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Review, Discussion, and Summary of Epidemiological Studies

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This paper reviews and summarizes the epidemiological studies presented at the Symposium on the Health Effects of Acid Aerosols. Two studies of acute episodes examined different indicators of respiratory morbidity before, during, and after the January 1985 air pollution event in western Europe. In the U.K. no increase in respiratory morbidity, as reported by a group of general practitioners, was observed, but measured concentrations of air pollutants failed to substantiate the existence of an identifiable episode. In the Federal Republic of Germany, the air pollution episode was documented and was associated with a 10 to 25% increase in several indicators of respiratory and cardiovascular morbidity, but could not be attributed to acidic aerosols as such. In two further studies, investigators related day-to-day variations in air pollution with admissions to acute care hospitals in southern Ontario for respiratory disease over a 9-year period, and with daily mortality in London from 1963 to 1972. In the study of hospital admissions, significant correlations were observed with sulfate, ozone, and SO_2 pollution, but the data were insufficient to isolate the separate or combined effects of these pollutants. In the London mortality analysis, the strongest correlations were observed for sulfuric acid levels of the prior day, but prefiltering of the mortality data may have dampened the true relationship, and age- and cause-specific analyses would have been desirable. Finally two reports on chronic effects of residence in high air pollution areas have thus far made little contribution to the evidence for an adverse effect of specific pollutants.

Introduction

The epidemiological studies reported at this conference dealt with three facets of the question, Have human health effects from exposure to ambient acidic aerosols been demonstrated? The three groups of presentations were: (a) studies of the acute effects of air pollution episodes, in the presentations of Ayres, who reported on the January 1985 air pollution event in the U.K. (*1*), and of Wichmann, who reported on the same January 1985 event in the Federal Republic of Germany (*2*); (b) studies of the acute effects of daily variations in ambient air pollution, in the presentations of Bates on hospital admissions in Southern Ontario (*3*), and of Thurston on mortality in London during 1963–1972 winters (*4*); and (c) studies of the chronic effects of residence in urban areas with contrasting levels of air pollution, reported by Jedrychowski from the Cracow study (*5*) and by Speizer (*6*), the latter presented as a study concept rather than a completed investigation.

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Acute Effects of Air Pollution Episodes

The Ayres report on the January 1985 acidic transport event in the U.K. appears to have been a study of a nonevent. The reported average weekly concentrations of sulfur dioxide (SO_2) and smoke were 104 and 45 $\mu g/m^3$, respectively, during the event (but these concentrations were only twice those for the same week in the previous and subsequent years and for previous and subsequent weeks of the same year in the same exposed area of the U.K.) and 72 $\mu g/m^3$ for SO_2 and 32 $\mu g/m^3$ for smoke in the comparison nonpolluted area of the U.K. during the week of the episode (*1*).

These concentrations suggest either a very minor rise in air pollution levels in the polluted area or a masking of the short duration of the episode by the aggregation of data into a week-long average value. Therefore, the failure to observe any differences in rates of total respiratory disease between polluted and nonpolluted areas or between time periods within the polluted area may be attributable to one of three possibilities: (a) a minor air pollution event has no effect on respiratory morbidity; (b) respiratory morbidity as measured by weekly reporting from

general practitioners is not a sensitive indicator of the effects of a minor episode; or (c) a small effect of the minor episode did occur, but was diluted by other (nonpollution) determinants of respiratory morbidity. Clearly, a more striking rise in air pollution levels would have been desirable to evaluate the usefulness of this potentially valuable respiratory morbidity data source.

The Weekly Returns System of the Royal College of General Practitioners provides a continuous weekly record of respiratory disease morbidity in the U.K. as measured by physician diagnoses (*1*). Several problems were encountered in using this data source to study an air pollution episode. First, air monitoring results were only reported as weekly averages, resulting in a loss of ability to characterize an episode of 2 or 3 days' duration. Second, other major influences on variations in respiratory morbidity, such as season of year or respiratory epidemics, could easily have swamped a minor effect of air pollution. Third, episodes of respiratory morbidity were counted only weekly, again diminishing the power to detect a short-lived effect of a brief episode.

