in mortality from this disease. The application of such principles in New Zealand, helped enormously by the decision of government on the recommendation of the Asthma Task Force to provide peak expiratory flow meters free of charge to patients, has been associated with a recent downward trend in the asthma mortality rates, particularly in young people. An interesting feature of this trend has been that the previously considerably increased mortality rates among the Maori and Polynesian races have fallen to equal the mortality rates in Europeans. If the recent increase in asthma mortality in the United States is real, and the consensus view is that it is real, especially in black subjects and among young people, then such strategies could be used equally effectively in the United States as in New Zealand. While we wait final confirmation of the reality of the reported trends in morbidity and mortality caused by asthma and explanations for these trends, management of asthma, especially its inflammatory component, can be taken more seriously and lives can be saved.

Malcolm R. Sears, *FRACP*
Associate Professor of Medicine
Department of Medicine
University of Otago Medical School
PO Box 913
Dunedin, New Zealand

REFERENCES

1. Jackson R, Sears MR, Beaglehole R, Rea HH. International trends in asthma mortality 1970-1985 [in press]. Chest.
2. Sly RM. Mortality from asthma, 1979-1984. J ALLERGY CLIN IMMUNOL 1988;82:705-17.
3. World Health Organization. Manual of the international statistical classification of diseases, injuries and causes of death: based on the recommendations of the ninth revision conference, 1975, vol 1. Geneva: WHO, 1977.
4. Sly RM. Increases in deaths from asthma. Ann Allergy 1984;53:20-5.
5. Stewart CJ, Nunn AJ. Are asthma mortality rates changing? Br J Dis Chest 1985;79:229-34.
6. Sears MR, Rea HH, Beaglehole R, et al. Asthma mortality in New Zealand: a two-year national study. NZ Med J 1985; 98:271-5.
7. Sears MR, Rea HH, de Boer G, et al. Accuracy of certification of deaths due to asthma: a national study. Am J Epidemiol 1986;124:1004-11.
8. Jackson RT, Beaglehole R, Rea HH, et al. Mortality from asthma: a new epidemic in New Zealand. Br Med J 1982; 285:771-4.
9. British Thoracic Association. Death from asthma in two regions of England. Br Med J 1982;285:1251-5.
10. Sears MR, Rea HH, Rothwell RPG, et al. Asthma mortality: comparison between New Zealand and England. Br Med J 1986;293:1342-5.
11. Gergen PJ, Mullally DI, Evans R. National survey of prevalence of asthma among children in the United States, 1976 to 1980. Pediatrics 1988;81:1-7.
12. Harrison AC, Asher MI, Pattemore PK, Mitchell EA, Rea HH, Stewart A. Do racial differences in asthma prevalence and severity account for racial differences in asthma admission and mortality rates? Am Rev Respir Dis 1986;133:A178.
13. Sears MR, Rea HH, Fenwick J, et al. 75 deaths in asthmatics prescribed home nebulisers. Br Med J 1987;294:477-80.
14. Kraan J, Koëter GH, van der Mark TW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. J ALLERGY CLIN IMMUNOL 1985;76:628-36.
15. Kerrebijn KF, van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. J ALLERGY CLIN IMMUNOL 1987;79:653-9.
16. Johnson AJ, Nunn AJ, Somner AR, Stableforth DE, Stewart CJ. Circumstances of death from asthma. Br Med J 1984; 288:1870-2.
17. Rea HH, Sears MR, Beaglehole R, et al. Lessons from the national asthma mortality study: circumstances surrounding death. NZ Med J 1987;100:10-13.
18. Rea HH, Scragg R, Jackson R, Beaglehole R. A case-control study of deaths from asthma. Thorax 1986;41:833-9.

Sulfur dioxide and asthma—A double-edged sword?

SO_2 is a ubiquitous air pollutant produced by combustion and processing of sulfur containing fossil fuels. It is thus a major constituent of polluted urban air. In addition, SO_2 is widely used in industry with an estimated 500,000 workers in the United States regularly exposed in settings ranging from smelters and paper-pulp mills to wineries and food-processing plants.

