

Ozone: A review of recent experimental, clinical and epidemiological evidence, with notes on causation

Part 2

DAVID V BATES MD FRCP FRCPC FACP FRSC

Department of Health Care and Epidemiology, University of British Columbia

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The first section of this concluding part reviews epidemiological studies relating to oxidant exposures. There are convincing data from the eastern section of the continent that ozone, in combination with aerosol sulphates and acid aerosols, is strongly associated with hospital emergency visits and in-patient admissions for acute respiratory disease, including asthma. There is some evidence that long term exposures may be associated with an increased prevalence of asthma; disturbing initial observations suggest the possibility that a chronic respiratory bronchiolitis may be induced. The second section of this article reviews the totality of information on ozone in the light of customary criteria of 'causality'. It is concluded that the present evidence justifies the conclusion that existing levels of tropospheric ozone are aggravating existing human disease, and probably increasing the prevalence and incidence of some diseases; however, it is uncertain whether this effect is being magnified by the concomitant presence of other pollutants. Although a great deal is known about the effects of ozone, there are still many important unresolved questions in relation to it.

Key Words: *Air pollution, Asthma, Ozone, Photochemical oxidants, Tropospheric ozone*

L'ozone : une revue des données épidémiologiques, cliniques et expérimentales récentes accompagnée d'un commentaire sur la causalité

RÉSUMÉ : La première section de cette dernière partie passe en revue les études épidémiologiques portant sur l'exposition aux oxydants. Des données convaincantes provenant de la façade est du continent prouvent que l'ozone, combiné à des sulfates en aérosol et à des aérosols acides, est fortement associé au nombre de visites à l'urgence des hôpitaux et au nombre d'admissions résultant d'une pathologie respiratoire aiguë, y compris l'asthme. Il semble que des expositions à long terme soient associées à une augmentation de la prévalence de l'asthme; des observations initiales troublantes laissent supposer qu'une atteinte chronique des bronchioles respiratoires pourrait être causée par ces expositions. La deuxième section de cette article passe en revue la totalité des informations sur l'ozone en tenant compte du critère habituel de causalité. On conclut que les données actuelles apportent la preuve que les niveaux d'ozone contenus dans la troposphère aggravent les maladies existantes chez l'homme et accroissent la prévalence et l'incidence de certaines maladies; cependant, on ne sait pas si cet effet est renforcé par la présence concomitante d'autres polluants. Bien que nous disposions d'une quantité appréciable d'informations sur les effets de l'ozone, un bon nombre de questions importantes concernant ces effets ne sont encore pas résolues à l'heure actuelle.

Correspondence and reprints: Dr DV Bates, Department of Health Care and Epidemiology, Mather Building, 5804 Fairview Avenue, Vancouver, British Columbia V6T 1Z2. Telephone 604-822-4530, Fax 604-822-4994

EPIDEMIOLOGICAL STUDIES

Field studies and panel studies

Studies of forced expiratory volume in 1 s (FEV₁) in children at summer camps in Canada and the United States have indicated that the summer mix of pollutants, including ozone, is associated with measurable declines in function. Kinney et al (1) compared data from these studies and showed that there was reasonable conformity among them. Adults jogging in their lunch hour were studied by Spektor and colleagues (2). Many of their subjects were found to have ventilation levels in excess of 60 L/min (they had selected their own exercise level). Changes in forced vital capacity (FVC) and FEV₁ were related to the ambient ozone on the day of their jogging.

Lioy et al (3) found evidence that the effect of ozone on peak expiratory flow rate may last for several days. In a recent summer camp protocol, Spektor and colleagues (4) studied 46 children aged eight to 14 years at a camp for a four-week period. The highest ozone encountered was 150 ppb. They noted that regressions of morning function on the previous day's ozone were significant. No correlations were observed for hydrogen ion (in previous studies it had proved difficult to be sure that the response might not be due to accompanying acid aerosols). These authors concluded that camp studies generally yield higher effects of ozone than do chamber exposures, for four possible reasons: first, the exposures in the field are longer; second, there may be potentiation by other factors; third, there may be persistence of effects from the previous day's exposure; and fourth, there may be persistence of a transient response associated with the daily peak exposure.

The authors cautioned that "It follows that projections of likely effects in the real world from controlled chamber studies should either have a large margin of safety, or the judgement of the extent of effects likely to occur among populations should be based directly on the effects observed in field studies".

Lebowitz and colleagues (5) studied panels of asthmatics and others in Tucson, Arizona drawn from 117 white families from a stratified sample. Detailed measurements of air pollutants, pollen, bacilli, fungi and algae were made in and around a random cluster sample of 41 households. Thirty-five asthmatics provided daily peak flow measurements. The very complex resulting data showed that both ozone levels and temperature had effects on the peak flow data. Javitz et al (6) reanalyzed a study of 286 subjects with asthma and chronic bronchitis (probably with and without accompanying emphysema) in Houston, Texas. Daily symptom diaries were kept, and home spirometry testing was done in about one-third of the subjects. Respiratory symptoms and medication use increased as the daily ozone maxima increased. In the same city, Holguin and colleagues (7) conducted an asthma panel study in 1985. They carefully defined an 'asthmatic attack' and followed the panel for six months. Ozone levels ranged up to 0.27 ppm. They showed that an increase in the 1 h maximum ozone of 0.1 ppm increased the attack probability from a baseline value of 10% to 16%. This 60%

increase in risk was four times that observed by Whittemore and Korn (8), who published their analysis of a panel study of asthmatics in Los Angeles in 1980. Although by contemporary criteria their cases were not characterized in sufficient detail, they found convincing evidence that asthma was worsened by both ozone and particulate pollution exposure.