Nevertheless, the Weekly Reporting System has several attractive features for epidemiological studies of air pollution. The System includes 100 general practitioners, serving a sizable at-risk population of 200,000 persons (*1*). Although diagnostic standards are not imposed on the reporting practitioners, temporal variations in respiratory morbidity rates should be unbiased over an interval of 12 to 24 months, since one would expect little within-group reporting variability over a 1- or 2-year interval. This suggests that the best use of this reporting system may be to examine, over the course of 1 or 2 years, the effect of weekly air pollution variations, or of maximum 24-hr peak levels within each week, on reported respiratory morbidity rates in the population served by these practitioners. During a 1- or 2-year interval, one would expect to encounter several weekly periods of elevated air pollution. A pattern suggesting an association between respiratory morbidity and air pollution might then be observed. It is unlikely that other determinants of respiratory morbidity would be correlated with the distribution of weeks with high air pollution levels, thus allowing one to disentangle air pollution effects from other temporal factors affecting respiratory morbidity rates. Further, as air quality data are obtained for each day, it would be possible to investigate peak 24-hr concentrations, rather than weekly averages.

In Wichmann's report, air pollution concentrations were considerably elevated during the January 1985 event, with 24-hr maximum levels of 260 and 440 $\mu g/m^3$ for SO_2 and suspended particulates, respectively (*2*). Increases of 10 to 25% were observed in frequencies of hospitalizations, ambulance use, and emergency room visits for respiratory and cardiovascular illnesses in the polluted area, comparing the period during the smog episode with a before and after interval and comparing the polluted area with a control area.

As is usually the case for a one-time episode, several problems of interpretation were encountered. Given the regional distribution of finely dispersed acid aerosol pollution, it may be inappropriate to contrast the morbidity of exposed and control areas within a relatively small geographical region or state. Considerable geographical overlap in air pollution concentrations is likely to exist. More importantly, it is not clear that the reported excesses in hospitalizations and other morbidity indicators should be attributed to acid aerosols, as neither sulfates nor hydrogen ion concentrations were monitored. The possibility that the morbidity indicators were responding to a nonpollution, unmeasured confounder was not seriously addressed, e.g., whether a respiratory epidemic happened to hit at the same time, or whether this was a normal seasonal peak in respiratory morbidity.

One would like to see the analysis of morbidity indicators subdivided at least into broad age groups, such as children, working-age adults, and the elderly. A stronger effect on infants and the elderly would be consistent with other studies. Control for the effect of psychogenic factors on such end points as ambulance and emergency room use might have been attempted by studying the simultaneous changes in frequencies of presumably unrelated conditions, such as musculoskeletal or gastrointestinal morbidity.

In summary, the two studies of acute episodes at this conference examined different indicators of respiratory morbidity before, during, and after the January 1985 air pollution event in western Europe. In the U.K. no increase in respiratory morbidity, as reported by a group of general practitioners, was observed, but measured concentrations of air pollutants failed to substantiate the existence of an identifiable episode (*1*). In the Federal Republic of Germany, the air pollution episode was documented and was associated with a 10 to 25% increase in several indicators of respiratory and cardiovascular morbidity, but could not be attributed to acidic aerosols as such (*2*). Other possible explanations for the observed morbidity increase were not fully considered nor were morbidity rates stratified within age groups.

Acute Effects of Day-to-Day Variations in Air Pollution Levels

Using admission data for 79 acute care hospitals in Southern Ontario and relating these to air quality measurements from adjacent sampling stations, Bates observed the highest correlations between asthma admissions and daily sulfate (SO_4) concentrations, although statistically significant associations were also observed with ozone (O_3) and SO_2 (*3*). However, in June 1983 when O_3 concentrations were particularly high, no increase was reported for total respiratory admissions, nor for any subcategory of respiratory

diagnoses. Although these data were obtained for 4 months of each of 9 years, they were insufficient to identify the separate or combined effects of O_3, SO_2, SO_4, and hydrogen ion concentrations, in spite of the large population of 6 million persons served by the 79 hospitals. However, air pollution variables and temperature account for less than 6% of the variation in hospital admissions for respiratory disease, suggesting an overall weak association with these atmospheric factors. For this reason, hospital admission data may only be useful in detecting generalized air pollution effects, whereas individual air pollutants may be very weak determinants of variations in hospital admissions, particularly in the moderate range of concentrations commonly experienced in the U.S. and Canada in the 1970s and 1980s.