Abbreviations used
SO_2: Sulfur dioxide
OSHA: Occupational Safety and Health Administration
EPA: Environmental Protection Agency

The first suggestion that SO_2 might produce important adverse effects on human health came from observations of increases in mortality in association with several episodes of severe air pollution that occurred in the middle of this century.[1-3] Although information about the specific pollutants present during these episodes is incomplete, the best estimates suggest that the concentrations of SO_2 were quite high. For example, during a severe episode of polluted fog in London in 1952, the maximal average concentration of SO_2 during 24 hours was estimated at 1.5 ppm, more than 10 times the current standard set by the United States EPA.[4] The excess deaths attributable to pollution during these episodes were generally clustered among patients with preexisting cardiopulmonary disease, suggesting that the pollutants present might be exerting their adverse effects on the lung. Patients with asthma were found to be especially susceptible to these episodes of pollution. For example, in one study, 88% of patients with asthma experienced exacerbations during the pollution episode that occurred in Donora, Pa., in 1948.[2]

Stimulated by these associations between air pollution and respiratory morbidity and mortality, investigators have examined the effects of SO_2 on several species of animals, including mice, guinea pigs, rats, dogs, cats, donkeys, and monkeys. The two most important effects observed have been an increase in airflow resistance and an alteration in mucus secretion.[5-8] Acute inhalation of SO_2 has been reported to increase, rapidly, the airflow resistance in dogs, cats, and guinea pigs. Generally, this effect has only occurred after inhalation of concentrations of $SO_2 > 5$ ppm, well in excess of the concentrations encountered in polluted outdoor air. The one exception to this statement is a report of a statistically significant increase in pulmonary resistance in guinea pigs exposed to concentrations of $SO_2 < 1$ ppm.[5] This response, although it was statistically significant, was quite small. The same investigator found that 46 ppm of SO_2 was required to increase resistance by 50% above baseline. In general, SO_2 has not caused morphologic evidence of lower respiratory injury in animals unless it was inhaled in high concentrations (>25 ppm). Thus, extrapolation from these experiments in normal healthy animals would not predict an important acute effect of SO_2 on airflow resistance in the concentrations encountered in polluted air (generally <1 ppm).

Several studies have examined the effects of acute inhalation of SO_2 on normal human subjects. In most of these studies, inhalation of concentrations >5 ppm was demonstrated to cause small but significant decrements in airway function.[8, 9] Occasional "sensitive" subjects were found to respond in a similar fashion to concentrations as low as 1 ppm.[9, 10] Because these effects were small, and usually required inhalation of concentrations of SO_2 well in excess of those encountered in polluted outdoor air, these results were interpreted to imply that SO_2 itself was not likely to be responsible for the adverse health effects of air pollution.

However, studies from several different laboratories have now demonstrated that concentrations of SO_2 that have little or no effect on normal healthy subjects can produce marked, symptomatic bronchoconstriction in subjects with asthma.[11-17] The bronchoconstrictor effect of SO_2 is greatly potentiated by exercise. Thus, exercising subjects with even mild asthma routinely develop bronchoconstriction when they inhale concentrations of $SO_2 > 0.4$ ppm during moderate or heavy exercise. This effect occurs after periods of exposure as brief as 2 minutes and is associated with symptoms typical of an acute exacerbation of asthma.[18, 19] As with all stimuli to acute bronchoconstriction, airway obstruction and symptoms usually remit spontaneously but can perist for periods in ex-

cess of 1 hour if they are untreated. For many subjects with mild asthma, the exacerbations induced by ambient concentrations of SO_2 in the laboratory are as severe as, or more severe than, any exacerbations that they experience from stimuli outside the laboratory. The concentrations required to produce these effects ($\geq$0.4 ppm) can be exceeded in air in the vicinity of point sources of SO_2 emission and in indoor air of homes heated with kerosene space heaters. Much higher concentrations are encountered in the workplace in which the present standard set by the United States OSHA allows exposure to up to 5 ppm as a time-weighted average during an 8-hour workshift.

It is thus clear that exposure to SO_2 in indoor and outdoor ambient air and in the workplace can be an important cause of acute symptomatic bronchoconstriction in patients with asthma. As noted above, the present OSHA standard, designed to protect healthy workers, allows exposure to concentrations of SO_2 more than an order of magnitude higher than those known to cause symptomatic exacerbations of asthma. Unfortunately, the present primary National Ambient Air Quality Standard for SO_2, the standard set by the United States EPA to protect even the most sensitive segments of the population, is also inadequate. This standard is based on a 24-hour averaging time, whereas symptomatic SO_2-induced bronchoconstriction occurs after exposure as short as 2 minutes in duration.