Gong (9) studied 83 asthmatics in Los Angeles between February and December 1983. He reported that 39 of the subjects were 'ozone responders', with symptoms and medication use consistently related to ozone levels, although the total group results had not shown a significant relationship. The cases were relatively mild, since 77% of the total group had peak flow measurements within the normal range.

In the early 1980s, Linn and colleagues (10) carried out an extensive series of studies in Los Angeles using a mobile van that contained an exposure chamber and pulmonary function testing equipment. After an initial finding that suggested that function decrements in the natural environment with photochemical pollutants was greater than that found in chamber exposures, they finally concluded that the observations of decreased function were explicable on the basis of the ozone exposure. Later studies of competitive cyclists in the same mobile facility (11,12) showed that FEV₁ declines occurred at ozone levels as low as 0.16 ppm (a result in accord with the controlled exposure data described above). They concluded that the decrement in function in the Los Angeles atmosphere was attributable to the ozone present.

Castillejos et al (13) reported studies on a panel of normal children in Mexico City. This showed that the FEV₁ and the maximal midexpiratory flow (FEF₂₅₋₇₅) decrements were strongly related to ozone levels averaged over 24 to 168 h before spirometry, but not to the ozone in the previous hour. The authors suggested that the results might reflect an inflammatory response in the airways as opposed to an acute physiological response. One-hour average ozone levels in the hour preceding the tests had ranged up to 0.287 ppm, with a mean of 0.099 ppm.

Hospital admissions or emergency visits

Sterling and colleagues (14) in 1966 and 1967 reported a positive association between oxidant levels and admissions of Blue Cross patients to Los Angeles Hospitals with more than 100 beds. In 1981, Richards et al (15) reported finding no association in the same city between emergency visits at a children's hospital for asthma and oxidant levels. The study period extended from August 1979 to January 1980, which may have been too short. Goldsmith et al (16) studied emergency room visits in four southern California communities during 1974 and 1975. Maximum hourly averages of oxidants and temperature were associated with daily visits in the high oxidant area (Azusa). A significant association was demonstrated. In retrospect, it is surprising that this finding did not trigger follow-up epidemiological studies.

In 1983, Bates and Sizto (17) reported finding an association between acute respiratory admissions to 79 acute care hospitals in southern Ontario and ozone levels. A later and more detailed analysis including data on concomitant sul-

phate measurements was published in 1987 (18). Admissions on a given day were compared with the mean admissions for that day of the week in the same season of the same year to correct for day of the week effects and long term trends. This conservative approach to the data confirmed the association between summer ozone levels and hospital admissions for acute respiratory disease and showed that the association was as strong for sulphates as for ozone. It was shown that asthma admissions for children 24 h after ozone had exceeded the Canadian objective of 0.08 ppm for 1 h were consistently elevated compared with admissions on all summer days (19). In this and similar studies, it has proved difficult to separate the effects of these pollutants, which, in this region, commonly rise and fall together (20). The association of hospital admissions with sulphate levels in southern Ontario was confirmed by Plagiannakos and Parker (21). They analyzed all acute respiratory admissions over a period of six years, and reported significant regression associations between hospital admissions, expressed as a rate for each county, and both sulphur dioxide and sulphate. This study used all the available sulphate and sulphur dioxide data for the region and attempted to ensure that differences in socioeconomic status had not interfered with the analysis. An indirect regional index of tobacco consumption was also used. The importance of this study was that the two analyses in southern Ontario, though planned and conducted independently, served to reinforce each other in terms of the relationship between morbidity indices and sulphates. Unfortunately, Plagiannakos and Parker did not analyze ozone levels.

A significant association between ozone levels and respiratory admissions was found by Ozkaynak and associates (22) in Massachusetts. Using hospital emergency visits rather than admissions as an index, Bates et al (23) found no summer relationship between ozone levels in Vancouver and visits for acute respiratory conditions. Ozone levels there were about half what they were in southern Ontario. Since the summer period included September, when a peak in asthma visits occurred that was unrelated to pollutants when ozone levels were low, a summer relationship to ozone might have been obscured; however, a reanalysis of the data for June, July and August only showed no relationship between ozone and asthma attendances.

Lipfert and Hammerstrom (24) reanalyzed the southern Ontario data used by Bates and Sizto and extended them to 1985. They confirmed that significant associations occurred in the summer and showed that no changes occurred in admissions for a group of nonrespiratory causes. They calculated that the pollutant mean effect might account for 19 to 24% of summer respiratory admissions.