Thurston and colleagues re-examined existing data sets for daily mortality during nine winters in London, from 1963 to 1972 (*4*). The interesting feature of their study was the incorporation into the analysis of acid aerosol measurements, taken at St. Bartholemew's Hospital in London. The strongest correlations were observed between daily mortality and sulfuric acid (H_2SO_4) levels of the prior day, but these relationships were diminished when mortality data were prefiltered using a modified 15-day moving average to remove effects of autocorrelation and short-term cyclical fluctuations. The authors also observed a tapering of the mortality effect at high air pollution concentrations and suggested as explanation for this phenomenon either that the population of susceptibles was depleted (which seems implausible) or that more precautions were taken by the population on days of particularly high pollution, a behavior that could possibly be substantiated by examining traffic data or similar measures of outdoor human activity within the city.

Several aspects of the report can be challenged. First, the method of prefiltering mortality data using a moving average may itself dampen any real relationship between air pollution and mortality. Alternative analyses to deal with autocorrelation effects have been proposed (*7*). Second, age-specific mortality, and possibly mortality specific to broad categories of respiratory and cardiovascular causes, should be considered in the analysis scheme, since one would expect greater effects among the very young and very old segments of the population and for causes of death directly affected by peak concentrations of air pollutants. These more age-specific and cause-of-death-specific effects may well be masked by a global all-age and all-cause analysis.

Third, bias toward the null hypothesis will result due to the mixing in the same analysis of persons more intensely exposed with persons minimally exposed to the same ambient air pollutant, the latter group being protected by a relatively clean indoor environment. For example, elderly persons dying in a heated or air-conditioned hospital or nursing home might have considerably less exposure to ambient air pollutants than elderly persons in a lower social class home environment (a difference that could be easily documented). The point is that important differences in population exposure to outdoor ambient air pollution may well exist and could be taken into account by obtaining more data on the personal environment of individuals included in such studies.

Chronic Effects of Residence in Areas of High Air Pollution Levels

The last two studies in the epidemiology session provided little evidence regarding chronic effects of ambient pollutant exposures. Jedrychowski and Krzyzanowski's analysis of pulmonary function and chronic cough prevalence in three areas of Cracow (*5*) reveal inconsistent relationships with air quality measurements. On the one hand, area A, which had the lowest average level of particulate matter and SO_2 but slightly higher concentrations of SO_4 than the two other study areas, manifested the greatest decline in pulmonary function values between 1968 and 1981 but, among females, had the lowest age and smoking adjusted prevalence of chronic cough. However, area differences in SO_4 concentrations were trivial, ranging from 19 $\mu g/m^3$ in the low area to 23 $\mu g/m^3$ in the high area (area A) and would not be expected to account for the observed difference in change of lung function over time. Given the regional dispersion of SO_4 air pollution, it is unlikely that a single city study could reveal an exposure contrast between subareas of the same city. It would appear to be more appealing to search for individual exposure differences based on activity profiles and/or indoor versus outdoor exposures. In addition, an analysis of changes in lung function by strata of age and preexisting disease status would be desirable.

Although Speizer's report discussed only the concept of a proposed multi-city air pollution study, expanding on the investigator's experience with the Harvard Six-Cities Study (*6*), several interesting questions were raised. Can acute effects of short-term summer peaks in O_3 and/or acid aerosol concentrations be addressed in such studies? Frequent serial, even daily, measurements of health end points appear to be necessary to detect these events. Second, can a study of 300 children in each of 24 or more cities be accomplished, considering the multitude of logistical problems that must be faced in each city? Finally, can distinct exposure groups be identified to tease apart the effects of ozone, hydrogen ions, and nitrates, as the investigators propose?

Conclusions and Observations

Wichmann's results from the Federal Republic of Germany are important in that they provide evidence for acute respiratory and cardiovascular morbidity effects even in the more controlled air pollution envi-

ronment of the mid-1980s. However, we still cannot determine whether one or a combination of specific pollutants accounts for these episode-related effects.

Bates' findings lend further credence to the conclusion that contemporaneous temporal variations in air pollution are still a significant factor in respiratory morbidity, as evidenced by hospital admissions for these diseases. And yet, in spite of the large number of observations, based on 9 years of data from 79 hospitals and from adjacent air monitoring stations, it was not possible to disentangle the effects of O_3, sulfates, and SO_4. This shortcoming should not detract, however, from the contribution of these two studies in demonstrating acute respiratory morbidity effects attributable to current levels of air pollution. Clearly, air pollution of the 1980s can still produce detrimental health effects in an exposed population, even though exposures are usually held below established air quality standards. None of the studies reported at this session implicates acid aerosols, or any one specific pollutant, as the causal agent of the observed effects on morbidity.

