Endnotes

1. $PM_{10–2.5}$ 24-hour standard: A daily standard of 70 $\mu g/m^3$ is proposed for particles between 2.5 and 10 µm. The new $PM_{10–2.5}$ category would include coarse particles that come from sources typically found in urban areas,
[266]
POPE, C.A.III., BURNETT, R.T., THUN, M.J., CALLE, E.E., KREWSKI, D., ITO, K., & THURSTON, G.D.
Lung Cancer, Cardiopulmonary mortality, and long-term exposure to fine particulate air pollutionJAMA 2002; 287; 1132–1141.
American Cancer Society cohort recruited in 1982. Analysis of over 500,000 people in an average of 51 metropolitan districts. Interesting data showing reductions in $PM_{2.5}$ from 1979 to1983 and from 1999 to 2000, values ranging from 10 to 30 in the first period, and from 5 to 20 in the second. Nonparametric smoothed response functions shown for the three categories of diagnosis; conclude that for a 10 $\mu g/m^3$ change in PM_{10}, all-cause mortality increased by 4 percent; cardiopulmonary mortality increased by 6 percent, and lung cancer mortality increased by 8 percent. 95 percent confidence levels of all indices of RR were above 1.0. Coarse particle fraction and TSP not consistently associated with mortality. Other pollutants considered were sulfate, sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone. Numbers of metropolitan areas that could be considered varied with the different pollutants. Cox proportional hazards model with inclusion of a metropolitan-based random effects component in a two stage analysis. The continuous smoking variables included nine different indices (such as "current smokers years of smoking squared" and eight others). Controls also devised for educational level and occupational exposures. A two-dimensional term was inserted to account for spatial trends. Higher regressions were noted in men than in women, and lower educational status was associated with higher risks. Risks in never smokers were also generally higher than in former or current smokers.

Authors conclude: "The findings of this study provide the strongest evidence to date that long-term exposure to fine particulate air pollution common to many metropolitan areas is an important risk factor for cardiopulmonary mortality."

The US EPA Draft Criteria Document (June 2002) makes these points about the new analysis: "(a) doubles the follow-up time from eight years to sixteen years, and triples the number of deaths; (b) expands the ambient air pollution data substantially, including two recent years of fine particle data, and adds data on gaseous co-pollutants; (c) improves statistical adjustment for occupational exposure; (d) incorporates data on dietary covariates believed to be important factors in mortality, including total fat consumption, and consumption of vegetables, citrus fruit, and high-fiber grains; and (e) uses recent developments in non-parametric spatial smoothing and random effects statistical models as input to the Cox Proportional hazards model."

2. [1401]
JERRETT, M., BURNETT, R.T., MA, R., POPE, C.A.III, KREWSKI, D., NEWBOLD, K.B., THURSTON, G., SHI, Y., FINKELSTEIN, N., CALLE, E.E., & THUN, M.J.
Spatial Analysis of Air Pollution and Mortality in Los Angeles
Epidemiology 2005: 16: 727–736
Data on 22,905 Los Angeles subjects extracted from the ACS cohort for the period 1982–2005, for a total of 5,856 deaths. Total of 434 lung cancers, and 1462 cases of ischemic heart disease. Pollution exposures were interpolated from 23 $PM_{2.5}$ and 42 ozone monitors. Subjects with a P.O. Box address were excluded. The proximity of the individual to expressways was used as a

measure of traffic pollution. Associations between variables was tested by standard and spatial multilevel Cox regression models. The data were controlled for 44 individual covariates, and the RR was 1.17 (95%CI=1.05–1.30) for an increase of 10 $\mu g/m^3$ in $PM_{2.5}$, and if maximal control for both individual and contextual confounders was used, RR was 1.11. The RRs for both ischemic heart disease and lung cancer deaths were elevated in the range of 1.24 to 1.60 depending on the model used. Results were robust to adjustments for O_3 and expressway exposure. Map of Los Angeles basin with $PM_{2.5}$ data interpolated with a hybrid universal-multiquartic model, and values from zero up to a maximum of a mean $PM_{2.5}$ of 24.4 to 27.1 $\mu g/m^3$ are shown. Table shows different models used, and it is clear from this that most of the adjustments make little difference to the RR values calculated.

The authors conclude: "Our results suggest the chronic health effects associated with within-city gradients in exposure to $PM_{2.5}$ may be even larger than preciously reported across metropolitan areas. We observed effects nearly three times greater than in models relying on comparisons between communities. We also found specificity in cause of death, with $PM_{2.5}$ associated more strongly with ischemic heart disease than with cardiopulmonary or all-cause mortality."

I think this revolutionizes the field of $PM_{2.5}$ sensitivity and standards, and make obsolete such discussions based only on the time-series data. This is because it indicates a substantial increase in risk in a sensitive population followed longitudinally who are living in the higher $PM_{2.5}$ districts of LA. I think an immediate high priority replication of the Jarrett methodology applied to Boston and New York is indicated.

3. POPE CA 3RD, 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. 1995 Mar;151(3 Pt 1):669–74.
Time-series, cross-sectional, and prospective cohort studies have observed associations between mortality and particulate air pollution but have been limited by ecologic design or small number of subjects or study areas. The present study evaluates effects of particulate air pollution on mortality using data from a large cohort drawn from many study areas. We linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December, 1989. Exposure to sulfate and fine particulate air pollution, which is primarily from fossil fuel combustion, was estimated from national data bases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality was examined using multivariate analysis which controlled for smoking, education, and other risk factors. Although small compared with cigarette smoking, an association between mortality and particulate air pollution was observed. Adjusted relative risk ratios (and 95 percent confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted equaled 1.15 (1.09 to 1.22) and 1.17 (1.09 to 1.26) when using sulfate and fine particulate measures respectively. Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes. Increased mortality is associated with sulfate and fine particulate air pollution at levels commonly found in U.S. cities. The increase in risk is not attributable to tobacco smoking, although other unmeasured correlates of pollution cannot be excluded with certainty.

4. POPE CA 3RD, BURNETT RT, THUN MJ, CALLE EE, KREWSKI D, ITO K, THURSTON GD.
Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.

JAMA. 2002 Mar 6;287(9):1132–41.
CONTEXT: Associations have been found between day-to-day particulate air pollution and increased risk of various adverse health outcomes, including cardiopulmonary mortality. However, studies of health effects of long-term particulate air pollution have been less conclusive. OBJECTIVE: To assess the relationship between long-term exposure to fine particulate air pollution and all-cause, lung cancer, and cardiopulmonary mortality. DESIGN, SETTING, AND PARTICIPANTS: Vital status and cause of death data were collected by the American Cancer Society as part of the Cancer Prevention II study, an ongoing prospective mortality study, which enrolled approximately 1.2 million adults in 1982. Participants completed a questionnaire detailing individual risk factor data (age, sex, race, weight, height, smoking history, education, marital status, diet, alcohol consumption, and occupational exposures). The risk factor data for approximately 500,000 adults were linked with air pollution data for metropolitan areas throughout the United States and combined with vital status and cause of death data through December 31, 1998. MAIN OUTCOME MEASURE: All-cause, lung cancer, and cardiopulmonary mortality. RESULTS: Fine particulate and sulfur oxide—related pollution were associated with all-cause, lung cancer, and cardiopulmonary mortality. Each 10 $\mu g/m^3$ elevation in fine particulate air pollution was associated with approximately a 4, 6, and 8 percent increased risk of all-cause, cardiopulmonary, and lung cancer mortality, respectively. Measures of coarse particle fraction and total suspended particles were not consistently associated with mortality. CONCLUSION: Long-term exposure to combustion-related fine particulate air pollution is an important environmental risk factor for cardiopulmonary and lung cancer mortality.

5. POPE CA, THUN MJ, NAMBOODIRI MM, ET AL.
Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults.
Am J Respir Crit Care Med. 1995; 151 (pt 1): 669–674.
Time-series, cross-sectional, and prospective cohort studies have observed associations between mortality and particulate air pollution but have been limited by ecologic design or small number of subjects or study areas. The present study evaluates effects of particulate air pollution on mortality using data from a large cohort drawn from many study areas. We linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December, 1989. Exposure to sulfate and fine particulate air pollution, which is primarily from fossil fuel combustion, was estimated from national data bases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality was examined using multivariate analysis which controlled for smoking, education, and other risk factors. Although small compared with cigarette smoking, an association between mortality and particulate air pollution was observed. Adjusted relative risk ratios (and 95 percent confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted equaled 1.15 (1.09 to 1.22) and 1.17 (1.09 to 1.26) when using sulfate and fine particulate measures respectively. Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes. Increased mortality is associated with sulfate and fine particulate air pollution at levels commonly found in U.S. cities. The increase in risk is not attributable to tobacco smoking, although other unmeasured correlates of pollution cannot be excluded with certainty.

6. POPE CA, THUN MJ, NAMBOODIRI MM, ET AL.
Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults.
Am J Respir Crit Care Med. 1995; 151 (pt 1): 669–674.
Time-series, cross-sectional, and prospective cohort studies have observed associations between

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7. Murray M. Finkelstein, Michael Jerrett, Patrick Deluca, Norm Finkelstein, Dave K. Verma, Kenneth Chapman, and Malcolm R. Sears; Relation between income, air pollution and mortality: a cohort study. CMAJ. 2003 September 2; 169(5): 397–402. Also, Burrough PA, McDonnell RA. Principles of geographical information systems. New York: Oxford University Press.