Burnett et al (25) included all Ontario hospitals below the 47th parallel in their recent analysis of admissions between 1983 and 1988. To improve the exposure metric, they analyzed data from individual hospitals rather than aggregating the results by region. Ozone showed a positive association with respiratory admissions in 91% of the 168 hospitals. Six per cent of the summertime respiratory admissions were attributed to ozone and, surprisingly, they found that summer

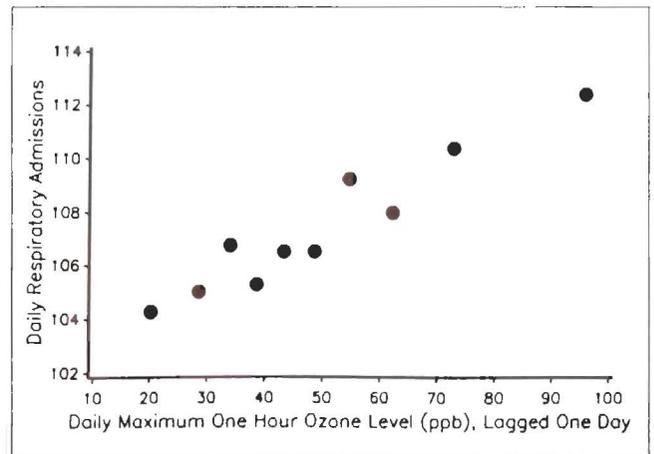


Figure 1) Data from 168 hospitals in Ontario, 1983-1988. Reproduced with permission from reference 25

pollutants accounted for 16% of the hospital admissions of infants. The relationship between daily maximum 1 h ozone level, lagged one day, and daily respiratory admissions appeared to be monotonic, rising from 104 admissions when ozone was 20 ppb to 113 admissions when ozone was about 100 ppb (Figure 1). This regression may form the basis for a more formal risk estimate than has been possible in the past. Temperature was shown to have no effect on the pollution-respiratory relationship.

A recent more detailed analysis of data from Toronto for the summers of 1987, 1988 and 1989 was prepared by Thurston et al (26). Using similar prefiltering methods to those used in an earlier paper, they showed that ozone was the summertime haze constituent of greatest importance to respiratory and asthma admissions, but that elevated hydrogen ion was a possible 'potentiator' of this effect (Figure 2). A sensitivity analysis showed that if days when ozone was above 0.12 ppm (two out of a total of 177) were dropped from the analysis, the ozone coefficients were unchanged. It was estimated that 19 to 20% of all summer respiratory admissions were associated with air pollution, and that admissions rose by about a third above expected levels on the highest ozone day, when the concentration was 0.159 ppm. Thurston et al (26) also showed that data from Buffalo and Toronto, which experience almost identical air pollution patterns, were essentially the same, in spite of different populations and patterns of medical care.

Cody et al (27) studied emergency room visits for asthma, bronchitis and finger wounds (as a control) at nine hospitals in central New Jersey. Data were collected for May to August 1988 and 1989, and data on ozone and sulphur dioxide were collected from the nearest of five monitoring sites. No associations were seen for bronchitis or for the control diagnosis. Simultaneous regressions of asthma visits yielded significant positive coefficients for ozone and negative coefficients for temperature, suggesting that temperature acted as a long wave control variable. Day of the week effects were found to be unimportant. In an extension of these observations, Weisel et al (28) conducted a five-year retrospective analysis of

