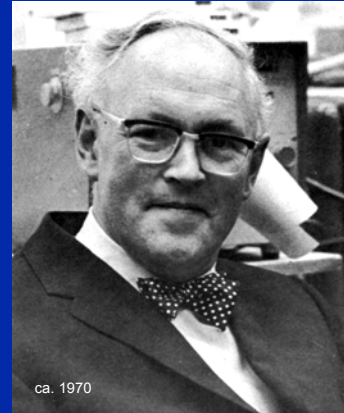


Historical Perspective on D. V. Bates' Work on Ozone

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2007 Annual Conference
Chicago, IL, April 15-17, 2007



ca. 1970

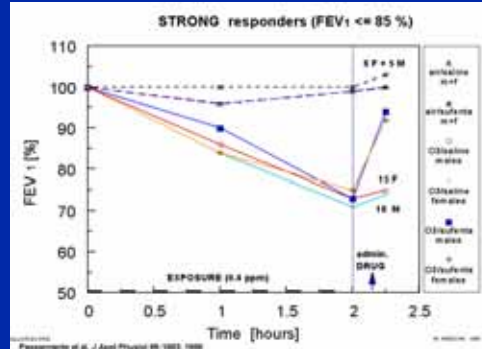
Acute Effects of Ozone Inhalation ($C \times t \times \dot{V}$) (inspired by D.V. Bates, 1995)

A) Lung Function

- Reversible decrease of FVC and FEV_1 without changes in C_L or substantial increase in R_{aw}
- Neural inhibition of inspiration (bronchial C fibers)
- Blunted by pretreatment with COX inhibitors (?PGE2)
- Rapid reversal by opioid agonist, not bronchodilators

Nociceptive mechanisms modulate ozone-induced human lung function decrements

Passanante A.N., Hazucha M.J., Bromberg P.A., Seal E., Folinsbee L., and G. Koch



B) Factors that affect degree of acute lung function response

- Age
- ? Gender (?? BMI in women)
- Large inter-individual response range
- Intra-individual responses more (but not highly) reproducible over months
- Adaptation
- Nutritional, genetic
- Smokers less responsive
- COPD not susceptible
- Asthmatics not unusually susceptible

C) Neutrophilic airways inflammation

- Longer time course than lung function effects
- Not correlated with ΔFEV_1
- Not inhibited by pre-Rx with COX inhibitor
- Associated with \uparrow dendritic cell-like mononuclear cells in induced sputum
- Increased lung epithelial permeability
- ? altered mucociliary clearance

D) “Priming” for subsequent bronchoconstrictive response to:

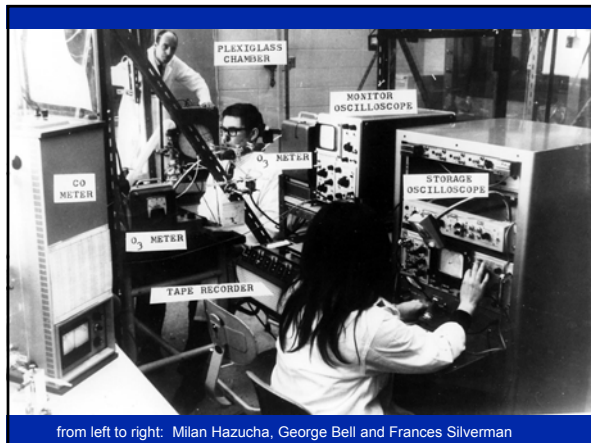
- Methacholine
- Histamine
- SO₂
- Specific allergen in allergic asthmatics
- (?) viral or bacterial infection.

Early Studies: Young et al (J. Appl. Physiol. 1964)

- Mouthpiece (oral) exposure of 11 subjects
- 0.6-0.8 ppm O₃ (also a sham exposure) at rest for 2 h.
- Sophisticated lung function measures repeated up to 48 hrs post-exposure
- Formal statistical analysis
 - ✓ 8% immediate reduction of mean VC (reversible)
 - ✓ 20% immediate reduction of mean D_L CO (reversible)

Interpretation:

“Inability” to make a max. insp. effort
? possible inability to make a max. exp. effort.