8. Lave LB, Seskin EP. Air pollution and human health. Science. 1970;169:723–33

9. The Annapolis Center For Science-Based Public Policy, "A Critique of the Campaign Against Coal-Fired Power Plants," http://www.united4jobs.com/media/pdf/coalstudy%5B1%5D.pdf

10. [1121] BROOK, R.D., FRANKLIN, B., CASCIO, W., HONG, Y., HOWARD, G., LIPSETT, M., LUEPKER, R., MITTLEMAN, M., SAMET, J., SMITH, S.C.Jr., & TAGER, I. Air Pollution and Cardiovascular Disease: A Statement for Healthcare Professionals from the Expert Panel on Population and Prevention Science of the American Heart Association Circulation 2004: 109; 2655–2671
Summary (with 194 references) of the epidemiological data indicating that current levels of air pollution are having a detrimental effect on people with heart disease. Abstract notes: "Several plausible mechanistic pathways have been described, including enhanced coagulation/thrombosis, a propensity for arrhythmias, acute arterial vasoconstriction, systemic inflammatory responses, and the chronic promotion of atherosclerosis".
Summarise present data on PM_{10} as indicating that a 10 $\mu g/m^3$ increase in 90 cities increases daily total and cardiopulmonary mortality in the short-term by 21 percent and totally by 31 percent. Reviews SO_2 and ozone as well as particles. ETS exposure also reviewed. Detailed review of possible mechanistic links.
Notes: "On the basis of these conclusions and the potential to improve the public health, the AHA writing group supports the promulgation and implementation of regulations to expedite the attainment of the existing NAAQS. Moreover, because a number of studies have demonstrated associations between particulate air pollution and adverse cardiovascular effects even when levels of ambient $PM_{2.5}$ were within current standards, even more stringent standards for $PM_{2.5}$ should be strongly considered by the EPA."

11. 42 U.S.C. 7401 et. seq.

12. Sec. 109 provides that—
(a) Promulgation
(1) The Administrator—
(A) within 30 days after December 31, 1970, shall publish proposed regulations prescribing a national primary ambient air quality standard and a national secondary ambient air quality standard for each air pollutant for which air quality criteria have been issued prior to such date; and,
(B) after a reasonable time for interested persons to submit written comments thereon (but no later than 90 days after the initial publication of such proposed standards) shall by regulation promulgate such proposed national primary and secondary ambient air quality standards with such modifications as he deems appropriate.
(2) With respect to any air pollutant for which air quality criteria are issued after December 31, 1970, the Administrator shall publish, simultaneously with the issuance of such criteria and information, proposed national primary and secondary ambient air quality standards for any such pollutant. The procedure provided for in paragraph (1)(B) of this subsection shall apply to the promulgation of such standards.
(b) Protection of public health and welfare
(1) National primary ambient air quality standards, prescribed under subsection (a) of this section shall be ambient air quality standards the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health. Such primary standards may be revised in the same manner as promulgated.
(2) Any national secondary ambient air quality standard prescribed under subsection (a) of this section shall specify a level of air quality the attainment and maintenance of which in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air. Such secondary standards may be revised in the same manner as promulgated.

13. 40 CFR pt. 50 (1975), 36 Fed. Reg. 8186 (1971).

14. That review of PM air quality criteria and standards was completed in July 1987 with notice of a final decision to revise the existing standards (52 FR 24854, July 1, 1987). In that decision, EPA changed the indicator for particles from total suspended particles (TSP) to PM_{10}. Identical primary and secondary PM_{10} standards were set for two averaging times: 1) 50 $\mu g/m^3$, expected annual arithmetic mean, averaged over 3 years, and 2) 150 $\mu g/m^3$, 24-hour average, with no more than one expected exceedance per year.

15. Ultrafine particles are defined as those less than 100nm, so they are nano-sized. However, these ultrafine particles are not purposefully manufactured nor are they necessarily of a constant composition or size. See EPA-funded research projects on ultrafine particles at http://cfpub2.epa.gov/ncer_abstracts/index.cfm/fuseaction/searchControlled.main?RequestTimeout=180.

16. Whitman, Administrator of EPA, et al. v. American Trucking Associations, Inc., et al. (Browner, Administrator of EPA v. American Trucking Associations, Inc., et al.) 531 U.S. 457 (2001).

17. Section 109(d)(1).

18. American Lung Association, "100+ Scientists Endorse Stringent New PM Standards," Dec. 5, 2005, http://www.cleanairstandards.org/article/articleview/404/1/38/
"As doctors, scientists, and public health professionals, we are writing to urge you to act on the recommendations of your staff and the Clean Air Scientific Advisory Committee to revise both the annual and the 24-hour average National Ambient Air Quality Standards (NAAQS) for fine particulate matter ($PM_{2.5}$) significantly downward to protect public health, and to establish a stringent new 24-hour standard for coarse particulate matter ($PM_{10–2.5}$)."

19. California Air Resources Board, "Ambient Air Quality Standards," http://64.233.179.104/search?q=cache:rfKZuegGOTYJ:www.arb.ca.gov/aqs/aaqs2.pdf+california+fine+particle+annual+standard+arb&hl=en&gl=us&ct=clnk&cd=2

20. Dockery DW, Pope CA, Xu X, et al. An association between air pollution and mortality in six US cities. N Engl J Med. 1993; 329: 1753–1759.

21. For an engaging account of the Study's genesis and subsequent history, go to http://www.hsph.harvard.edu/review/a_tale.shtml.

22. DOCKERY DW, POPE CA 3RD, 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. 1993 Dec 9;329(24):1753–9.
BACKGROUND. Recent studies have reported associations between particulate air pollution and daily mortality rates. Population-based, cross-sectional studies of metropolitan areas in the United States have also found associations between particulate air pollution and annual mortality rates, but these studies have been criticized, in part because they did not directly control for cigarette smoking and other health risks. METHODS. In this prospective cohort study, we estimated the effects of air pollution on mortality, while controlling for individual risk factors. Survival analysis, including Cox proportional-hazards regression modeling, was conducted with data from a 14- to 16-year mortality follow-up of 8,111 adults in six U.S. cities. RESULTS. Mortality rates were most strongly associated with cigarette smoking. After adjusting for smoking and other risk factors, we observed statistically significant and robust associations between air pollution and mortality. The adjusted mortality-rate ratio for the most polluted of the cities as compared with the least polluted was 1.26 (95 percent confidence interval, 1.08 to 1.47). Air pollution was positively associated with death from lung cancer and cardiopulmonary disease but not with death from other causes considered together. Mortality was most strongly associated with air pollution with fine particulates, including sulfates. CONCLUSIONS. Although the effects of other, unmeasured risk factors cannot be excluded with certainty, these results suggest that fine-particulate air pollution, or a more complex pollution mixture associated with fine particulate matter, contributes to excess mortality in certain U.S. cities.

23. POPE CA, THUN MJ, NAMBOODIRI MM, ET AL.
Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults
Am J Respir Crit Care Med. 1995; 151 (pt 1): 669–74
Time-series, cross-sectional, and prospective cohort studies have observed associations between mortality and particulate air pollution but have been limited by ecologic design or small number of subjects or study areas. The present study evaluates effects of particulate air pollution on mortality using data from a large cohort drawn from many study areas. We linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138

adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December, 1989. Exposure to sulfate and fine particulate air pollution, which is primarily from fossil fuel combustion, was estimated from national data bases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality was examined using multivariate analysis which controlled for smoking, education, and other risk factors. Although small compared with cigarette smoking, an association between mortality and particulate air pollution was observed. Adjusted relative risk ratios (and 95 percent confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted equaled 1.15 (1.09 to 1.22) and 1.17 (1.09 to 1.26) when using sulfate and fine particulate measures respectively. Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes. Increased mortality is associated with sulfate and fine particulate air pollution at levels commonly found in U.S. cities. The increase in risk is not attributable to tobacco smoking, although other unmeasured correlates of pollution cannot be excluded with certainty.

24. 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 Resp Crit Care Med. 1999; 159: 373–82
Long-term ambient concentrations of inhalable particles less than 10 µm in diameter (PM_{10}) (1973–1992) and other air pollutants—total suspended sulfates, sulfur dioxide, ozone (O_3), and nitrogen dioxide—were related to 1977–1992 mortality in a cohort of 6,338 nonsmoking California Seventh-day Adventists. In both sexes, PM_{10} showed a strong association with mortality for any mention of nonmalignant respiratory disease on the death certificate, adjusting for a wide range of potentially confounding factors, including occupational and indoor sources of air pollutants. The adjusted relative risk (RR) for this cause of death as associated with an interquartile range (IQR) difference of 43 d/yr when PM_{10} exceeded 100 $\mu g/m^3$ was 1.18 (95 percent confidence interval [CI]: 1.02, 1.36). In males, PM_{10} showed a strong association with lung cancer deaths—RR for an IQR was 2.38 (95% CI: 1.42, 3.97). Ozone showed an even stronger association with lung cancer mortality for males with an RR of 4.19 (95% CI: 1.81, 9.69) for the IQR difference of 551 h/yr when O_3 exceeded 100 parts per billion. Sulfur dioxide showed strong associations with lung cancer mortality for both sexes. Other pollutants showed weak or no association with mortality.

25. See, e.g., Lorraine Woellert and Viki Reath, "New Air Standards Could Cost Billions," *Washington Times*, Nov. 28, 1996, p. A1; Joby Warrick and John E. Yang, "Stricter Air Quality Rules May Test Hill's New Veto," *Washington Post* , Nov. 28, 1996, p. A1; John J. Falka, "Group Gears Up to Block EPA Proposals on National Air-Quality Standards," *Wall Street Journal*, Nov. 29, 1996, p. B3; Gregg Easterbrook, "Ignore All Doomsayers on EPA Laws," *Los Angeles Times* [Washington Edition], Dec. 6, 1996, p. A2.

26. A number of industries joined to create the Air Quality Standards Coalition, headed C. Boyden Gray, an multi-millionaire who served at White House Counsel in the administration of the first President Bush.
Interviewed on the Public Broadcasting program Newshour on Nov. 27, 1996, shortly after the regulations were proposed, Gray answered some questions.
MARGARET WARNER: Mr. Gray, why are you opposed, and the industries you represent opposed?
C. BOYDEN GRAY, Air Quality Standards Coalition: Well, we don't think the health effects are anywhere convincing at all. We think the evidence, indeed, is quite thin. And our position is

that since these pollutants are all being driven down rather dramatically by the current Clean Air Act and will be so driven down well into the next century that there is time for EPA to do some more research to be sure that we are targeting the right pollutants to deal with the right health problems. EPA has told us on the PM, on the particulate matter issue, for example, that they really don't have enough data and don't have enough research to know what or how to regulate, but they need to put a standard out there in order to generate the data and do the research. And we say no, why don't you put the monitors out, gather the data, find out what's going on, and then put a standard in. You can still regulate in time to catch up with the current Clean Air Act. There are many provisions in the Clean Air Act which have not yet been implemented, and we have a long way to go to see—in our effort to see these pollutants reduced under the current statute.

