteins of the lung and postulated the occurrence of accompanying structural changes. Recently, while testing another hypothesis, we found evidence of altered elasticity in rabbits' lungs one week after an exposure to ozone (23). Our procedure allowed us to expose only the right lung to ozone on the first day of the experiment, and to expose both lungs to the gas on the eighth day: Thereafter, we killed the animals, excised and separated the right and left lungs and compared their pressure-volume relations. In each of nine experiments, the right side (exposed twice) was less distensible than the paired left side (exposed once). The results are shown in Figure 4. We did not determine the threshold level of ozone necessary to produce the change in elasticity, nor how persistent the change might be, nor whether repeated exposures might have even greater consequences. Other investigators have reported that the prolonged administration of low levels of NO_2, another oxidizing pollutant, to rats produces lesions bearing resemblance to emphysema (24).

I suspect we will have to rely principally on animal studies in this area of research. The problem of assessing the contribution that air pollution may make to such gradual and poorly defined processes as aging and degeneration in the human lung is awesome.

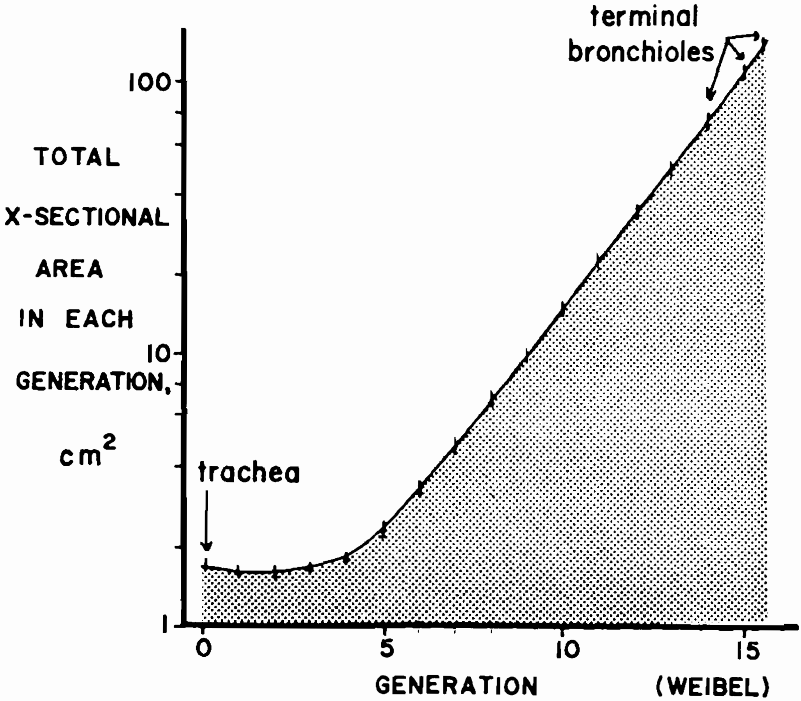
terminal
bronchioles
100
TOTAL
X-SECTIONAL
AREA
IN EACH
GENERATION,
cm²
10
trachea
1
0
5
10
15
GENERATION
(WEIBEL)

Figure 1

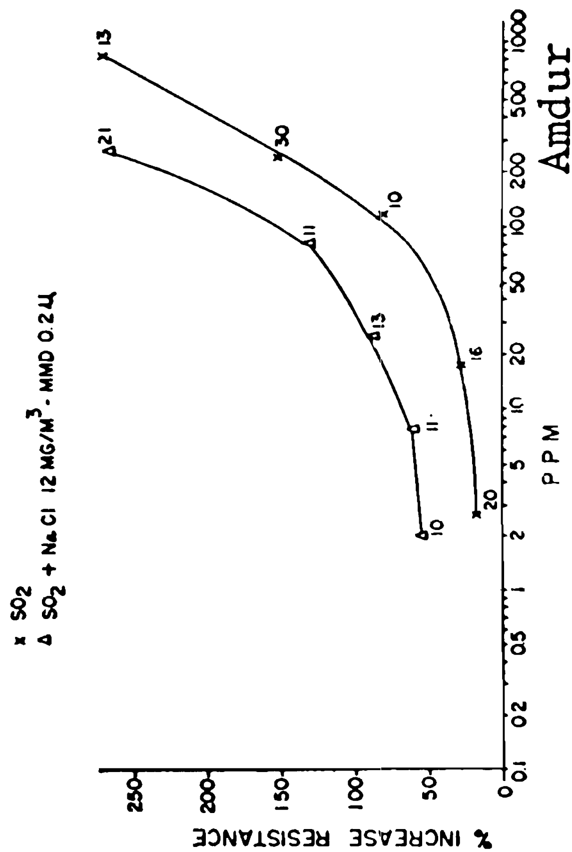
x SO2
Δ SO2 + NaCl 12 MG/M3 - MMD 0.2 μ
% INCREASE RESISTANCE
0
50
100
150
200
250
0.1
0.2
0.5
1
2
5
10
20
50
100
200
500
1000
PPM
Amdur

