Lines That Connect: Assessing the Causality Inference in the Case of Particulate Pollution

David Vincent Bates

Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada

The question of when it would be appropriate to conclude that the associations between particulate pollution and various outcomes (including mortality) should be judged as causal in nature has been difficult and controversial. Although such a judgment must be subject to revision, the volume of new information and new experimental findings has been so great that such a reevaluation is required at frequent intervals. The useful summary by Gamble [$PM_{2.5}$ and Mortality in Long-Term Prospective Cohort Studies: Cause–Effect or Statistical Associations? Environ Health Perspect 106:535–554 (1998)] of the reasons why a causal inference was, in his opinion, not justified provides a basis for reevaluation in the light of new data. Such a reexamination indicates that the associative evidence is now stronger and that the biologic basis for a number of adverse effects has now been demonstrated. All of the useful guideline criteria customarily applied to such questions seem to have been met, although there is still much to be learned about interactive effects and the possibility of statistical thresholds. *Key words*: adverse health effects of air pollutants, air pollution, inference of causality, particle pollution, PM_{10}. *Environ Health Perspect* 108:91–92 (2000). [Online 20 December 1999]

http://ehpnet1.niehs.nih.gov/docs/2000/108p91-92bates/abstract.html

In 1998, Gamble (*1*) published a research review in which he discussed the data on particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and mortality and subtitled it "Cause–Effect or Statistical Associations?" In 1999, Künzli and Tager (*2*) questioned this critique on the basis that many of the studies quoted were not truly ecologic and were not similar to those that Gamble had imputed were probably misleading. In concluding that the existing data did not justify a causal inference (and by implication inviting others to take the same position), Gamble (*1*) laid out the reasons for his conclusion. This enables his position to be reanalyzed in the light of new data. At about the same time, Vedal (*3*) also provided reasons why a causal inference could be justified or denied; his paper was subtitled "Lines That Divide." The Third Colloquium on Particulate Air Pollution and Human Health held in Durham, North Carolina, on 6–8 June 1999 provides a convenient framework within which to examine this question (*4*).

Critique of Studies

Gamble's first major point was the inherent weakness of ecologic studies; this has been discussed in detail by Künzli and Tager (*2*) and there is little to add to their critique. His second point was the difficulty of knowing what the exposures to $PM_{2.5}$ had been; he wrote that

> total personal exposures to $PM_{2.5}$ are critical in assessing the association of PM [particulate matter] exposure and mortality and morbidity.

The improvement in exposure attribution is important; however, individual estimates are not possible when the large databases that give epidemiologic studies their power are being assessed. Nevertheless, the concordance between ambient sulfate measurements and personal exposures might be noted (*5*), as might the fact that the smaller the particle, the more uniform the concentration across wide urban regions and also between indoor and outdoor values (*6*). In some studies, such as one in Southern Ontario (*7*), when the exposure metric was refined by using the monitor closest to the hospital at which the admissions are being recorded, or when it was further refined by noting the zip code of the admitted patient and back-calculating the exposure 48 hr before admission, the associations between the exposure and the admissions became more significant. This strengthens the causal inference. Gamble relied on a detailed comparison between PM exposure and cigarette smoking; an "Appendix" included a comparison of risk estimates based on group-level exposure and individual-level cigarette smoke exposure from the Six Cities and American Cancer Society cohorts (*9,10*). He calculated the individual-level exposure to fine PM from smoking a cigarette, and concluded that ambient PM would constitute a small fraction of the total exposure in a typical smoker. He did not consider the evidence based on secondhand smoke exposure (ETS). These levels might be closer to ambient exposures than to direct inhalation. ETS exposure adversely affects the status of asthmatic children (*8*) in much the same way as respiratory symptoms and lower lung function in asthmatic children are influenced by levels of particulate matter ≤ 10 μm in aerodynamic diameter (PM_{10}) (*11,12*). This is a more compelling analogy than we can derive from the risks of cigarette smoking itself. Although there is not complete uniformity in the data relating ETS to lung cancer, this effect appears to be of the same order of magnitude as the effect of exposure to urban atmospheres on the risk of lung cancer (*13*). It may be questioned whether it is appropriate to assume that the complex effects of cigarette smoking can be attributed solely to the particles inhaled; it is less contentious to use ambient particles as an indicator of the complex mixture of air pollutants. Nevertheless, detailed comparisons of the two exposures require considerable justification. The exposure to atmospheres with increased particulate matter and SO_2 due to coal burning interacts with cigarette smoking in relation to the decrement of forced expiratory volume in 1 sec (FEV_1), as published in 1965 (*14*). Gamble treated the FEV_1 as a confounder but did not note that it could not be operative in the many time–series studies that have been published.