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MARGARET WARNER: Mr. Gray, are you contending that these health effects haven't been documented enough, or they simply aren't there?

C. BOYDEN GRAY: Well, I think it's a bit bizarre to say that the Bush administration blocked review of clean air, since he put through the most sweeping environmental statute ever adopted. The question is: What has surfaced in the science since 1990, when the Congress adopted this very sweeping statute, which is only now beginning to be implemented? And we don't know of what—of what Carol Browner is—Ms. Browner is talking about. There are only two studies on $PM_{2.5}$, for example.

MARGARET WARNER: Those are particulates.

C. BOYDEN GRAY: That's right. The particulate. There are only two studies that have been conducted. They are quite thin in terms of their research, and we think a lot more work needs to be done, and, in fact, EPA has acknowledged that they need to do work and have said that they have to go abroad to study PM, because the ambient levels of PM, particulate matter, in this country are so relatively low. And we think there's plenty of time to get this straight. If, for example, on asthmatics, which EPA says is not a problem with PM, particulate matter, it's the problem with ozone, they say, if, in fact, it is outdoor ozone which is causing this, that's something we can—we have time to find out. But if EPA is wrong about that and the problem relates to indoor air pollution, smoke, cooking, allergens, cockroaches, other things that go on indoors, if that's the problem, then we will have wasted quite a bit of money, billions of dollars, and about ten or fifteen years when we could have done better for our children. These pollutants, these problems are being driven down very dramatically now under the current Clean Air Act. There is ten years at least to figure out precisely where we should go in the future.

MARGARET WARNER: I want to get back to you, Ms. Browner, but let me just ask Mr. Gray to clarify something for us. Are you saying the science isn't conclusive on the levels of this particulate matter, or ozone, or are you saying the science isn't conclusive about what health effects it has?

C. BOYDEN GRAY: The science isn't conclusive about either, about both. The science is inconclusive. We—on ozone, for example, the science advisory committee has said that they cannot see any significant additional health benefit from reducing a standard.

MARGARET WARNER: All right. Let me get Ms. Browner to respond just to that.

CAROL BROWNER: I think it's important to set the questions here. The science is overwhelming. Sixteen thousand studies were reviewed. The scientific peer review panels agreed that current standards leave far too many Americans at risk. What is at debate, I think the debate here is about who do we protect and what do we protect against. I think some in industry are suggesting that asthma cases made more severe are, quite frankly, not worth protecting against. We don't agree with that. We've put forward a proposal that would provide protection to asthmatics, to children, to our seniors, and we're asking the public to comment on it. But to suggest that the science isn't there I think is really to distort the debate. The debate is about and

there's a public policy debate about who we decide to protect in this country and against what health effects.
MARGARET WARNER: Do you want to weigh back in on that point, or should I go into the cost issue?
C. BOYDEN GRAY: I'd like to say that if we're talking about the elderly, for example, take Chicago and the big heat wave two or three summers ago, when Mayor Daley was faced with that, he didn't call up the local utility and tell them to shut their operations, he called them up and said crank it so we can get more air conditioning. If the problem of the elderly has to do with indoor ventilation, fans, air conditioning, heat versus humidity, versus cooler air, we may be diagnosing—may be coming up with a mis-diagnosis here. And since these pollutants again I repeat are all coming down very dramatically and will continue to go down well into the next century, there is time to do more research. There is very little data about PM, fine particulate matter in this country. There are only a handful of monitors throughout the country. We don't know—nobody knows what the ambient levels are in this country and what those ambient levels are doing.
MARGARET WARNER: Tell me this, Ms. Browner, what about the point he made that the Clean Air Act, as it was written, hasn't even been fully complied with? Why wouldn't EPA say, all right, let's fulfill that first and then move on?
CAROL BROWNER: The Act is very clear. Congress has been very specific for the last 26 years. President Bush reaffirmed that commitment. EPA at least every five years determined whether or not the public's health is being adequately protected. That is what the law says. It says then once you've made that determination, look at how best to meet the standards. We agree that there are things underway, there are things about to come online that are very important in reducing pollution. We believe that 70 percent of the areas where the air might not meet tougher standards will be able to do so through currently available or about-to-be-available technologies. But I think this argument that somehow or another there aren't studies that we don't know is just confusing the public. The real question is how many asthmatics do we want to protect, how many seniors do we want to protect. EPA has articulated a position, but we are asking for the public's comment.
MARGARET WARNER: All right. Mr. Gray, what about the cost issue, how much do you think it would cause for industry to comply with both of these new proposals?
C. BOYDEN GRAY: We haven't had a chance to study the proposals as they're just being made today to know exactly how much it will cost, but we do know that the ozone proposal would roughly cost in Chicago alone 3 to 7 billion dollars. And that's typical for a city of that size. That's a lot of money. And that doesn't even get into what the particulate matter rules would cost. It's very difficult at this point to say what they would cost, but we do know is that utility bills would be higher for individuals, it would be harder to get air conditioning, harder to get heating in the cold winter. But we do know that it would be more expensive. Gasoline, it might be 3 to 5 to 8 cents more per gallon, like a 5 or 8 cent gasoline tax. We know that gasoline is getting cleaner. We have been through one phase of reformulated gasoline which the California Air Resources Board just a month ago said was responsible for reducing ozone, peaks some 40 percent. Phase 2 will kick in, in the next few years, both there and in some other major cities in the United States. Let's let that go into effect and take more time to study what needs to be done after that is completed sometime early next century.
MARGARET WARNER: What's your assessment of the cost?
CAROL BROWNER: First of all, I think it's important to understand that some in industry, quite frankly, are putting forward horror stories. They're absolutely positively not true. There's a long history under the Clean Air Act of industry, government working together to find common sense cost effective solutions. Every single time we have sought to strengthen the public health protections to reduce air pollution in this country, the actual costs have been far less than anyone

projected, including EPA. We project costs on the order of 6 to 8 1/2 billion dollars. We project benefits—benefits—of $120 billion. I think it is important again to understand that this phase of the process is about the public's health. It is about who we protect and what kind of protection we provide them. That is where the discussion is now. That is what we solicit comment on. We will work with industry to find cost-effective, common sense solutions, as we have done to reduce or ban chlorofluorocarbons, as we have done to address the acid rain problem very successfully.
MARGARET WARNER: Boyden Gray, will the—very briefly before we go, will your industry groups be working with EPA to try to modify these standards, or is your objective to just stop them outright?
C. BOYDEN GRAY: Our objective at the moment is to try to make sure we're doing the right thing. That's what the comment period is about. But, of course, we'll work with EPA; industry always has, and it's always done its best to comply with these rules. My only point is we're flat out right now trying to meet the current law and will be so flat out well into the next century, and let's try to make sure we've got it right before we overlay yet another set of requirements.
MARGARET WARNER: All right. Well, thank you, Boyden Gray and Administrator Browner. Thanks for being with us.

27. Interestingly, a "friend of the court" brief challenging the Constitutionality of the Clean Air Act was written by C. Boyden Gray, the same man who ran the industry lobbying alliance, the Air Quality Standards Coalition, that sought to kill the proposal in Congress.
WHITMAN v. AMERICAN TRUCKING ASSNS., INC. (99–1257)
175 F.3d 1027 and 195 F.3d 4, affirmed in part, reversed in part, and remanded. 531 U.S. 457; 121 S. Ct. 903; 149 L. Ed. 2d 1; 2001 U.S. LEXIS 1952; 69 U.S.L.W4136; 51 ERC (BNA) 2089; 31 ELR 20512; 2001 Colo. J. C.A.R. 1098; 14 Fla. L.Weekly Fed. S 101
The opinion of the Court included the following discussion:
"The scope of discretion §109(b)(1) allows is in fact well within the outer limits of our nondelegation precedents. In the history of the Court we have found the requisite "intelligible principle" lacking in only two statutes, one of which provided literally no guidance for the exercise of discretion, and the other of which conferred authority to regulate the entire economy on the basis of no more precise a standard than stimulating the economy by assuring "fair competition." See Panama Refining Co. v. Ryan, 293 U. S. 388 (1935); A. L. A. Schechter Poultry Corp. v. United States, 295 U. S. 495 (1935). We have, on the other hand, upheld the validity of §11(b)(2) of the Public Utility Holding Company Act of 1935, 49 Stat. 821, which gave the Securities and Exchange Commission authority to modify the structure of holding company systems so as to ensure that they are not "unduly or unnecessarily complicate[d]" and do not "unfairly or inequitably distribute voting power among security holders." American Power & Light Co. v. SEC, 329 U. S. 90, 104 (1946). We have approved the wartime conferral of agency power to fix the prices of commodities at a level that "will be generally fair and equitable and will effectuate the [in some respects conflicting] purposes of th[e] Act." Yakus v. United States, 321 U. S. 414, 420, 423–426 (1944). And we have found an "intelligible principle" in various statutes authorizing regulation in the "public interest." See, e.g., National Broadcasting Co. v. United States, 319 U. S. 190, 225–226 (1943) (FCC's power to regulate airwaves); New York Central Securities Corp. v. United States, 287 U. S. 12, 24–25 (1932) (ICC's power to approve railroad consolidations). In short, we have "almost never felt qualified to second-guess Congress regarding the permissible degree of policy judgment that can be left to those executing or applying the law." Mistretta v. United States, 488 U. S. 361, 416 (1989) (Scalia, J., dissenting); see id., at 373 (majority opinion).
"It is true enough that the degree of agency discretion that is acceptable varies according to the scope of the power congressionally conferred. See Loving v. United States, supra, at 772–773;