Protocol designed to mimic natural exposures

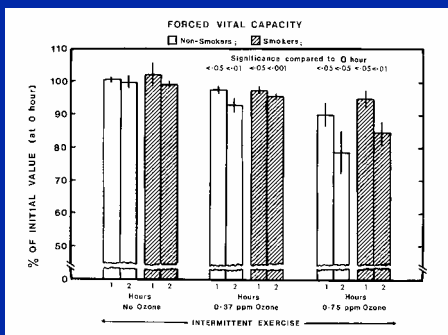
- No mouthpiece or nose-clip
- 2 hr. exposure at rest or with 15 min. exercise stints alternating with rest
- Subject remains in-chamber during multiple functional measurements

Results : Bates et al. (J. Appl. Physiol. 1972)

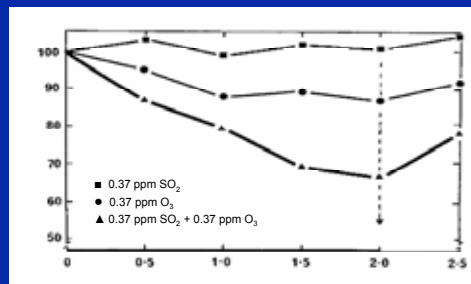
- 10 resting volunteers exposed to 0.75 ppm O₃
- Very modest mean effects
- Much more dramatic effects in two of three subjects re-exposed to 0.75 ppm O₃ while performing mild exercise

“...we would like to suggest that the maximal desirable exposure to a gas as dangerous as O₃ should be, at the very outside, not more than half the concentration which produces adverse effects in normal subjects engaged in normal activities [in the chamber]. One cannot be sure that an exceptionally sensitive subject or one with some pre-existing lung disease might not be adversely influenced even by this concentration.”

Cigarette smokers are less responsive (Hazucha et al., 1973)
0.37 ppm O₃ 2 hr., intermittent exercise



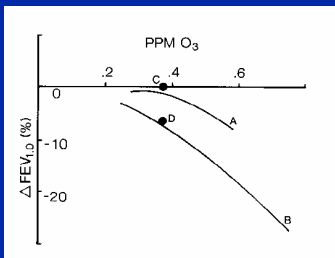
Combined effects of ozone and sulphur dioxide on human pulmonary function.
Hazucha M. and D.V. Bates, Nature 257: 50, 1975



? mechanism ? de novo generation of aerosolized oxy-organics (proposed by Hackney group in 1977)

Los Angeles – Montreal collaboration

(Hackney, Linn et al. – Hazucha, Bates et al., Arch. Envir. Health 32:110, 1977)



Los Angeles (curve A, point C) to be less responsive than Montrealers (curve B, point D)

“Neither is there any obvious indication of differences between the Californians and the Canadians in genetic constitution, nutrition or environmental stresses other than air pollution that could be the source of their differences in reactivity.”

Air Pollution as an Underappreciated Cause of Asthma Symptoms (editorial)

G.D. Thurston and D. V. Bates, J. Am. Med. Assoc. 290:1915-7, 2003.

“...the preventive use of asthma medications may reduce these acute adverse effects of [ozone] air pollution [in asthmatic children]”.

Mechanism of action of ozone on the human lung
Hazucha M.J., Bates D.V. and P.A. Bromberg, J. Appl. Physiol. 67:1535, 1989

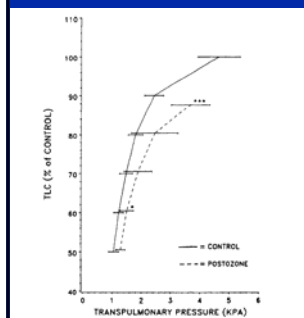


FIG. 2. Quasi-static average pressure-volume curves obtained before (solid line) and after (dashed line) exposure to ozone (O₃) (n = 9-11); bars indicate mean ± SD. Statistical significance levels: * P = 0.04, *** P = 0.001. After O₃ curve shifted upward by 1/4% to avoid overlap of the SD lines.

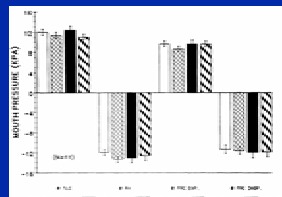


FIG. 3. Maximal mean ± SE respiratory pressures at residual volume and functional residual capacity and maximal mean ± SE expiratory pressures at total lung capacity and functional residual capacity. The pressures were measured at mouth before and after exposure, on both air and ozone days.

Association vs. Causality

(Bradford Hill, 1965)

- Consistency
- Coherence
 - Among related phenomena in a given study
 - Between different types of experiments
 - Panel of subjects vs. general population
 - Epidemiologic vs. controlled exposures (human, animal, cellular).