Gamble relied on the Seventh-Day Adventist study (*15*) for his analysis of asthma and symptoms. The Seventh-Day Adventist study has since indicated that in nonsmokers, exposure to higher particulate levels is indeed associated with an increased risk of lung cancer.

Biologic Plausibility

So much information has become available since Gamble's paper was published on this issue that it is hard to begin to summarize it. Inhalation of very low levels of concentrated urban PM_{10} causes effects on other systems, as shown by changes in heart rate, in heart rate variability, and in the release of neutrophils from the bone marrow. These unexpected results do not directly explain the relationship between PM exposure and mortality, but they do indicate potential mechanisms that were not anticipated. Diesel exhaust is toxic both in animals and in humans, eliciting an inflammatory reaction

Address correspondence to D.V. Bates, Department of Health Care and Epidemiology, University of British Columbia, Mather Building, 5804 Fairview Avenue, Vancouver, British Columbia, Canada. Telephone: (604) 228-0484. Fax: (604) 228-4412. E-mail: dvbates@home.com

Received 23 June 1999; accepted 19 August 1999.

and, what may be more important, increasing the effect of a subsequently administered allergen in humans and animals that were sensitized. Gamble concluded that

> there is evidence that chronic exposure concentrations of $PM_{2.5}$ several orders of magnitude higher than ambient air concentrations may have little effect on mortality in experimental studies of rodents.

Setting aside an implied parallelism between a healthy rat and an elderly individual with congestive heart failure, the current state of work described in the more than 40 posters at the The Third Colloquium (*4*) provides a basis for arguing that biologic implausibility can hardly now be used as a basis for denying a causal inference.

Summary

In Table 6 in his paper, Gamble summarized the reasons why, in his opinion, a causal inference was not justified. It is instructive to reexamine these reasons under the headings he used:

Chance. Gamble noted that statistical significance was achieved.

Confounding. Inadequate adjustment for potential confounders was noted. This may be still a problem in longitudinal cross-sectional analyses, but it would not affect the time–series data. Enough analyses have been completed to ascertain that weather is not an important confounder. However, there is still room for controversy as to whether other pollutants such as NO_2, SO_2, and CO play some role in determining the effects.

Bias. Gamble noted that misclassification of exposure would exert bias; he did not show that it would bias the data toward a false positive association.

Strength of association. Strength of association detracted from a causal inference "because association is weak due, in part, to very low exposure." When the exposure metric is improved, the association is strengthened, at least in relation to hospital admissions. Environmental epidemiology studies are always difficult when the differences between exposures in different populations are small as well as when actual exposures are low.

Exposure response. Gamble noted that "trends are not plausible based on comparison with individual-level smoking data." Comparison with exposure to environmental tobacco smoke provides some striking analogies. Equating personal cigarette smoke exposure in smokers with air pollution exposures is questionable.

Consistency. Gamble said that consistency detracted from a causal inference "because results are contrary to individual-level studies of smokers." Consistency is normally interpreted to mean that the same epidemiologic studies give the same results when different populations living in different climates are studied (*16*). The time–series data across many cities on different continents indicate that this criterion, as usually interpreted, has been met.

Coherence. Gamble concluded that coherence was not met because "morbidity (pulmonary function test) should show stronger association than mortality." This seems to be a remarkable confusion. PM affects children's pulmonary function in the absence of other pollutants (*11*), hospital admissions for respiratory disease and cardiovascular disease, and even the pulse rate of elderly at-risk individuals (*17*). Most observers would conclude that the coherence criterion had been met.

Analogy. Gamble concluded that analogy detracted from a causal inference because "risk is overestimated compared to tobacco combustion products." His analogy here is questionable—a more valid comparison might have been with ETS studies.

Biologic plausibility. The avalanche of new data on biologic plausibility shows that inhalation of urban particles leads to a number of unforeseen biologic consequences which, taken together, indicate reasons why asthma might be aggravated and why a cardiovascular system might be stressed.

Temporality. Gamble (*1*) noted that

> [Temporality] eliminates possibility of causal associations because estimates of exposure either do not precede disease or do not provide adequate latency.