United States v. Mazurie, 419 U. S. 544, 556–557 (1975). While Congress need not provide any direction to the EPA regarding the manner in which it is to define "country elevators," which are to be exempt from new-stationary-source regulations governing grain elevators, see §7411(i), it must provide substantial guidance on setting air standards that affect the entire national economy. But even in sweeping regulatory schemes we have never demanded, as the Court of Appeals did here, that statutes provide a "determinate criterion" for saying "how much [of the regulated harm] is too much." 175 F. 3d, at 1034. In Touby, for example, we did not require the statute to decree how "imminent" was too imminent, or how "necessary" was necessary enough, or even—most relevant here—how "hazardous" was too hazardous. 500 U. S., at 165–167. Similarly, the statute at issue in Lichter authorized agencies to recoup "excess profits" paid under wartime Government contracts, yet we did not insist that Congress specify how much profit was too much. 334 U. S., at 783–786. It is therefore not conclusive for delegation purposes that, as respondents argue, ozone and particulate matter are "nonthreshold" pollutants that inflict a continuum of adverse health effects at any airborne concentration greater than zero, and hence require the EPA to make judgments of degree. "[A] certain degree of discretion, and thus of lawmaking, inheres in most executive or judicial action." Mistretta v. United States, supra, at 417 (Scalia, J., dissenting) (emphasis deleted); see 488 U. S., at 378–379 (majority opinion). Section 109(b)(1) of the CAA, which to repeat we interpret as requiring the EPA to set air quality standards at the level that is "requisite"—that is, not lower or higher than is necessary—to protect the public health with an adequate margin of safety, fits comfortably within the scope of discretion permitted by our precedent."

28. Clean Air Trust, "Special Report: Clean Air Act under Siege," http://www.cleanairtrust.org/release.091800.html.

29. Jennifer Couzin, "Making science an open book," U.S. News & World Report, March 29, 1999.

30. Frederick Anderson, "Science Advocacy and Scientific Due Process," Issues in Science and Technology, Summer 2000.

31. The Health Effects Institute (HEI) is an independent, nonprofit corporation chartered in 1980 to support science on the health effects of air pollution. Supported jointly by the U.S. Environmental Protection Agency (EPA) and industry, HEI has funded over 170 studies and published over 100 Research Reports, and several Special Reports, producing important research findings on the health effects of a variety of pollutants, including carbon monoxide, methanol and aldehydes, nitrogen oxides, diesel exhaust, ozone, and most recently, particulate air pollution. http://www.healtheffects.org/about.htm

32. One of the more bizarre critics is industry-funded, self-described "junk scientist" Steven Milloy, who claimed in "EPA's Peer-review Perversion," http://www.junkscience.com/news/prma2.html
"Dr. Fred Lipfert of Brookhaven Laboratories showed that the levels of fine particles correlated with sedentary lifestyles¯ lifestyles low in exercise, high in alcohol and high in fat intake. In other words, the people who were supposedly dying early from exposure to fine particles might have actually died from unhealthy lifestyles."

33. Jocelyn Kaiser, "AIR POLLUTION: Panel Backs EPA and 'Six Cities' Study Science," Science, Aug. 4, 2000.

34. [1093]
NATIONAL ACADEMY OF SCIENCES
Final PM Research Report, March 2004
Summarizes results of research to date, confirming the serious risk from exposure to particulate pollution. Notes new evidence in relation to cardiovascular effects and susceptible populations. Also cites confirmatory toxicological studies. Leaves no doubt of the seriousness of the problem of $PM_{2.5}$ exposure.
Notes that about $300 million has been spent in federal research funding.

35. KREWSKI D, BURNETT RT, GOLDBERG MS, HOOVER BK, SIEMIATYCKI J, JERRETT M, ABRAHAMOWICZ M, WHITE WH.
Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of Particulate Air Pollution and Mortality.
J Toxicol Environ Health A. 2003 Aug 22–Oct 10;66 (16–19)
This article provides an overview of the Reanalysis Study of the Harvard Six Cities and the American Cancer Society (ACS) studies of particulate air pollution and mortality. The previous findings of the studies have been subject to debate. In response, a reanalysis team, comprised of Canadian and American researchers, was invited to participate in an independent reanalysis project to address the concerns. Phase I of the reanalysis involved the design of data audits to determine whether each study conformed to the consistency and accuracy of their data. Phase II of the reanalysis involved conducting a series of comprehensive analyses using alternative statistical methods. Alternative models were also used to identify covariates that may confound or modify the association of particulate air pollution as well as identify sensitive population subgroups. The audit demonstrated that the data in the original analyses were of high quality, as were the risk estimates reported by the original investigators. The sensitivity analysis illustrated that the mortality risk estimates reported in both studies were found to be robust against alternative Cox models. Detailed investigation of the covariate effects found a significant modifying effect of education and a relative risk of mortality associated with fine particles and declining education levels. The study team applied spatial analytic methods to the ACS data, resulting in various levels of spatial autocorrelations supporting the reported association for fine particles mortality of the original investigators as well as demonstrating a significant association between sulfur dioxide and mortality. Collectively, our reanalysis suggest that mortality may be attributable to more than one component of the complex mixture of ambient air pollutants for U.S. urban areas.

36. KREWSKI D, BURNETT RT, GOLDBERG MS, HOOVER BK, SIEMIATYCKI J, JERRETT M, ABRAHAMOWICZ M, WHITE WH.
Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of Particulate Air Pollution and Mortality.
J Toxicol Environ Health A. 2003 Aug 22–Oct 10;66 (16–19)
This article provides an overview of the Reanalysis Study of the Harvard Six Cities and the American Cancer Society (ACS) studies of particulate air pollution and mortality. The previous findings of the studies have been subject to debate. In response, a reanalysis team, comprised of Canadian and American researchers, was invited to participate in an independent reanalysis project to address the concerns. Phase I of the reanalysis involved the design of data audits to determine whether each study conformed to the consistency and accuracy of their data. Phase II of the reanalysis involved conducting a series of comprehensive analyses using alternative statistical methods. Alternative models were also used to identify covariates that may confound or modify the association of particulate air pollution as well as identify sensitive population subgroups. The audit demonstrated that the data in the original analyses were of high quality, as

were the risk estimates reported by the original investigators. The sensitivity analysis illustrated that the mortality risk estimates reported in both studies were found to be robust against alternative Cox models. Detailed investigation of the covariate effects found a significant modifying effect of education and a relative risk of mortality associated with fine particles and declining education levels. The study team applied spatial analytic methods to the ACS data, resulting in various levels of spatial autocorrelations supporting the reported association for fine particles mortality of the original investigators as well as demonstrating a significant association between sulfur dioxide and mortality. Collectively, our reanalysis suggest that mortality may be attributable to more than one component of the complex mixture of ambient air pollutants for U.S. urban areas.

37. [266] POPE, C.A.III., BURNETT, R.T., THUN, M.J., CALLE, E.E., KREWSKI, D., ITO, K., & THURSTON, G.D.
Lung Cancer, Cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.
JAMA 2002; 287; 1132–1141American Cancer Society cohort recruited in 1982. Analysis of over 500,000 people in an average of 51 metropolitan districts. Interesting data showing reductions in $PM_{2.5}$ from 1979–1983 and from 1999 to 2000, values ranging from 10 to 30 in the first period, and from 5 to 20 in the second. Nonparametric smoothed response functions shown for the three categories of diagnosis; conclude that for a 10 $\mu g/m^3$ change in PM_{10}, all cause mortality increased by 4 percent; cardiopulmonary mortality increased by 6 percent, and lung cancer mortality increased by 8 percent. 95 percent confidence levels of all indices of RR were above 1.0. Coarse particle fraction and TSP not consistently associated with mortality. Other pollutants considered were sulfate, sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone. Numbers of metropolitan areas that could be considered varied with the different pollutants. Cox proportional hazards model with inclusion of a metropolitan-based random effects component in a two stage analysis. The continuous smoking variables included nine different indices (such as “current smokers years of smoking squared” and eight others). Controls also devised for educational level and occupational exposures. A two-dimensional term was inserted to account for spatial trends. Higher regressions were noted in men than in women, and lower educational status was associated with higher risks. Risks in never smokers were also generally higher than in former or current smokers.
Authors conclude: “The findings of this study provide the strongest evidence to date that long-term exposure to fine particulate air pollution common to many metropolitan areas is an important risk factor for cardiopulmonary mortality.”
The US EPA Draft Criteria Document (June 2002) makes these points about the new analysis: “(a) doubles the follow-up time from eight years to sixteen years, and triples the number of deaths; (b) expands the ambient air pollution data substantially, including two recent years of fine particle data, and adds data on gaseous co-pollutants; (c) improves statistical adjustment for occupational exposure; (d) incorporates data on dietary covariates believed to be important factors in mortality, including total fat consumption, and consumption of vegetables, citrus fruit, and high-fiber grains; and (e) uses recent developments in non-parametric spatial smoothing and random effects statistical models as input to the Cox Proportional hazards model.”