These observations suggest several issues regarding future epidemiological investigations of air pollution exposure. In order to disentangle the effects of individual pollutants, we need more studies that make use of serial observations of both exposure and effect in the same individuals or populations. Such research might take the form of serial measurements of physiological function over a period of several weeks, as in some of the summer camp studies of Lippmann et al. (*8*) and Spektor et al. (*9*), or over a longer time interval. These studies can yield multiple points on a dose-response curve and thereby make it possible to distinguish the effects of individual air pollutants. This consideration leads to the second issue: combinations of air pollutants. Although it might seem more desirable to rely solely on controlled exposure chamber studies to study pollutant combinations, it is unlikely that the complex mixture of ambient air pollution can be reproduced in the laboratory. Furthermore, nature provides the exposure conditions for us; we need to take advantage of these situations by studying groups of people exposed to the variable ambient mixtures of ozone, hydrogen ions, and organic aerosols and simultaneously measuring exposures to each atmospheric component while noting physiological or adverse health responses to these mixtures. Very few epidemiological studies of this type have been conducted in the past decade.

Important modifiers of human response to air pollution exposure need to be considered in epidemiological studies. Potential modifiers internal to the study subject are age, extent of outdoor physical activity, preexisting disease state, and possibly some marker of respiratory hypersensitivity. External modifiers may be season of year and ambient temperature.

A final issue is that of estimating relevant human exposures. In epidemiological studies we typically measure human exposure externally and assume that the same ambient concentration will yield the same average delivered dose to the target organ of different persons. Some adjustments can be made to this assumption by factoring respiratory rate into the exposure estimation process. If we had some biological markers of delivered dose, we could do far better in discriminating between persons at greater risk of responding adversely to the same external exposure. Considerable variations must exist in the delivery of air pollutants to the target organ and in the effective absorption of these delivered doses. Our inability to make this discrimination usually biases our estimates of dose-response functions toward the null.

REFERENCES

1. Ayres, J., Fleming, D., Williams, M., and McInnes, G. Measurement of respiratory morbidity in general practice in the United Kingdom during the acid transport event of January 1985. Environ. Health Perspect. 79: 83–88 (1988).
2. Wichmann, H. E., Mueller, W., Allhoff, P., Beckmann, M., Bocter, N., Csicsaky, M. J., Jung, M., Molik, B., and Schoeneberg, G. Health effects during a smog episode in West Germany in 1985. Environ. Health Perspect. 79: 89–99 (1988).
3. Bates, D. V., and Sizto, R. The Ontario Air Pollution Study: Identification of the causative agent. Environ. Health Perspect. 79: 69–72 (1988).
4. Thurston, G. D., Ito, K., and Lippmann, M. Re-examination of London, England, mortality in relation to exposure to acidic aerosols during 1963-1972 winters. Environ. Health Perspect. 79: 73–82 (1988).
5. Jedrychowski, W., and Krzyzanowski, M. Ventilatory lung function and chronic chest symptoms among the inhabitants of urban areas with various levels of acid aerosols: Prospective study in Cracow. Environ. Health Perspect. 79: 101–107 (1988).
6. Speizer, F. E. Studies of acid aerosols in six cities and in a new multi-city investigation: Design issues 1-3. Environ. Health Perspect. 79: 61–67 (1988).
7. Whittemore, A. S., and Korn, E. L. Asthma and air pollution in the Los Angeles area. Am. J. Public Health 70: 687–696 (1980).
8. Lippmann, M., Lioy, P. J., Leikauf, F., and Green, K. B., Baxter, D., Morandi, M., Pasternak, B. S., Fife, D., and Speizer, F. E. Effects of ozone on the pulmonary function of children. Adv. Mod. Environ. Toxicol. 5: 423–446 (1983).
9. Spektor, D., Lippmann, M., Lioy, P. J., Thurston, G.D., Citak, K., James, D. J., Bock, N., Speizer, F. E., and Hayes, C. Effects of ambient ozone on respiratory function in active normal children. Am. Rev. Resp. Dis. 137: 313–320 (1988).