The temporality criterion has been met in time–series data. It is unclear how this criticism would apply to longitudinal studies.

Conclusion

At The Third Colloquium, the U.S. Environmental Protection Agency group at Chapel Hill, North Carolina, presented a poster (*18*) that should be studied in detail by anyone who denies an inference of causality. In this study, Ghio et al. (*18*) reported that they had obtained PM material from filters used in the Utah Valley at the time of Pope's first study (*19*). Pope reported that the admissions of children to hospital with respiratory disease fell dramatically during a year in which the local steel mill was on strike (*19*). Ghio et al. (*18*) prepared aqueous extracts from the filters and showed that the metal content was lower during the year when the steel mill was closed. The PM material was instilled into rats and also into a lingular subsegment of the lung in humans. The material from the years when the mill was operating caused a significant inflammatory response in both humans and in rats, whereas the material from the year that the mill was closed had a much smaller effect. Histologic examination of the affected rat lungs showed that acute bronchiolitis had been caused by the material. Acute bronchiolitis was also one of the diagnoses in the Utah children admitted to hospital (*19*).

It would be interesting to learn how much more evidence Gamble and others would need to draw a causal inference.

References and Notes

1. Gamble JF. $PM_{2.5}$ and mortality in long-term prospective cohort studies: cause–effect or statistical associations? Environ Health Perspect 106:535–549 (1998).
2. Künzli N, Tager IB. Comments on "$PM_{2.5}$ and mortality in long-term prospective cohort studies: cause-effect or statistical association?" [Letter]. Environ Health Perspect 107:A234–A235 (1999).
3. Vedal S. Ambient particles and health: lines that divide. J Air Waste Manag Assoc 47:551–581 (1997).
4. Proceedings of the Third Colloquium on Particulate Air Pollution and Human Health, 6–8 June 1999, Durham, North Carolina. Irvine, CA:Air Pollution Effects Laboratory, University of California, 1999;11/23.
5. Ozkaynak H, Xue J, Spengler J, Wallace L, Pellizzari E, Jenkins P. Personal exposure to airborne particles and metals: results from the particle TEAM study in Riverside, California. J Expos Anal Environ Epidemiol 6:57–78 (1996).
6. Anuszewski J, Larson TV, Koenig JQ. Simultaneous indoor and outdoor particle light-scattering measurements at nine homes using a portable nephelometer. J Expos Anal Environ Epidemiol 8:483–488 (1998).
7. Zidek JV, White R, Le ND, Sun W, Burnett RT. Imputing Unmeasured Explanatory Variables in Environmental Epidemiology with Application to Health Impact Analysis of Air Pollution. Biostatistics Research Rpt No. 11. Vancouver, British Columbia, Canada:University of British Columbia Department of Statistics, 1996.
8. O'Byrne PM, Ostma S. The many faces of airway inflammation: asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:S41–S66 (1999).
9. Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753–1759 (1993).
10. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151:669–674 (1995).
11. Vedal S, Petkau J, White R, Blair J. Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am J Respir Crit Care Med 157:1034–1043 (1998).
12. Pope CA III, Dockers DW, Spengler JD, Raizenne ME. Respiratory health and PM_{10} pollution. Am Rev Respir Dis 144:668–674 (1991).
13. Cohen AJ, Pope CA III. Lung cancer and air pollution. Environ Health Perspect 103(suppl 8):219–224 (1995).
14. Holland WW, Eid DD. The urban factor in chronic bronchitis. Lancet 1:445–448 (1965).
15. Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson WL, Yang JX. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159:373–382 (1999).
16. Bates DV. Environmental Health Risks and Public Policy: Decision Making in Free Societies. Seattle, WA:University of Washington Press, 1994;117.
17. Pope CA III, Dockery DW, Kanner RE, Villegas GM, Schwartz J. Oxygen saturation, pulse rate, and particulate air pollution. Am J Respir Crit Care Med 159:365–372 (1999).
18. Ghio AJ, Costa DL, Devlin RB. Pulmonary toxicity of particles collected from the Utah Valley [Abstract]. In: Proceedings of the Third Colloquium on Particulate Air Pollution and Human Health, 6–8 June 1999, Durham, North Carolina. Irvine, CA:Air Pollution Effects Laboratory, University of California, 1999;11/23.
19. Pope CA. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 79:623–628 (1989).