Figure 2

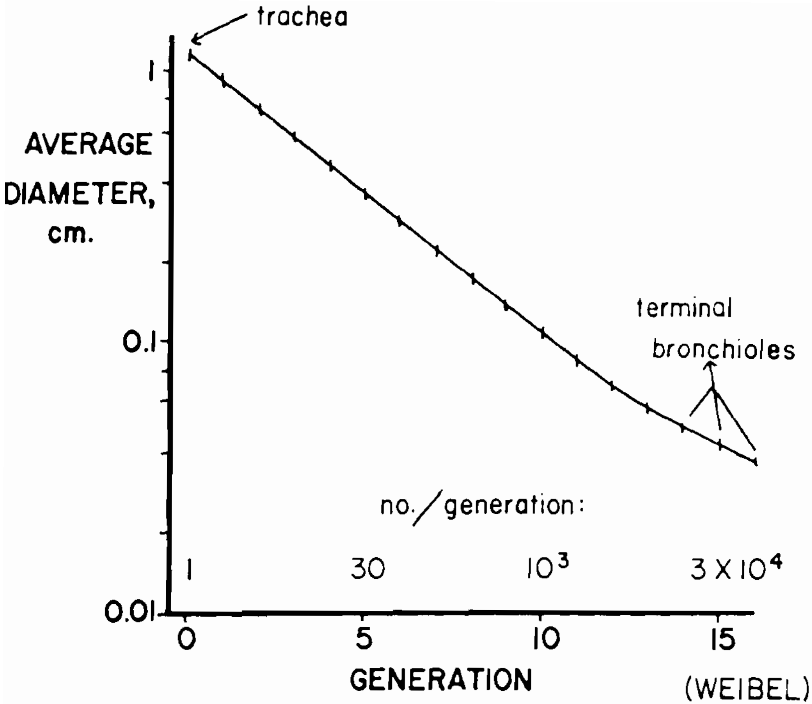
trachea
1
AVERAGE
DIAMETER,
cm.
0.1
0.01
terminal
bronchioles
no./generation:
1
30
10^3
3×10^4
0
5
10
15
GENERATION
(WEIBEL)

Figure 3

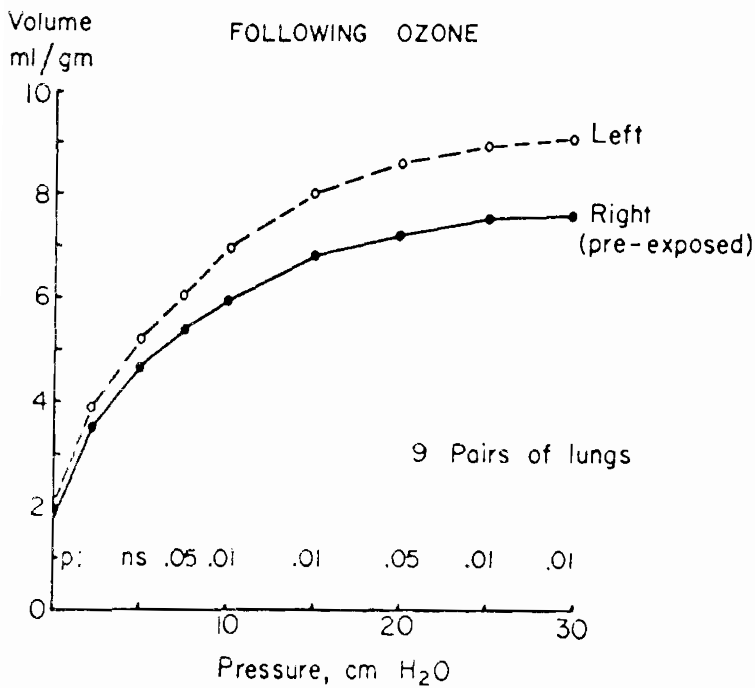
Volume
ml / gm
FOLLOWING OZONE
10
8
6
4
2
0
Left
Right
(pre-exposed)
9 Pairs of lungs
p: ns .05 .01 .01 .05 .01 .01
10
20
30
Pressure, cm H_2O

Figure 4

Legends

Figure 1. Based on the data of Weibel. The trachea is designated as "0 generation". Note the increase in the number of airways per generation as branching progresses.

Figure 2. Percentage changes in pulmonary flow resistance after one hour of exposure. The number of animals studied is shown next to each point on the two curves.

Figure 3. Based on the data of Weibel (4). Since resistance to flow through parallel tubes bears an inverse relation to their cumulative cross-sectional diameter, most of the lung's flow resistance is found in the trachea and initial generations of bronchi. Narrowing of the central airways may be easier to detect than narrowing of the peripheral airways (pollutants may cause either), even though the latter may have more serious consequences.

Figure 4. Mean pressure/volume behavior of paired rabbits' lungs measured during deflation following inflation to a peak distending pressure of 30 cm H_2O. Gas volume is expressed per gram of lung weight to correct for differences in size. The significance of the paired differences at each point on the curve is shown near the bottom of the figure. See text for details of ozone exposure.

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