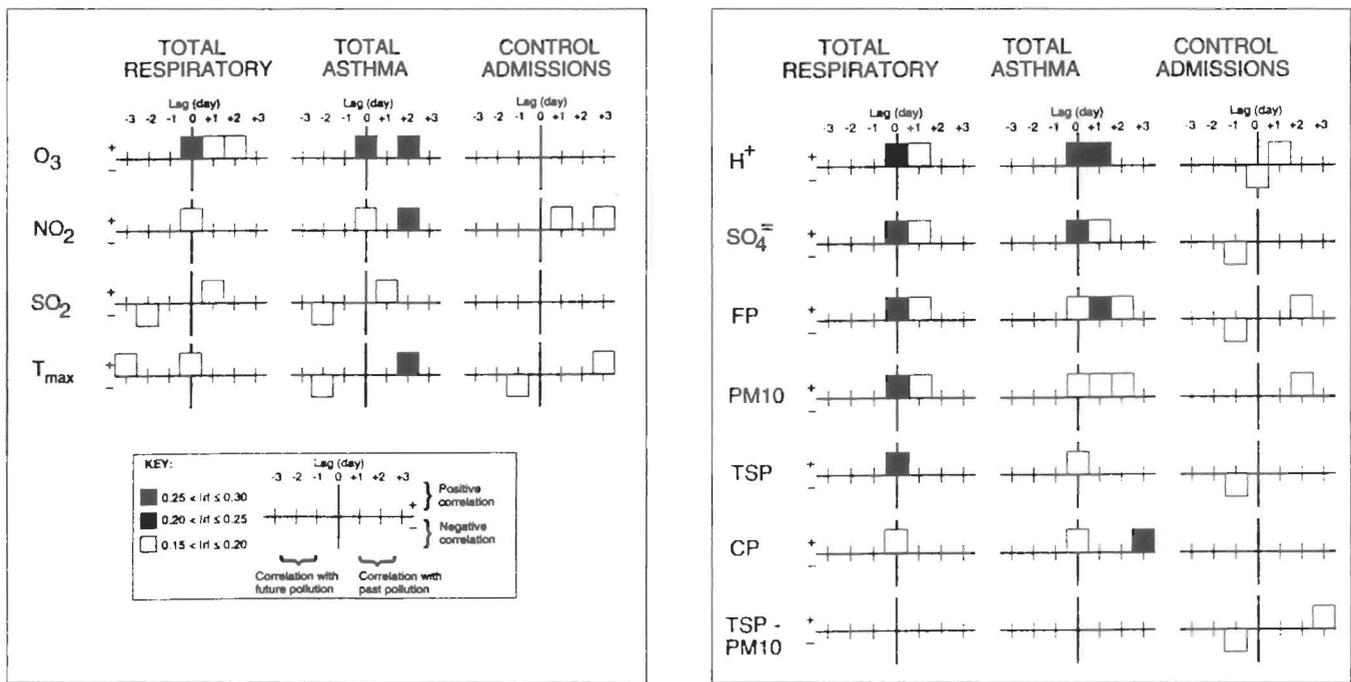


Figure 2) Left Data from Metropolitan Toronto for the summers of 1987, 1988 and 1989. Cross-correlations of daily hospital admissions with gaseous pollutants and temperature after detrending and day of the week control are shown. **Right** Cross-correlations between daily hospital admissions for Metropolitan Toronto and various measures of particulate pollution after detrending and day of the week control. CP Coarse particle fraction; FP Fine particle fraction; PM10 Particles less than 10 µm in size; Tmax Maximal daily temperature; TSP Total suspended particulates. Reproduced with permission from reference 26

emergency department visits for asthma in the same nine New Jersey hospitals. This showed that in every year, emergency visits occurred 28% more frequently when ozone levels were above 0.06 ppm than they did when ozone was less than this value. They concluded that there was consistency in reported ozone effects in relation to the time lag between exposure and four different outcomes – symptom reports, decrements in expiratory flow, emergency department visits, and hospital admissions – and concluded that “This supports a proposition that ozone adversely affects asthmatics at levels below the current US standard”.

White and colleagues (29) at the United States Centers for Disease Control and Prevention recently reported a summer study conducted from June to the end of August 1990 at a children’s hospital in Atlanta, Georgia. This showed a close and highly significant association between attendances for acute asthma (n=609) and ozone levels. The model yielded a 1.42 admission rate ratio for the number of asthma visits following days with ozone equal to or exceeding a 1 h maximum of 0.11 ppm. No admission relationship with ozone was seen below 0.11 ppm or with an 8 h average ozone value. The sulphuric acid aerosol levels at the Grady Hospital in Atlanta reach a maximum of 314 neq/m³ in summer with an average value of 117 neq/m³. Sulphates at Georgia College of Technology in Atlanta average 273 neq/m³ with a peak 24 h value of 535 neq/m³ (30). These values are not much different from those in the summer in New Jersey, and are slightly lower than values recorded in Toronto. Ozone was highly correlated (r=0.61) with hydrogen ion levels in

Atlanta, just as it was in the more northern sites. The children attending the Grady Hospital were predominantly without any regular health coverage (see below). Local pollen counts were slightly higher on high ozone days, but were not significantly related to emergency visits.

Thurston et al (31) analyzed emergency admissions to acute care hospitals in three New York metropolitan areas during the summers of 1988 and 1989. The data were prefiltered using sine and cosine waves with annual periodicities. Ozone was significantly related to acute respiratory admissions, the relationship being stronger in Buffalo and New York City than in the wealthier community of Albany. The high intercorrelations between ozone, hydrogen (measured as acid sulphuric acid aerosol every 24 h) and sulphates prevented a definitive identification of one of these as the causal factor. Hospital admissions for control conditions were unrelated to pollution data.

The validity of using hospital based statistics has often been questioned (32). Delfino et al (33) recently reported a validation study of Quebec hospitals in terms of respiratory diagnoses (n=679). Although there was some discrepancy between the diagnosis reported by the hospital to the computer file and that reached by an expert after perusal of the hospital records, in the case of asthma, the agreement was 94.9% and was 90% for all respiratory diagnoses if minor differences in classification were ignored. Martinez et al (34) also reported a validation study of emergency visits to hospitals in Barcelona.

Many factors must be involved in relation to the use of

hospital emergency departments or the criteria for admission. Halfon and Newacheck (35) recently reported on the 1988 National Health Interview Survey on Child Health in the United States. They showed that poorer economic groups used private doctors less and hospital emergency departments more in relation to acute exacerbations of asthma. Furthermore, the poorer groups spent more days in hospital and suffered more morbidity than wealthier groups. Thus it follows that hospital emergency visits, as an outcome indicator, might be expected to be more frequent if the hospital serves lower income groups. This might explain the higher associations found by Thurston in Buffalo between ozone and hospital admissions than occurred in Albany, which is a wealthier community. In spite of this, of course, it must be assumed that the adverse impact of ozone takes no account of economic status, except possibly in terms of the protection conferred by air conditioned homes.