38. DAVID E. ABBEY, NAOMI NISHINO, WILLIAM F. MCDONNELL, RAOUL J. BURCHETTE, SYNNØVE F. KNUTSEN, W. LAWRENCE BEESON, and JIE X. YANG
Long-Term Inhalable Particles and Other Air Pollutants Related to Mortality in Nonsmokers
Am. J. Respir. Crit. Care Med., Volume 159, Number 2, February 1999, 373–382
Long-term ambient concentrations of inhalable particles less than 10 µm in diameter (PM_{10}) (1973–1992) and other air pollutants—total suspended sulfates, sulfur dioxide, ozone (O_3), and

nitrogen dioxide—were related to 1977–1992 mortality in a cohort of 6,338 nonsmoking California Seventh-day Adventists. In both sexes, PM_{10} showed a strong association with mortality for any mention of nonmalignant respiratory disease on the death certificate, adjusting for a wide range of potentially confounding factors, including occupational and indoor sources of air pollutants. The adjusted relative risk (RR) for this cause of death as associated with an interquartile range (IQR) difference of 43 d/yr when PM_{10} exceeded 100 $\mu g/m^3$ was 1.18 (95 percent confidence interval [CI]: 1.02, 1.36). In males, PM_{10} showed a strong association with lung cancer deaths—RR for an IQR was 2.38 (95% CI: 1.42, 3.97). Ozone showed an even stronger association with lung cancer mortality for males with an RR of 4.19 (95% CI: 1.81, 9.69) for the IQR difference of 551 h/yr when O_3 exceeded 100 parts per billion. Sulfur dioxide showed strong associations with lung cancer mortality for both sexes. Other pollutants showed weak or no association with mortality.
All subjects completed a detailed lifestyle questionnaire as part of the AHS in 1976. This questionnaire ascertained anthropometric (height, weight) data, exercise patterns, use of alcohol and tobacco, occupation, current and past dietary habits, parental history of cancer, and history of selected medical conditions. Monthly residence and work location histories were obtained for each study subject for the period 1960 through April 1992 or date of death (if subject died prior to April 1, 1992) by using mailed questionnaires (1977, 1987, and 1992), tracing by telephone, and interviewing of surrogates for deceased subjects. Only 156 (2.5 percent) subjects were lost to follow-up. These latter individuals were censored at date of last contact for purposes of inclusion in risk sets. The 1977, 1987, and 1992 questionnaires also contained standardized respiratory symptoms questions, now included as part of the American Thoracic Society questionnaire. Computer algorithms were used to classify individuals as to whether they had definite, possible, or no symptoms of asthma, chronic bronchitis, or emphysema. The questionnaires also ascertained lifestyle and housing characteristics pertinent to relative exposure to ambient air pollutants as well as indoor sources of air pollutants.

39. LIE HONG CHEN, SYNNOVE F. KNUTSEN, DAVID SHAVLIK, W. LAWRENCE BEESON, FLOYD PETERSEN, MARK GHAMSARY, AND DAVID ABBEY
The Association between Fatal Coronary Heart Disease and Ambient Particulate Air Pollution: Are Females at Greater Risk?
Environ Health Perspect 113:1723–1729 (2005)
The purpose of this study was to assess the effect of long-term ambient particulate matter (PM) on risk of fatal coronary heart disease (CHD). A cohort of 3,239 nonsmoking, non-Hispanic white adults was followed for 22 years. Monthly concentrations of ambient air pollutants were obtained from monitoring stations [PM < 10 μm in aerodynamic diameter (PM_{10}), ozone, sulfur dioxide, nitrogen dioxide] or airport visibility data [PM < 2.5 μm in aerodynamic diameter ($PM_{2.5}$)] and interpolated to ZIP code centroids of work and residence locations. All participants had completed a detailed lifestyle questionnaire at baseline (1976), and follow-up information on environmental tobacco smoke and other personal sources of air pollution were available from four subsequent questionnaires from 1977 through 2000. Persons with prevalent CHD, stroke, or diabetes at baseline (1976) were excluded, and analyses were controlled for a number of potential confounders, including lifestyle. In females, the relative risk (RR) for fatal CHD with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.42 [95 percent confidence interval (CI), 1.06–1.90] in the single-pollutant model and 2.00 (95% CI, 1.51–2.64) in the two-pollutant model with O_3. Corresponding RRs for a 10 $\mu g/m^3$ increase in $PM_{10–2.5}$ and PM_{10} were 1.62 and 1.45, respectively, in all females and 1.85 and 1.52 in postmenopausal females. No associations were found in males. A positive association with fatal CHD was found with all three PM fractions in females but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants, especially O_3, and were highest for $PM_{2.5}$. These findings could have great

implications for policy regulations. Key words: air pollution, coronary disease, ischemic heart disease, long-term exposure, mortality, particulate matter.

40. [1387]
KREWSKI, D., BURNETT, R., JERRETT, M., POPE. C.A., RAINHAM, D., CALLE, E., THURSTON, G.., & THUN, M.
Mortality and long-term exposure to ambient air pollution: ongoing analyses based on the American Cancer Society Cohort
J Toxicol & Environmental Health, Part A, 68; 1093–1109, 2005A re-analysis of the ACS cohort, bringing it up to date to the year 2000 confirm the RRs as follows:

	Fine Particulate	Sulfate
All causes	1.18	1.16
Cardiopulmonary disease	1.30	1.27
Cardiovascular disease	1.36	1.36
Respiratory disease	1.00	0.83
Lung cancer	1.02	1.36

Level of education still a significant effect modifier. No other pollutant has any effect.

41. National Academy of Sciences, Research Priorities for Airborne Particulate Matter, IV: Continuing Research Progress (March, 2004).
[1093]
NATIONAL ACADEMY OF SCIENCES
Final PM Research Report, March 2004
Summarizes results of research to date, confirming the serious risk from exposure to particulate pollution. Notes new evidence in relation to cardiovascular effects and susceptible populations. Also cites confirmatory toxicological studies. Leaves no doubt of the seriousness of the problem of $PM_{2.5}$ exposure.
Notes that about $300 million has been spent in federal research funding.

42. FREDERICK W. LIPFERT, H. MITCHELL PERRY JR, J. PHILIP MILLER, JACK D. BATY, RONALD E. WYZGA, SHARON E. CARMODY
The Washington University-EPRI Veterans' Cohort Mortality Study: Preliminary Results
Inhalation Toxicology 12: 41–74, Dec. 2000
This article presents the design of and some results from a new prospective mortality study of a national cohort of about 50,000 U.S. veterans who were diagnosed as hypertensive in the mid 1970s, based on approximately 21 years of follow-up. This national cohort is male with an average age at recruitment of 51–12 yr; 35 percent were black and 81 percent had been smokers at one time. Because the subjects have been receiving care at various U.S. Veterans Administration (VA) hospitals, access to and quality of medical care are relatively homogeneous. The health endpoints available for analysis include all-cause mortality and specific diagnoses for morbidity during VA hospitalizations; only the mortality results are discussed here. Nonpollution predictor variables in the baseline model include race, smoking (ever or at recruitment), age, systolic and diastolic blood pressure (BP), and body mass index (BMI). Interactions of BP and BMI with age were also considered. Although this study essentially controls for socioeconomic status by design because of the homogeneity of the cohort, selected ecological variables were also considered at the ZIP code and county levels, some of which were found to be significant predictors. Pollutants were averaged by year and county for TSP, PM_{10}, CO, O_3, and NO_2; SO_2

and Pb were considered less thoroughly. Both mean and peak levels were considered for gases. SO_2 data from the AIRS database and $PM_{2.5}$, coarse particles, PM_{15}, and SO_2 from the U.S. EPA Inhalable Particulate (IP) Network were also considered. Four relevant exposure periods were defined: 1974 and earlier (back to 1953 for TSP), 1975–1981, 1982–1988, and 1989–1996. Deaths during each of the three most recent exposure periods were considered separately, yielding up to 12 combinations of exposure and mortality periods for each pollutant. Associations between concurrent air quality and mortality periods were considered to relate to acute responses; delayed associations with prior exposures were considered to be emblematic of initiation of chronic disease. Pre-exposure mortality associations were considered to be indirect (noncausal). The implied mortality risks of long-term exposure to air pollution were found to be sensitive to the details of the regression model, the time period of exposure, the locations included, and the inclusion of ecological as well as personal variables. Both positive and negative statistically significant mortality responses were found. Fine particles as measured in the 1979–1984 U.S. EPA Inhalable Particulate Network indicated no significant (positive) excess mortality risk for this cohort in any of the models considered. Among the positive responses, indications of concurrent mortality risks were seen for NO_2 and peak O_3, with a similar indication of delayed risks only for NO_2. The mean levels of these excess risks were in the range of 5–9 percent; Peak O_3 was dominant in two-pollutant models and there was some indication of a threshold in response. However, it is likely that standard errors of the regression coefficients may have been underestimated because of spatial auto correlation among the model residuals. The significant variability of responses by period of death cohort suggests that aggregation over the entire period of follow-up obscures important aspects of the implied pollution—mortality relationships, such as early depletion of the available pool of those subjects who may be most susceptible to air pollution effects.

43. Frederick Lipfert, http://fermat.nap.edu/books/0309067820/html/42.html.

44. Ron Wyzga, http://www4.nas.edu/webcr.nsf/CommitteeDisplay/BEES-J-99-01-A?OpenDocument.

45. Michael Jerrett was the first to graduate from the collaborative MA in political science and environmental studies at the University of Toronto (U of T) in 1987. He subsequently completed a PhD in Geography at U of T and then worked for two years as a postdoctoral fellow in Environmental Health with Dr. John Eyles at McMaster University. Building on his specialties, Michael currently assesses air pollution-health associations in the United States and Canada, with special reference to geographic exposure models and social-spatial effect modifiers. He also pursues research in environmental accounting focusing on the determinants of and evaluation of environmental costs and benefits. He has designed and analyzed local, provincial, state, and national level health and environment databases in North America, Europe, and Asia.http://umbc7.umbc.edu/~earickso/Profiles/Jerrett.html

46. The Health Effects Institute, “Synopsis of the Particle Epidemiology Reanalysis Project,” http://www.healtheffects.org/Pubs/st-reanalysis.htm.

47. Office of Environmental Health Hazard Assessment, “Cardiovascular Health Effects,” http://www.oehha.ca.gov/pdf/chapter8.

48. Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities
Francine Laden,[1] Lucas M Neas,[2] Douglas W Dockery,[1, 3] and Joel Schwartz[1, 3]

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[2]Epidemiology and Biomarkers Branch, Human Studies Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA
[3]Environmental Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA

Abstract
Previously we reported that fine particle mass (particulate matter less than/equal to 2.5 µm; $PM_{2.5}$), which is primarily from combustion sources, but not coarse particle mass, which is primarily from crustal sources, was associated with daily mortality in six eastern U.S. cities (1). In this study, we used the elemental composition of size-fractionated particles to identify several distinct source-related fractions of fine particles and examined the association of these fractions with daily mortality in each of the six cities. Using specific rotation factor analysis for each city, we identified a silicon factor classified as soil and crustal material, a lead factor classified as motor vehicle exhaust, a selenium factor representing coal combustion, and up to two additional factors. We extracted daily counts of deaths from National Center for Health Statistics records and estimated city-specific associations of mortality with each source factor by Poisson regression, adjusting for time trends, weather, and the other source factors. Combined effect estimates were calculated as the inverse variance weighted mean of the city-specific estimates. In the combined analysis, a 10 µg/m^3 increase in $PM_{2.5}$ from mobile sources accounted for a 3.4 percent increase in daily mortality [95% confidence interval (CI), 1.7–5.2%], and the equivalent increase in fine particles from coal combustion sources accounted for a 1.1 percent increase [CI, 0.3-2.0%). $PM_{2.5}$ crustal particles were not associated with daily mortality. These results indicate that combustion particles in the fine fraction from mobile and coal combustion sources, but not fine crustal particles, are associated with increased mortality. Key words: air pollution, coal combustion, fine particles, mobile sources, mortality, $PM_{2.5}$, source apportionment. Environ Health Perspect 108:941–947 (2000). [Online 29 August 2000]
49. LADEN, F., SCHWARTZ, J., SPEIZER, F.E. AND DOUGLAS W DOCKERY, D.W. Reduction in Fine Particulate Air Pollution and Mortality: Extended follow-up of the Harvard Six Cities Study
Am. J. Respir. Crit. Care Med. 2006 (on line at http://ajrccm.atsjournals.org/cgi/content/abstract/200503-443OCv1)
A large body of epidemiologic literature has found an association of increased fine particulate air pollution ($PM_{2.5}$) with acute and chronic mortality. The effect of improvements in particle exposure is less clear. Objectives: Earlier analysis of the Harvard Six Cities adult cohort study showed an association between long-term ambient $PM_{2.5}$ and mortality between enrollment in the mid-1970s and follow-up until 1990. We extended mortality follow-up for eight years in a period of reduced air pollution concentrations. Methods: Annual city-specific $PM_{2.5}$ concentrations were measured between 1979–1988, and estimated for later years from publicly available data. Exposure was defined as (1) city-specific mean $PM_{2.5}$ during the two follow-up periods, (2) mean $PM_{2.5}$ in the first period and change between these periods, (3) overall mean $PM_{2.5}$ across the entire follow-up, and (4) year-specific mean $PM_{2.5}$. Mortality rate ratios were estimated with Cox proportional hazards regression controlling for individual risk factors. Measurements and Main Results: We found an increase in overall mortality associated with each 10 µg/m^3 increase in $PM_{2.5}$ modeled either as the overall mean (RR=1.16, 95%CI=1.07-1.26) or as exposure in the

year of death (RR=1.14, 95%CI=1.06-1.22). $PM_{2.5}$ exposure was associated with lung cancer (RR=1.27, 95%CI=0.96–1.69) and cardiovascular deaths (RR=1.28, 95%CI=1.13–1.44). Improved overall mortality was associated with decreased mean $PM_{2.5}$ (10 µg/m^3) between periods (RR=0.73, 95% CI=0.57–0.95). Conclusion: Total, cardiovascular, and lung cancer mortality were each positively associated with ambient $PM_{2.5}$ concentrations. Reduced $PM_{2.5}$ concentrations were associated with reduced mortality risk.

50. The Clean Air Scientific Advisory Committee (CASAC) provides independent advice to the EPA Administrator on the technical bases for EPA's national ambient air quality standards.

The CASAC was established in 1977 under the Clean Air Act (CAA) Amendments of 1977 (see 42 U.S.C. § 7409(d)(2)) to provide advice, information and recommendations to the Administrator on the scientific and technical aspects of issues related to the criteria for air quality standards, research related to air quality, sources of air pollution, and the strategies to attain and maintain air quality standards and to prevent significant deterioration of air quality. The Chair of the CASAC also serves as a member of the chartered Science Advisory Board. See http://yosemite.epa.gov/sab/sabpeople.nsf/WebCommittees/CASAC

51. [Click to change filter selection through My NCBI.]

Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. Lancet. 2002 Oct 19;360(9341):1210–4.
BACKGROUND: Particulate air pollution episodes have been associated with increased daily death. However, there is little direct evidence that diminished particulate air pollution concentrations would lead to reductions in death rates. We assessed the effect of air pollution controls—i.e., the ban on coal sales—on particulate air pollution and death rates in Dublin. METHODS: Concentrations of air pollution and directly-standardised non-trauma, respiratory, and cardiovascular death rates were compared for 72 months before and after the ban of coal sales in Dublin. The effect of the ban on age-standardised death rates was estimated with an interrupted time-series analysis, adjusting for weather, respiratory epidemics, and death rates in the rest of Ireland. FINDINGS: Average black smoke concentrations in Dublin declined by 35.6 µg/m(3) (70%) after the ban on coal sales. Adjusted non-trauma death rates decreased by 5.7 percent (95% CI 4-7, p<0.0001), respiratory deaths by 15.5 percent (12-19, p<0.0001), and cardiovascular deaths by 10.3 percent (8–13, p<0.0001). Respiratory and cardiovascular standardised death rates fell coincident with the ban on coal sales. About 116 fewer respiratory deaths and 243 fewer cardiovascular deaths were seen per year in Dublin after the ban. INTERPRETATION: Reductions in respiratory and cardiovascular death rates in Dublin suggest that control of particulate air pollution could substantially diminish daily death. The net benefit of the reduced death rate was greater than predicted from results of previous time-series studies.

52. OCHS, M., NYENGAARD, J.R., JUNG, A., KNUDSEN., LARS, ET AL.
Number of Alveoli in the Human Lung
Am. J. Resp. and Crit. Care Med. Jan 1, 2004
In six adult human lungs, the mean alveolar number was 480 million (range: 274–790 million; coefficient of variation: 37 percent). Alveolar number was closely related to total lung volume, with larger lungs having considerably more alveoli. The mean size of a single alveolus was rather constant with 4.2 (10^sup 6^µm^sup 3^ (range: 3.3–4.8 (10^sup 6^µm^sup 3^; coefficient of variation: 10 percent), irrespective of the lung size. One cubic millimeter lung parenchyma would then contain around 170 alveoli.

53. "Exchanging Oxygen and Carbon Dioxide," The Merck Manual, http://www.merck.com/mmhe/sec04/ch038/ch038d.html.

54. Pope, C. A., D. W. Dockery, R. E. Kanner, G. M. Villegas, and J. Schwartz; 1999; "Oxygen saturation, pulse rate, and particulate air pollution: a daily time series panel study;" Am. J. Respir. Crit. Care Med. 158: 365–372.

55. Abbey, D. E., N. Nishino, W. F. McDonnell, R. J. Burchette, S. F. Knutsen, W. I. Beeson, and J. X. Yang; 1999; "Long-term inhalable particles and other air pollutants related to mortality in nonsmokers;" Am. J. Respir. Crit. Care Med. 158: 373–382 .

56. Investigators from Harvard Medical School used data on the elemental composition of size-fractionated particles to identify the sources of fine particles in six eastern U.S. cities that have been the subject of a long-term air pollution study: Watertown, MA, Kingston-Harriman, TN, St. Louis, MO, Steubenville, OH, Portage, WI, and Topeka, KS. For example, lead was used as a tracer for motor vehicle exhaust, selenium for coal combustion, and silicon for soil and crustal matter. Each of these fractions was examined in association with daily mortality rates in each city. The study reported that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ from mobile sources accounted for a 3.4 percent increase in daily mortality, while the equivalent increase in fine particles from coal combustion sources accounted for a 1.1 percent increase. Fine particles from crustal sources were not associated with mortality. The study concludes that "the results indicate that combustion particles in the fine fraction from mobile and coal combustion sources, but not fine crustal particles, are associated with increased mortality."

Laden, F. Neas, L.M., Dockery, D.W., and Schwartz, J.; "Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities;" Environmental Health Perspectives 108:941–947; October 2000.

57. Punchard, N., Whelan, C. and Adcock, I. Editorial: The Journal of Inflammation. Journal of Inflammation 2004, 1:1
This editorial is on the occasion of the first issue of The Journal of Inflammation on 27 Sep. 2004.

58. Bingham CO 3rd. The pathogenesis of rheumatoid arthritis: pivotal cytokines involved in bone degradation and inflammation. J Rheumatol Suppl. 2002 Sep;65:3–9.
Proinflammatory cytokines, notably interleukin 1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), play an important role in initiating and perpetuating inflammatory and destructive processes in the rheumatoid joint. These cytokines regulate many nuclear factor kappaB inducible genes that control expression of other cytokines, cell adhesion molecules, immunoregulatory molecules, and proinflammatory mediators. The expression of cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) and thereby production of prostaglandins (PG) and NO are regulated by cytokines. PGE2 and NO further promote inflammation and likely participate in destructive mechanisms in the rheumatoid joint. In some experimental systems, the effects of IL-1 and TNF-alpha appear synergistic, and correspondingly, concomitant inhibition of both cytokines provides greater than additive antiarthritic effects. Although the actions of IL-1 and TNF-alpha show a large degree of overlap, some differences have been observed in animal models. However, in patients with active rheumatoid arthritis, blockade of either cytokine results in clinical improvement and less radiographic progression.