The article by Riedel et al.[20] suggests another possible interaction between SO_2 and asthma. In their study, guinea pigs exposed to SO_2 or filtered air for 8 hours daily on 5 consecutive days were also exposed to an aerosol of ovalbumin on the third through fifth days. Animals exposed to all three concentrations of SO_2 were subsequently found to be more likely to develop bronchoconstriction on reexposure to ovalbumin than were animals exposed to air. Furthermore, SO_2 exposure appeared to result in higher concentrations of IgG antibodies against ovalbumin in both bronchoalveolar lavage fluid and serum.

These findings are based on observations in a relatively small number of animals and in a species (guinea pig) that differs from the human in that it depends primarily on IgG antibodies to mediate immediate hypersensitivity responses. The finding of only one animal of 14 exposed to air that developed bronchomotor sensitivity to ovalbumin is somewhat surprising, given the usual ease with which guinea pigs can be sensitized to this antigen. In addition, the measurements of lung function used (calculation of "trapped air" and "compressed air") are not standard. Nonetheless, if this is confirmed, the results would raise the provocative suggestion that SO_2 could act as a double-edged sword in patients with asthma, both inducing bronchoconstriction and increasing the likelihood of bronchoconstrictor responses to allergens.

The notion that inhalation of irritant gases might increase the likelihood of allergic sensitization through the respiratory tract is not new. As noted by Riedel et al.,[20] Matsumura[21-23] first reported this phenomenon in a series of articles published in 1970 describing the effects of high concentrations of ozone, nitrogen dioxide, and SO_2 on ovalbumin sensitization and ovalbumin-induced bronchoconstriction in guinea pigs. However, in those studies, brief exposures to high concentrations of each gas were used, and enhanced sensitization to ovalbumin only occurred after exposure to concentrations of ozone $>$ 5 ppm, nitrogen dioxide $>$ 70 ppm, and SO_2 $>$ 330 ppm. These concentrations exceed those encountered in polluted outdoor air by one to three orders of magnitude. More recently, Osebold et al.[24] extended these observations on the effects of ozone to concentrations closer to those levels encountered in the environment. In those experiments, mice were sensitized to inhaled ovalbumin in association with continuous exposures to ozone (0.8 or 0.5 ppm) for 3- to 4-day periods repeated four times during a month. Although lung function was not monitored, fatal and nonfatal anaphylactic responses to ovalbumin were significantly more common in ozone-exposed than in control animals, even after exposure to 0.5 ppm.

The mechanism(s) by which exposure to noxious gases increase sensitization to inhaled antigens remain to be determined. Acute mucosal injury could result in increased uptake of antigen across the airway epithelium and in impaired mucociliary clearance, resulting in more prolonged contact between any antigen and antigen-processing cells within the respiratory tract. After exposure to ozone, both effects almost certainly occur. For example, Matsumura[21-23] demonstrated that after exposure to 8 ppm of ozone, the initial uptake of inhaled radiolabeled ovalbumin into the blood was greatly accelerated, suggesting an increase in airway epithelial permeability. During the subsequent 24 hours, however, the retention of ovalbumin in the lungs was increased by ozone exposure. More recently, exposure to near ambient concentrations of ozone has been demonstrated to increase epithelial permeability in a variety of species, including humans.[25] Exposure of mice to 0.8 ppm of ozone in a protocol similar to that used by Osebold et al.[24] and Ibrahim et al.[26] caused widespread destruction of cilia, as demonstrated by scanning electron microscopy.

In contrast to ozone, near ambient concentrations of SO_2 have not generally been found to produce morphologic evidence of mucosal injury, even after prolonged periods of exposure. Effects on morphology have primarily been reported after exposure to concentrations of SO_2 orders of magnitude higher than those encountered in polluted air. Little is known about the effects of repeated exposures to low concentrations of SO_2 on airway epithelial permeability or mucociliary clearance. If any such effects do occur, they must be due to functional alterations that are not associated with morphologic evidence of injury. Alternatively, SO_2 could be affecting one or more of the cells involved in antigen processing and immunoglobulin synthesis. Such an effect could be direct or, more likely, mediated through the well-described action of SO_2 on airway afferent nerves. It is now clear that in addition to initiating classic reflex reponses, airway afferent nerves are the source of a variety of peptide mediators that can alter the function of both macrophages and lymphocytes.[27]

Forty years ago SO_2 was considered one of the leading causes of adverse respiratory effects of air pollution. During the next three decades, a large number of studies in several mammalian species, including healthy humans, led most scientists to conclude that the concentrations of this pollutant present in ambient air were probably benign. The present OSHA and EPA standards were established from that data base. It is now clear that this erroneous conclusion was based on a failure to study the appropriate population and that the acute adverse effects of near ambient concentrations of SO_2 on patients with asthma can be quite profound. If the effects of repeated exposures to low concentrations of SO_2 reported by Riedel et al.[20] are confirmed and extended to other species (especially humans), interest in this common pollutant as a cause of adverse respiratory effects of air pollution may yet come full circle.