Cross-sectional comparisons

Hodgkin et al (36) found some evidence of more respiratory symptoms in nonsmokers in higher oxidant regions, but the difference was not great. Linn and colleagues (37) could not demonstrate consistent differences in either respiratory symptomatology or function among populations of office workers in areas with different levels of oxidant pollution.

Abbey and colleagues (38,39) reported on a continuing study of Seventh Day Adventists resident in California over 25 years of age who had resided 11 years or more in areas with different levels of oxidant air pollution. They found evidence that worsening of asthma was associated with the annual average exceedance frequency of ozone thresholds of 0.10 and 0.12 ppm. Although this study did not account for the possible confounding effect of fine particulate pollution, it provided significant evidence of worsening of asthma in those living in a higher oxidant environment.

An interesting comparison has been published of children in Austria living in relatively high and low ozone regions (40). Two hundred and eighteen children (mean age 11.6 years) lived in the high ozone region in which ozone exceeded 100 ppb 9.68% of the time, and 281 children lived in a low ozone region where that value was never exceeded. Other pollutants were similar among the regions. There were no specific exposure data for any of the children. There were no differences in allergic background, as judged by immunoglobulin E levels or asthma symptoms, no differences in cough or breathlessness, nor in pulmonary function status. But there was a higher incidence of bronchial hyperresponsiveness to methacholine in the high ozone group, and there were differences in the ratios of types of lymphocytes. The 'high ozone' children showed a decrease in T helper lymphocytes and an increase in T suppressor cells compared with the children in the low ozone area. Although the significance of these hematological differences is unclear, the authors interpreted their overall findings to indicate that ozone had caused a significant difference in status.

Other epidemiological evidence of long term adverse effects of ozone exposure has come from the analysis of the

NHANES II Survey data in the United States provided by Schwartz (41). He reported a decrement in FVC in boys in relation to calculated long term ozone exposure; however the analysis did not account for possible concomitant pollutants. Ostro and Rothschild (42) used data from the Health Interview Survey in the United States between 1976 and 1981, and reported a relationship between ozone exposure and minor reduced activity days. This study confirmed earlier observations by Portney and Mallahy (43), who noted a relationship between ozone levels and reduced activity days by combining aerometric and survey data.

Longitudinal studies

Detels and colleagues (44) planned an ambitious longitudinal study of smoking and nonsmoking subjects in different regions of Los Angeles. This showed a faster rate of longitudinal decline in more polluted regions when subjects were retested after an interval of five years; however, there was a considerable loss of sample between the two observations, making interpretation difficult. Bresnitz and Rest (45), in a review of oxidant epidemiological data, noted difficulties in the interpretation of the University of California at Los Angeles (UCLA) longitudinal study. The question of whether the differences in rate of longitudinal decline could be attributed to sample loss is a difficult one. Lippmann (46) in his review of the effects of ozone felt that the preliminary evidence from this study could not be dismissed. A more recent presentation of the UCLA results (47) concludes that the continuing follow-up confirms the faster rate of decline of FEV₁ in more polluted regions, and gives reasons why the loss of about half the original groups studied initially is unlikely to have affected the results. It may be noted that on theoretical grounds, longitudinal studies should be more sensitive indicators of long term adverse effects of oxidant pollutant exposure, but such studies are very difficult to organize, and it is difficult to avoid loss to follow-up of a significant fraction of the surveyed population. If this occurs, the interpretation of any result becomes open to question.

Hackney and Linn (48) recently demonstrated that the level of airway responsiveness changes with the seasons in Los Angeles, increasing during and just after the high ozone season and thereafter declining.

Kilburn et al (49) in Los Angeles conducted spirometry on 556 Mexican-American children in 1984. In 1987, the investigators conducted spirometry on 251 Mexican-American children, including 106 of the children who had been measured in 1984. They standardized all pulmonary function test values for growth by expressing them as percentages of predicted values based on sex and height. In 1987, the mean values for FEV₁ and FEF₂₅₋₇₅ were lower by 4.5% predicted and 13.6% predicted, respectively, compared with 1984. Vital capacities were not different (this is an important control for the test procedure). For the 106 children tested on both occasions, FEV₁ was 2.0% lower and FEF₂₅₋₇₅ 7.0% lower. There was no significant difference between the 1987 mean value for 145 children tested for the first time in 1987 and that of the 106 retested children. The authors concluded that the

TABLE 1
Percentage prevalence of asthma in the United States

	All incomes	Poor	Nonpoor
All children	4.3	4.8	4.2
Caucasian	4.1	4.6	4.1
Black	5.1	5.2	5.1
Age (years)			
0-5	3.2	4.2	3.1
6-11	5.1	5.6	5.1
12-17	4.5	4.5	4.6

Data from the 1988 National Health Interview Survey on Child Health

effects might be due to ambient air pollution, but the data in their paper are not easy to interpret.

Mortality data

It is remarkable that, although Mahoney (50) in 1971 reported that respiratory mortality rates in Los Angeles seemed to follow the contours of oxidant pollution, until last year no definitive study of the relationship between ozone levels and mortality had been conducted.