59. Gourine AV, Dale N, Gourine VN, Spyer KM. Fever in systemic inflammation: roles of purines. Front Biosci. 2004 Jan 1;9:1011–22.
Extracellular purine nucleotide and nucleoside signalling molecules, such as ATP and adenosine, acting through specific receptors (P2 and P1, respectively) play significant roles in the mechanisms underlying the febrile response. A variety of P2 and P1 receptor subunits have been identified in the hypothalamus, the area of the brain that orchestrates the febrile response. Importantly, both ATP and adenosine have been shown to modulate release and/or action of cytokines that are implicated in fever, as well as to be involved in the central mechanisms of cardiovascular and respiratory control. Data indicate that at the level of the anterior hypothalamus extracellular ATP is involved in the control of the development of fever. A population of warm-sensitive neurones in the anterior hypothalamus is likely to be the site of action of ATP on body temperature. ATP-induced cytokine release does not appear to play a significant role in the hypothalamic mechanisms leading to the development of the febrile response. However, the blockade of fever by P2 receptor antagonists given systemically suggests that ATP-mediated signaling may play a role in the release of pyrogenic cytokines in the periphery. At the level of the anterior hypothalamus adenosine appears to be released tonically, and acts to maintain body temperature under afebrile conditions. There is also evidence that adenosine-mediated signaling may play a role in the hypothalamic mechanisms controlling the degree of body temperature increase during fever. Our investigations have identified possible mechanisms by which purines modulate the febrile response. The actions of purines on body temperature during fever are most likely “site specific” (brain vs. periphery), may or may not involve their effect on cytokine release and/or action, and are likely to involve P2 and P1 receptors of different subtypes. Further extensive studies are needed to elucidate these mechanisms in greater detail and may lead to the development of new approaches for modifying febrile, cytokine and acute-phase responses to infection.

60. Fujii T, Hayashi S, Hogg JC, Vincent R, Van Eeden SF. Particulate matter induces cytokine expression in human bronchial epithelial cells. Am J Respir Cell Mol Biol. 2001 Sep;25(3):265–71.
The study was designed to determine cytokines produced by primary human bronchial epithelial cells (HBECs) exposed to ambient air pollution particles (EHC-93). Cytokine messenger RNA (mRNA) was measured using a ribonuclease protection assay and cytokine protein production by enzyme-linked immunosorbent assay. Primary HBECs were freshly isolated from operated lung, cultured to confluence, and exposed to 10 to 500 microg/ml of a suspension of ambient particulate matter with a diameter of less than 10 microm (PM_{10}) for 2, 8, and 24 h. The mRNA levels of leukemia inhibitory factor (LIF), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1alpha, and IL-8 were increased after exposure to PM_{10}, and this increase was dose-dependent between 100 ($P < 0.05$) and 500 ($P < 0.05$) microg/ml of PM_{10} exposure. The concentrations of LIF, GM-CSF, IL-1beta, and IL-8 protein measured in the supernatant collected at 24 h increased in a dose-dependent manner and were significantly higher than those in the control nonexposed cells. The soluble fraction of the PM_{10} (100 microg/ml) did not increase these cytokine mRNA levels compared with control values and were significantly lower compared with HBECs exposed to 100 microg/ml of PM_{10} (LIF, IL-8, and IL-1beta; $P < 0.05$), except for GM-CSF mRNA (P = not significant). We conclude that primary HBECs exposed to ambient PM_{10} produce proinflammatory mediators that contribute to the local and systemic inflammatory response, and we speculate that these mediators may have a role in the pathogenesis of cardiopulmonary disease associated with particulate air pollution.

61. The Third National Health and Nutrition Examination Survey (NHANES III), 1988–94, was conducted on a nationwide probability sample of approximately 33,994 persons 2 months and

over. The survey was designed to obtain nationally representative information on the health and nutritional status of the population of the United States through interviews and direct physical examinations. Physical examinations and objective measures are employed because the information collected cannot be furnished or is not available in a standardized manner through interviews with the people themselves or through records maintained by the health professionals who provide their medical care.

Some of the 30 topics investigated in the NHANES III were: high blood pressure, high blood cholesterol, obesity, passive smoking, lung disease, osteoporosis, HIV, hepatitis, helicobacter pylori, immunization status, diabetes, allergies, growth and development, blood lead, anemia, food sufficiency, dietary intake-including fats, antioxidants, and nutritional blood measures.

62. Schwartz J.; "Air pollution and blood markers of cardiovascular risk;" Environ Health Perspect. 2001 Jun;109 Suppl 3:405–9.
This study examined the association between blood markers of cardiovascular risk and air pollution in a national sample of the U.S. population. Air pollution concentrations were merged to subjects in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States, and the association with fibrinogen levels and counts of platelets and white blood cells were examined. The subjects in NHANES III are a representative sample of the U.S. population. Regressions controlled for age, race, sex, body mass index, current smoking, and number of cigarettes per day. The complex survey design was dealt with using mixed models with a random sampling site effect. In single-pollutant models, PM_{10} (particulate matter with a mass median aerodynamic diameter less than 10 microm) was associated with all three outcomes ($p< 0.05$): Sulfur dioxide (SO_2) was significantly associated only with white cell counts, nitrogen dioxide (NO_2) with platelet counts and fibrinogen, and ozone with none of the outcomes. In two-pollutant models, PM_{10} remained a significant predictor of white cell counts controlling for SO_2 but not vice versa. PM_{10} was marginally significant in a model for platelet counts with NO_2, and the sign of the NO_2 coefficient was reversed. These results were stable with control for indoor exposures (wood stoves, environmental tobacco smoke, gas stoves, fireplaces), dietary risk factors (saturated fat, alcohol, caffeine intake, n-3 fatty acids), and serum cholesterol. The magnitude of the effects are modest [e.g., 13 microg/dL fibrinogen for an interquartile range (IQR) change in PM_{10}, 95 percent confidence interval (CI) 4.6–22.1 mg/dL]. However, the odds ratio of being in the top 10 percent of fibrinogen for the same IQR change was 1.77 (95% CI 1.26–2.49). These effects provide considerable biologic plausibility to the mortality studies. PM_{10}, but not gaseous air pollutants, is associated with blood markers of cardiovascular risk, and this may explain epidemiologic associations with early deaths.

63. [57]
SALVI, S., BLOMBERG, A., RUDELL, B., KELLY, F., SANDSTROM, T., HOLGATE, S.T., & FREW, A.
Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers
Am J Respir Crit Care Med 1999; 159; 702–709
15 healthy human volunteers exposed to air and diluted diesel exhaust for one hour with intermittent exercise. PM_{10} inhaled was 300 $\mu g/m^3$; NO_2 was 1.6 ppm; NO 4.5 ppm; CO 7.5 ppm; total hydrocarbons 4.3 ppm; formaldehyde 0.26 mg/m^3; suspended particles were 4.3 x 10^6 cm^3
6 hours after end of exposure, BAL performed.
Results showed no effects on lung function; significant increase in neutrophils and B lymphocytes in BAL; together with increases in histamine and fibronectin; Bronchial biopsies

showed increases in neutrophils, mast cells, CD4+ and CD8+, and T lymphocytes. Upregulation of endothelial adhesion molecules also found. Neutrophils and platelets increased significantly in peripheral blood following exposure.
Results showed no effects on lung function; significant increase in neutrophils and B lymphocytes in BAL; together with increases in histamine and fibronectin; Bronchial biopsies showed increases in neutrophils, mast cells, CD4+ and CD8+, and T lymphocytes. Upregulation of endothelial adhesion molecules also found. Neutrophils and platelets increased significantly in peripheral blood following exposure.
Authors conclude that "at high ambient concentration, acute short-term diesel exhaust exposure produces a well-defined and marked systemic and pulmonary inflammatory response in healthy human volunteers, which is underestimated by standard lung function measurements".
Important data.

64. [184]PEKKANEN, J., BRUNNER, E.J., ANDERSON, H.R., TIITANEN, P., & ATKINSON, R.W.
Daily concentrations of air pollution and plasma fibrinogen in London
Occup Environ Med 2000; 57; 818–8224982 male and 2223 female office workers had blood samples collected in a cross sectional survey between September 1991 and May 1993. The fibrinogen content was determined, and the association of level with mean concentrations of air pollutants during the day of blood sampling and during the preceding three days was assessed.

After adjustment for weather "an increase in the 24 hour mean NO_2 during the previous day from the 10^{th} to the 90^{th} percentile (61.7 $\mu g/m^3$) was associated with a 1.5 percent higher fibrinogen concentration. Also associated with CO. Associations stronger in warm season (April to September), when PM_{10} and BS also became significantly associated. No association with SO_2 or ozone. NO_2 and CO also associated with 2.8 percent and 3.6 percent increase in hospital admissions for myocardial infarction (see Occup Environ Med 1997; 54; 535–540). Interesting data.

65. [133]
SCHWARTZ, J.
Air Pollution and blood markers of cardiovascular risk
Environ Health Perspect 109 (suppl 3): 405–409; (2001)
Analysis of NHANES III data. Fibrinogen levels, platelet counts, and white blood cell (wbc) counts assessed. Regressions controlled for age, race, sex, body mass index, current smoking, and number of cigarettes/day. PM_{10} associated with all three outcomes; SO_2 associated with wbc counts; NO_2 with platelet counts and fibrinogen; and ozone exposure with nothing.

Further analyses in two pollutant models indicated that PM_{10} was probably the dominant effector. Magnitude modest since there was a 13 microg/dl change in fibrinogen for an interquartile range of PM_{10}. Results lend support to the mortality studies.

66. [134]
DYE, J.A., LEHMANN, J.R., MCKEE, J.K., WINSETT, D.W., LEDBETTER, A.D., EVERITT, J.I., GHIO, A.J., & COSTA, D.L.
Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiologic studies in Utah Valley residents
Environ Health Perspect 109 (suppl 3): 395–403 (2001)
Three sets of particulate matter filters collected in 1986, 1987 (when the steel mill was closed) and 1988 when it reopened. Water extraction and intratracheal instillation of rats with equivalent

volumes. 24 hours later, extracts from 1986 and 1988 caused significant pulmonary injury and neutrophilic inflammation but 1987 extract did not (excellent illustrations of the lesions). Airway responsiveness also increased in affected rats. Extracts from 1986 and 1988 had a higher metal content and this may have been responsible for the increased toxicity. Notes that these results are in accord with Pope's epidemiological studies of hospital admissions of children with acute bronchiolitis (which declined dramatically in the year of closure, 1987). Lung sections show extensive alveolitis plus pleocellular inflammatory exudates, with haemorrhage in the alveolar spaces.
Excellent discussion. "The strengths imparted by an integrated approach of epidemiologic, human, animal, and in vitro studies can only augment quantitative risk evaluations and regulatory decision making."