Dean Sheppard, MD
Lung Biology Center, Building 1, Room 150
San Francisco General Hospital
1001 Potrero Ave.
San Francisco, CA 94110

REFERENCES

1. Shy CM, Goldsmith JR, Hackney JD. Health effects of air pollution. New York: American Lung Association, 1978.
2. Schrenk HH, Heiman H, Clayton GD, Gafefer W, Wexler H. Air pollution in Donora, Pennsylvania. Epidemiology of the unusual smog episode of October 1948. Public Health Bulletin. Washington, D.C.: US Government Printing Office, 1949:306.
3. Logan WPD. Mortality in the London fog incident. Lancet 1953;1:336-9.
4. Holland WW, Bennett AE, Cameron IR, Florey CduV, Leeder SR, Schilling RSF, Swan AV, Waller RE. Health effects of particulate pollution: reappraising the evidence. Am J Epidemiol 1979;110:527-659.
5. Amdur MO. Respiratory absorption data and SO_2 dose-response curves. Arch Environ Health 1966;12:729-36.
6. Frank NR, Speizer FE. SO_2 effects on the respiratory system in dogs: changes in mechanical behavior at different levels of the respiratory system during acute exposure to the gas. Arch Environ Health 1965;11:624-34.
7. Hahn HL, Fabbri L, Graf PD, Nadel JA. Bronchokonstriktion und hypersekretion nack schwefeldioxid (SO_2)—ein laryngealer reflex? Prax Klin Pneumol 1983;37:666-9.
8. Nadel JA, Salem H, Tamplin B, Tokiwa G. Mechanism of bronchoconstriction during inhalation of sulfur dioxide. J Appl Physiol 1965;20:164-7.
9. Frank NR, Amdur MO, Worcester J, Whittenberger JH. Effects of acute controlled exposure to SO_2 on respiratory mechanics in healthy male adults. J Appl Physiol 1962;17:252-8.
10. Amdur MO. Toxicologic appraisal of particulate mater, oxides of sulfur and sulfuric acid. J Air Pollut Control Assoc 1969;19:638-44.
11. Sheppard D, Wong SC, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. Am Rev Respir Dis 1980;122:873-8.
12. Sheppard D, Saisho A, Nadel JA, Boushey HA. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. Am Rev Respir Dis 1981;123:486-91.
13. Linn WS, Venet TG, Shamoo DA, Valencia LM, Anzar UT, Spier CE, Hackney JD. Respiratory effects of sulfur dioxide in heavily exercising asthmatics: a dose-response study. Am Rev Respir Dis 1983;127:278-83.
14. Koenig JQ, Pierson WE, Horike M, Frank R. Effects of SO_2 plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. Environ Res 1981;25:340-8.
15. Bethel RA, Epstein J, Sheppard D, Nadel JA, Boushey HA. Sulfur dioxide-induced bronchoconstriction in freely breathing exercising asthmatic subjects. Am Rev Respir Dis 1983;128: 987-90.
16. Schachter EN, Witek TJ Jr, Beck GJ, Hosein RH, Colice G, Leaderer BP, Cain W. Airway effects of low concentrations of sulfur dioxide: dose-response characteristics. Arch Environ Health 1984;39:34-42.
17. Roger LJ, Kehrl HR, Hazucha M, Horstman DH. Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise. J Appl Physiol 1985;59:784-91.
18. Horstman DH, Seal E Jr, Folinsbee LJ, Ives P, Roger JL. The relationship between exposure duration and sulfur dioxide-induced bronchoconstriction in asthmatic subjects. Am Ind Hyg Assoc J 1988;49:38-47.
19. Balmes JR, Fine JM, Sheppard D. Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am Rev Respir Dis 1987;136:1117-21.
20. Riedel F, Krämer M, Scheibenbogen C, Rieger CHL. Effects of SO_2 exposure on allergic sensitization in the guinea pig. J Allergy Clin Immunol 1988;82:527-34.
21. Matsumura Y. The effects of ozone, nitrogen dioxide, and sulfur dioxide on the experimentally induced allergic respiratory disorder in guinea pigs. I. The effect of sensitization with albumin through the airway. Am Rev Respir Dis 1970;102: 430-7.
22. Matsumura Y. The effects of ozone, nitrogen dioxide, and sulfur dioxide on the experimentally induced allergic respiratory disorder in guinea pigs. II. The effects of ozone on the absorption and the retention of antigen in the lung. Am Rev Respir Dis 1970;102:438-43.
23. Matsumura Y. The effects of ozone, nitrogen dioxide, and