Kinney and Ozkaynak (51) recently published a very careful time series analysis of data from Los Angeles. It indicates clearly that ozone levels (lagged by one day) are associated with increases in mortality (from both respiratory and cardiovascular diseases). Their analysis by modern statistical techniques indicates that ozone is the important factor, and that temperature changes are unlikely to have interfered with the regression analyses. This study was supported by a complementary one (52) of data from New York for the period 1971 to 1976. Long wave cycles in mortality were removed before the analysis. A multiple simultaneous regression showed significant coefficients for one-day lagged ozone ($P=0.004$) and for temperature and coefficient of haze and humidity on the same day. Expressed as an 'elasticity', a 1% increase above the mean ozone concentration was associated with a 0.019% increase in mortality – a figure very similar to that found to apply in Los Angeles.

Autopsy data

Sherwin and Richters (53) described changes of severe respiratory bronchiolitis in a high proportion (27%) of autopsy lungs from 107 young adults aged 14 to 25 years who died in Los Angeles district from nonrespiratory causes. Although this study has not yet been compared with a control region and the degree of small airway disease has not been measured by quantitative morphometry, it seems likely that the lesion represents an aggravation of the respiratory bronchiolitis known to be a consequence of cigarette smoking. It may be significant that, as noted above, theoretical dosimetric calculations have indicated that ozone deposition in the human lung would be maximal in this region of the lung, and data in ozone-exposed nonhuman primates indicated that a respiratory bronchiolitis was the principal induced lesion. Adesina et al (54) in Vermont quantified bronchiolar wall inflamma-

tion and fibrosis in autopsy material from 42 smokers and 13 nonsmokers living in a relatively nonpolluted environment. They showed highly significant differences between the two groups, particularly in subjects below the age of 40. The question of whether living in an oxidant environment results in a more severe degree of bronchiolar inflammation, either in nonsmokers or in smokers, should be answerable if these data could be compared with similar data from Los Angeles.

THE BASIS OF A CAUSAL INFERENCE

Bronchial hyperresponsiveness and asthma

A considerable volume of work over the past five years has changed the perceptions of these two clinical conditions and their interrelationship; most important, the basic concept of asthma, based on new understanding of its pathology, is directly relevant to a decision about the possible role of ozone exposure.

In the normal population, some individuals with no history of respiratory symptoms and no atopy are found to be hyperresponsive when challenged with mecholyl or histamine. The prevalence of this state in different populations is not yet precisely known. It is known that bronchial hyperresponsiveness is uniformly present in those who have clinical asthma and in those who reply positively to questionnaires about asthma. Bronchial hyperresponsiveness is also increased in those with wheezy illnesses. It is also known that normal individuals are found with no such symptoms and with no history of asthma, but who are hyperresponsive. In Ontario, Fitzgerald (55) found that in a random cluster of 310 nine-year-old Canadian children, mild asthma was present in 8%, moderate asthma in 11% and severe asthma in 3%. Thirty-five per cent of the children were found to have an enhanced methacholine response, and of these 11% had no history suggestive of asthma. The fraction of hyperresponsive children was about double that found by identical methods in New Zealand. As previously noted, Hackney and Linn (48) in Los Angeles observed that the airway responsiveness in volunteers in that city varied between the high and low pollution seasons.

It seems reasonable to assume that hyperresponsive individuals in the population, even with negative respiratory questionnaire data, may be those at risk from exposure to environmental agents that increase hyperresponsiveness or induce inflammation in the lung.

Differences in asthma prevalence are difficult to evaluate because of the difficulty in defining the condition and because the factors that may lead to different answers to questionnaires are poorly understood. Halfon and Newacheck (35) analyzed data from the 1988 National Health Interview Survey on Child Health in the United States, which involved 47,485 households and 17,110 children. They noted the prevalence data for doctor-diagnosed asthma shown in Table 1.

The prevalence of a persistent wheeze in children is higher, being found in 9.2% of 650 children in Boston (56). If the question is asked about wheezing in respiratory illnesses, the percentage is increased again.

The prevalence of asthma has been carefully documented in the Nordic countries of Europe, where considerable effort has gone into standardizing the definitions (57). In Norway, estimates of prevalence have varied between 0.4 and 2.4%; in Sweden the prevalence estimates are generally higher, varying between 2.0% and 6.8% in different parts of the country and different age groups; in Finland, estimates vary between 1.0% and 3.0%. The variation within Denmark is large, from a low of 0.9% in one general practice to a high of 10.5% in another. The most recent estimate for Danish schoolchildren was 4.0%.

With the use of standardized questions, the prevalence of asthma in children aged between six months and 11 years living in the United States differed according to their ethnic origin (Table 2) (58).

Burrows (59) in a community survey in Tucson, Arizona found a prevalence of asthma of 8.2% in those between the ages of six and 34 years; 8.6% in those between 35 and 54 years; and 9.8% in those over 55 years of age. In a study in progress of 3600 children in Los Angeles in 10 different communities, the prevalence of asthma seems to be high (18% in some areas, personal communication).

There is some evidence that the prevalence of asthma has been increasing. From a comparison between two NHANES surveys in the United States in 1971-1974 and 1976-1980, Gergen et al (60) concluded that the prevalence of asthma in six- to 11-year-olds had increased from 4.8% to 7.6%. In 1990, Burney et al (61) in Britain compared data from 1973 with data from 1986 on 15,000 boys and 14,156 girls and concluded that asthma prevalence had increased by 6.9% in boys and 12.8% in girls over that period. There had also been increases in those who had a 'persistent wheeze'.

There is no doubt that the rate of hospital admissions for asthma in all age groups has increased over the past 10 years; it is unlikely that this reflects the admission of more patients with less severe degrees of asthma. Mao et al (62) summarized this data for Canada; it has also been shown to be true of the United States and in a number of countries in Europe.

If the severity of asthma has not changed in those admitted, then the increased hospital admissions for asthma, which have been very generally noted, must indicate an increase in the severity of the disease, an increase in prevalence or both. It is possible that a factor might change the severity of the disease without affecting prevalence, or by increasing prevalence, might increase the number of relatively severe cases.

There has been a striking change in the perceptions of the pathology of asthma. This change in thinking began with the initial observations by Laitinen and colleagues (63), who in 1985 reported on bronchial biopsies in eight nonsmoking asthmatics. None had had a respiratory infection within the past two months. All had evidence of epithelial destruction and inflammatory changes. The authors noted that "Epithelial destruction in the respiratory tract of the asthmatic with mild to severe bronchial hyperresponsiveness was prominent enough to expose the epithelial nerves for specific and non-specific stimuli". These observations have since been confirmed in a number of centres and were recently extended by

TABLE 2
Prevalence of asthma in children aged six months to 11 years according to ethnic origin in the United States

Ethnicity	Prevalence (%)
Puerto Rican	11.2
NonHispanic Caucasian	3.3
NonHispanic Black	5.9
Mexican-American	2.7
Cuban	5.2

Data from reference 58

the demonstration of severe chronic inflammatory changes in severe asthmatics and in fatal cases (64) as well as in the finding of inflammatory changes in the lungs of mild cases of recent onset (65).

Possible outcomes from ozone exposure

From this condensed review of human and animal data, it is clear that the following possible outcomes as a consequence of ozone exposure may reasonably be expected to occur:

- 1) Increased airway responsiveness in the population;
- 2) Increased prevalence of asthma;
- 3) Increased severity of asthma attacks;
- 4) Increased incidence of asthma attacks;
- 5) Increased severity of respiratory infections;
- 6) Increased incidence of respiratory infections;
- 7) Increased prevalence of chronic respiratory symptoms;
- 8) Development of chronic respiratory bronchiolitis.

In the following sections, the strength of a causality inference will be assessed in relation to these eight outcomes. There is no direct evidence that ozone causes emphysema in animals and no human evidence that it is related to an increased incidence of lung cancer, although, as noted above, the properties of ozone and its biological actions have suggested that this might be the case. These two outcomes are therefore not specifically addressed.

Bradford Hill's suggested criteria

In 1965, Hill (66) considered the criteria by which we might be guided in reaching a conclusion of causality. He listed nine issues that he had found helpful. Each of these is discussed in turn in relation to the effects of ozone. The question of causality in relation to demonstrated associations is always complex, and this is particularly the case when the exposure data are imprecise (67).

Strength of association: For the eight outcomes listed above, one might conclude that the strength was reasonably strong for numbers 3) and 4), and that for 1), 2), 5), 6) and 8) there were no data to enable the strength to be assessed. There is some evidence for 7).

It is important to note that the strength of the association might well have been weakened by the generally inexact exposure information. Also, because most of the outcomes involve multifactorial diseases, strong associations with any single factor are not to be expected.

Consistency: Has the relationship been observed by different persons, in different places, circumstances and times? In

relation to 3) and 4), the evidence in northeastern North America is consistent, but accompanying aerosol acidity may have been contributing to it. That ozone is the important pollutant is indicated in the New Jersey and Atlanta studies. Outcome 5) is probable but difficult to assess because the differentiation from asthma may well be confused. No data exist to evaluate 1) or 8).

Specificity: As noted above, the relatively strong data from the northeast may indicate that ozone accompanied by acid aerosol is more significant than ozone alone. There are animal data to support this.

Temporality: The significant associations between ozone and hospital admissions or emergency visits only occur 24 to 48 h after the ozone level has risen (Figure 2).

Biological gradient: Although the dose-response relationship can be clearly demonstrated in controlled clinical exposures, it is more difficult to demonstrate in epidemiological studies. Precise dose-response calculations are difficult to calculate since ozone effects do not follow a concentration \times time pattern; effects differ with sequential exposures; and there are many other determinants of each of the outcomes. However, the recent analyses of Ontario data by Burnett et al (25) do permit an approximate dose-outcome relationship to be adduced. The absence of an effect of ozone on hospital emergency visits in Vancouver (23) supports the view that a dose-response effect exists.

Plausibility: Ozone causes inflammation in the lung at very low concentrations, and it persists for at least 18 h after the exposure has ended. Hence, any of the possible outcomes must be considered highly plausible. The new understanding of asthma as an essentially inflammatory disease adds to the likelihood of outcomes 2), 3) or 4). Increased asthma prevalence has not yet been demonstrated, although 1) has been shown to occur. There is strong support from dosimetric studies and from data from nonhuman primates that supports the plausibility of 8). The reported occurrence of chronic respiratory bronchiolitis in autopsy data requires confirmation, however. Although there are interpretational difficulties in the case of the longitudinal studies that have been performed, both have shown evidence of a faster decline than normal in air flow rates.