sulfur dioxide on the experimentally induced allergic respiratory disorder in guinea pigs. III. The effect on the occurrence of dyspneic attacks. Am Rev Respir Dis 1970;102:444-7.
24. Osebold JW, Gershwin LJ, Zee YC. Studies on the enhancement of allergic lung sensitization by inhalation of ozone and sulfuric acid aerosol. J Environ Patho Toxicol 1980;3:221-34.
25. Kerhl HR, Vincent LM, Kowalsky RJ, Hostman DH, O'Neil JJ, McCartney WH, Bromberg PA. Ozone exposure increases respiratory epithelial permeability in humans. Am Rev Respir Dis 1987;135:1124-8.
26. Ibrahim AL, Zee YC, Osebold JW. The effects of ozone on the respiratory epithelium of mice. II. Ultrastructural alterations. J Environ Pathol Toxicol 1980;3:251-8.
27. Payan DG, Levine JD, Goetzl EJ. Modulation of immunity and hypersensitivity by sensory neuropeptides. J Immunol 1984;132:1601-4.

Original articles

The relationship of serum IgA concentration to human immunodeficiency virus (HIV) infection: A cross-sectional study of HIV-seropositive individuals detected by screening in the United States Air Force

John A. Fling, MD, MAJ, USAF, Joseph R. Fischer, Jr., MS, R. Neal Boswell, MD, COL, USAF, and Michael J. Reid, MD, COL, USAF
Lackland Air Force Base, Texas

Serum immunoglobulins were measured in 107 patients with human immunodeficiency virus seropositivity. Each patient was categorized by the Walter Reed staging classification and serum concentrations of immunoglobulins were compared with patient staging. Serum IgM concentrations were normal in all but nine patients. Serum IgG concentrations were elevated in 74 of 107 patients, with no significant differences noted between different stages of disease severity. Serum IgA concentrations were elevated in 38 of 107 patients, with a significant relationship noted between increasing staging category and increasing serum IgA concentration (p = 0.0001). Serum IgA concentrations in patients with human immunodeficiency virus seropositivity may be a useful marker of immunologic progression of disease. (J ALLERGY CLIN IMMUNOL 1988;82:965-70.)

AIDS is caused by infection with HIV. The Department of Defense has initiated a program to screen all military personnel for HIV seropositivity; every HIV-seropositive member of the United States Air Force is referred to WHMC for evaluation. This evaluation includes a detailed analysis of each patient's immune status, a serologic survey for concomitant viral infections, and a complete epidemiologic profile. Redfield et al.[1] recently described a staging classification for HIV infection. We would like to report our experience applying this classification to patients seen at WHMC in various stages of HIV infection. We found a direct relationship between serum IgA concentrations and progression of infection as defined by Redfield et al. This prompted a more thorough evaluation of the role of serum IgA in HIV infection, and raised the possibility that serum IgA concentrations may be predictive for the development of AIDS.

Abbreviations used

AIDS:	Acquired immunodeficiency syndrome
CMV:	Cytomegalovirus
EBV:	Epstein-Barr virus
HIV:	Human immunodeficiency virus
IFA:	Indirect immunofluorescence assay
WHMC:	Wilford Hall USAF Medical Center
WR-1 to -6:	Walter Reed stages 1 to 6

From the Allergy/Immunology Service, Department of Medicine, Wilford Hall United States Air Force Medical Center, Lackland Air Force Base, Texas.
Received for publication Oct. 2, 1987.
Accepted for publication April 2, 1988.
The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.
Reprint requests: Michael J. Reid, MD, Allergy/Immunology Service, Wilford Hall United States Air Force Medical Center, Lackland AFB, Texas 78236.

MATERIAL AND METHODS

Patients

All patients admitted to WHMC between October 1985 and August 1986 with positive ELISA and Western blot results to HIV were evaluated clinically and by the following laboratory parameters: complete blood and platelet count; chemistry profile; quantitative immunoglobulins performed