Coherence: In the consideration of air pollutants, this criterion has special dimensions (68). Although ozone has been found to relate, on a time-series basis, to daily mortality, the mechanism for the effect is not known; possibly it is the same as causes fine particulate pollution to be related to mortality (69). However, a 'cascade' of phenomena from mortality to increased hospital admissions and emergency visits for asthma and nonasthmatic acute respiratory disease as well as the association of ozone with 'reduced activity days' combine to suggest that the coherence criterion is met.

There is also coherence in the concordance among theoretical dosimetric data, the centriacinar lesions in long term nonhuman primate and rat exposures, and the (only available) human autopsy data from Los Angeles.

Experiment: Under this heading, Hill suggested that, in the occupational arena, changed conditions might be observed

to modify an outcome. If human exposures to ozone have become more common over the past 15 years, it is tempting to suggest that this might have led to an increased prevalence of asthma. In addition to the commonality of inflammation, pointed out above, this would have biological plausibility if ozone enhances the entry of allergens into lung tissue.

Analogy: Photochemical oxidant pollution is distinct from former patterns of pollution, consisting of large particles from coal burning together with high levels of sulphur dioxide; therefore, an analogy to this form of pollution would not be appropriate. Exposures to ozone in the workplace are too intermittent for any conclusions to be drawn.

A JUDGEMENT OF CAUSALITY

The present data, taken together, appear to be strong enough to permit the following conclusions.

Asthma: The agreement between the southern Ontario and Toronto data (now reworked by four different investigators) and the supporting data from New York State and from New Jersey indicates beyond any doubt that higher ozone levels aggravate asthma and increase its severity. This is supported by the observations on panels of asthmatics in Los Angeles and Houston. This has strong biological plausibility. Whether ozone exposure increases the prevalence of asthma is not known, but the effect of the gas on bronchial hyperresponsiveness (unmodified by repetitive exposures) suggest this possibility. Data from nonsmokers in California support the conclusion that living in a high ozone atmosphere may increase the likelihood of asthma developing. It is possible that coexistent acid aerosols heighten the effect of ozone; these were present in all eastern continental sites, including Atlanta. In Los Angeles, there are high levels of nitric acid aerosol. The question of the interaction between ozone and acid aerosols may be answered by an epidemiological study of ozone and hospital admissions in Holland (personal communication), where acid aerosols are not detectable and ozone levels are about the same as in southern Ontario.

It should be concluded, on the basis of present data, that ozone at existing tropospheric levels is having an adverse effect on the 5% or so of the population with asthma and may be increasing the airway responsiveness in the population as a whole. Balmes (70) recently reviewed the interaction of ozone with asthma and came to the same general conclusions.

Respiratory infections: There is strong biological plausibility in the suggestion that, by impairing lung defences (and particularly by incapacitating the macrophage), ozone may increase the severity and possibly the incidence of acute respiratory infections. Most of the data sets indicate that acute respiratory admissions are significantly associated with ozone when asthma has been excluded. Since bacterial pneumonias are much more common in the winter months when ozone is low, careful seasonal filtering is necessary in studying this possibility.

On present information, it should be concluded that aggravation of respiratory infections is a likely sequela of current ozone levels; aggravation by acid aerosols is also likely. This

conclusion is reinforced by the observation that all acute respiratory admissions, and not just asthma, appear to be influenced by summer air pollutants. This might be attributed to diagnostic misclassification; however, Burnett's (25) recent observation in Ontario that 16% of the summer hospital admissions of infants in that province are related to summer pollutants reinforces this possibility.

Long term effects: The concordance between theoretical dosimetric calculations and the site of the observed lesions in animals with low level long term exposures is noted above.

If quantitative morphometric studies and comparisons with control cities where ozone is low confirm the observation that centriacinar lesions are much more common in young adults living in high oxidant regions, then this logical chain is complete. Efforts to show whether chronic respiratory bronchiolitis is more common in young people living in higher oxidant regions will have to depend on something other than questionnaire data and the FEV₁ (which has been shown to be insensitive to small airway changes [71,72]). Survey data

indicating a lower FVC in relation to oxidant exposure would confirm such a finding. Animal data indicate the probability that contemporary high oxidant levels are likely to be producing some long term changes in the lung, but the epidemiological demonstration of this is, as yet, incomplete.

CONCLUSIONS

With the possible exception of carbon monoxide, we know much more about the effects of ozone in animals and humans than we know of any other inhaled pollutant. It is therefore frustrating that precise answers still cannot be given to many important questions. Does ozone increase the prevalence of asthma, aggravate it, or both? Does ozone affect the general population level of airway responsiveness and, if so, what are the implications of this? Do oxidant atmospheres affect the normal development of the lung? Is any penalty paid for repetitive oxidant exposures? In spite of the extensive database, there is clearly a need for continuing investigation.

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