67. [190]
GHIO, A.J., & DEVLIN, R.B.
Inflammatory lung injury after bronchial instillation of air pollution particles
Am J Respir Crit Care Med 164; 704–708, 2001
Filters of particles from Provo, Utah, before, during and after mill closure. Aliquots of extracts instilled through the bronchoscope into lungs of nonsmoking volunteers. 24 hours later, same segment was lavaged. Data show much less inflammatory response using extracts from material when the mill was closed. Authors note: "Findings suggest that mass may not be the most appropriate metric to use in assessing health effects after PM exposure, but rather specific components must be identified and assessed." Differences in lavage neutrophil percentages particularly impressive—range of 40 percent to 32 percent when the mill was open, and less than 10 percent with extracts during the year when it was closed. Proinflammatory mediators also much lower in 1987. Table of metal contents in the three PM extracts as follows:

	1986	1987	1988
Iron	82.2	14.8	257.5
Copper	402.8	29.1	471.8
Zinc	1276.5	20.2	690.2
Lead	186.6	5.7	286.7
Nickel	17.6	3.8	11.0
Vanadium		7.4	37.7

All units in NG metal/mg Extract.

68. [172]
PETERS, A., IBALD-MULLI, A., STADELER, S., WOELKE, G., TUCH, T., KREYLING, W.G., WICHMANN, H.E., PEKKANEN, J., & HEINRICH, J.
Symptoms increase in association with fine and ultrafine particles in patients with coronary heart disease.
Am J Respir Crit Care Med 161: A24: 2000
48 patients with CHD over 157 days. $PM_{2.5}$ and number concentration of ultrafines (< 100 nm) determined at central monitoring site in Erfurt. Odds ratios for change in pollutants from 25^{th} to 75^{th} percentile. Increase of ultrafine particles of 11,000 per cubic cm had OR of 1.40, and increase of $PM_{2.5}$ of 15 $\mu g/m^3$ had OR of 1.12. Severe angina also elevated in associated with both indices of pollution. Authors conclude that "overall health of patients with coronary artery

disease deteriorates in association with elevated concentrations of particles in ambient air."

69. [161]
SUNYER, J., SCHWARTZ, J., TOBIAS, A., MACFARLANE, D., GARCIA, J., & ANTO, J.M.
Patients with Chronic Obstructive Pulmonary Disease are at increased risk of death associated with urban particle air pollution; a case-crossover analysis.
Am J Epidemiol; 2000; 151; 50–56
1,845 men and 460 women from Barcelona who died during the period 1990–1995 and had visited Emergency Rooms because of COPD during the period of 1985–1989 included in analysis. Black smoke used and odds calculated for an interquartile range of 20 $\mu g/m^3$. For respiratory causes, OR of 1.182 found. CVS causes not significant. Older women, patients admitted to intensive care units, and those with a higher rate of emergency room visits were all at greater risk of dying associated with black smoke. No significant SO_2 association, but associations were positive. Correction for influenza epidemic applied.
Lag time of previous 2 days used.

70. National Heart Lung and Blood Institute, "What is COPD?"
http://www.nhlbi.nih.gov/health/dci/Diseases/Copd/Copd_WhatIs.html.

71. American Heart Association, Carotid Artery Stenosis,
http://www.americanheart.org/presenter.jhtml?identifier=4497.

72. American Heart Association, Atherosclerosis,
http://www.americanheart.org/presenter.jhtml?identifier=228.
73. O'LEARY DH, POLAK JF, KRONMAL RA, MANOLIO TA, BURKE GL, WOLFSON SK JR.
Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults.
N Engl J Med. 1999 Jan 7;340(1):14–22
BACKGROUND: The combined thickness of the intima and media of the carotid artery is associated with the prevalence of cardiovascular disease. We studied the associations between the thickness of the carotid-artery intima and media and the incidence of new myocardial infarction or stroke in persons without clinical cardiovascular disease. METHODS: Noninvasive measurements of the intima and media of the common and internal carotid artery were made with high-resolution ultrasonography in 5858 subjects 65 years of age or older. Cardiovascular events (new myocardial infarction or stroke) served as outcome variables in subjects without clinical cardiovascular disease (4476 subjects) over a median follow-up period of 6.2 years. RESULTS: The incidence of cardiovascular events correlated with measurements of carotid-artery intima-media thickness. The relative risk of myocardial infarction or stroke increased with intima-media thickness ($P<0.001$). The relative risk of myocardial infarction or stroke (adjusted for age and sex) for the quintile with the highest thickness as compared with the lowest quintile was 3.87 (95 percent confidence interval, 2.72 to 5.51). The association between cardiovascular events and intima-media thickness remained significant after adjustment for traditional risk factors, showing increasing risks for each quintile of combined intima-media thickness, from the second quintile (relative risk, 1.54; 95 percent confidence interval, 1.04 to 2.28), to the third (relative risk, 1.84; 95 percent confidence interval, 1.26 to 2.67), fourth (relative risk, 2.01; 95 percent confidence interval, 1.38 to 2.91), and fifth (relative risk, 3.15; 95 percent confidence interval, 2.19 to 4.52). The results of separate analyses of myocardial infarction and stroke paralleled those for the combined end point. CONCLUSIONS: Increases in the thickness of the intima and media of the carotid artery, as measured noninvasively by ultrasonography, are

directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease.

74. [1122]
KUENZLI, N., JERRETT, M., BECKERMAN, B., MACK, W., GILLILAND, F., THOMAS, D., & PETERS, J.
Association of subclinical atherosclerosis (carotid intima media thickness) with residential ambient $PM_{2.5}$ in healthy adults.
Abstract ISEE-24
Epidemiology 15; S 23; 2004
Carotid artery intima media thickness (IMT) steadily increases from childhood to death; increases with smoking and other risk factors; and is a noninvasive measurement. Between 1996 and 2003, IMT measured in 445 men and 356 women aged 40–89 with a mean age of 59 years. Individually assigned $PM_{2.5}$ exposures varied from 5.2 to 26.90 $\mu g/m^3$ with a mean of 20.3 $\mu g/m^3$. After correction for all known factors, there was a strong association between calculated residential $PM_{2.5}$ exposure and the degree of IMT.

75. [1214]
KUNZLI, N., JERRETT, M., MACK, W.J., BECKERMAN, B., LaBREE, L., GILLILAND, F., THOMAS, D., PETERS, J., & HODIS, H.N.
Environmental Health Perspectives (online November 22nd 2004)
^(6b,11c) Data from 798 participants in Los Angeles from two clinical trials, analysed to investigate the association between atherosclerosis and long-term exposure to ambient $PM_{2.5}$. Baseline measurement of carotid intima-media thickness. Individual residences geocoded to assign annual mean values of $PM_{2.5}$—these ranged from 5.2 to 26.9 $\mu g/m^3$. For a cross sectional exposure contrast of 10 $\mu g/m^3$ of $PM_{2.5}$, the carotid mean thickness was found to increase by 5.9 percent. This coefficient was slightly reduced by adjusting for age, but remained in the range 3.9 percent to 4.3 percent. The strongest association was in women aged 60 and over, and was higher in never smokers. The baseline criteria excluded subjects with diabetes, a raised diastolic pressure, thyroid disease, a raised serum creatinine (>0.065 mmol/L), life threatening diseases, or a high alcohol intake. High resolution B-mode ultrasound technique used over the right common carotid artery.

	Quartiles of $PM_{2.5}$ ($\mu g/m^3$)			
	5.2–19.1	19.1–20.73	20.74–22.0	22.1–26.9
Mean CIMT in microns	710	720	730	732

Remarkable data.

76. National Center for Health Statistics, "Chronic Obstructive Pulmonary Disease (COPD)," http://www.cdc.gov/nchs/fastats/copd.htm.
In 2003, data for lung diseases were—

Number of noninstitutionalized adults with diagnosed chronic bronchitis in the past year: 8.6 million

Percent of noninstitutionalized adults with diagnosed chronic bronchitis in the past year: 4.0.

Number of noninstitutionalized adults who have ever been diagnosed with emphysema: 3.1 million.

Percent of noninstitutionalized adults who have ever been diagnosed with emphysema: 1.5 million.

Number of noninstitutionalized adults who have ever been diagnosed with asthma: 20.7 million

Percent of noninstitutionalized adults who have ever been diagnosed with asthma: 9.7 million.

77. GARSHICK E, SCHENKER MB, DOSMAN JA.
Occupationally induced airways obstruction
Med Clin North Am. 1996 Jul;80(4):851–78
The studies reviewed in this article indicate the association of occupational exposure to a variety of organic and inorganic dusts and various gases and fumes with chronic bronchitis and decrements of FEV1. Usually an obstructive pattern was noted, although in some occupations a similar decrement in FVC was noted. The effect of smoking on chronic bronchitis, respiratory symptoms, and FEV1 was usually additive, although workers exposed to cotton dust in one study demonstrated an interaction between exposure and smoking, as did a study of a general population sample. In coal workers, exposure to dust in younger workers resulted in a greater decline in lung function than if the exposure occurred in older workers. Studies in coal miners and grain workers further suggest that occupational standards in effect are not sufficient to protect the working population from adverse effects. The magnitude of the effect of occupation on decrement in FEV1 is usually less than cigarette smoking. Studies in coal miners indicate, however, that a minority of workers could be more severely affected by exposure. When considered together with cigarette smoking, additional decrements in lung function because of occupational exposure could contribute to disability. Additional study is needed for better understanding of exposure-response relationships, host factors, potential interaction with cigarette smoking, and pathophysiology of the development of occupationally induced airway disease.

78. HNIZDO E, VALLYATHAN V.
Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence.
Occup Environ Med. 2003 Apr;60(4):237–43
Occupational exposure is an important risk factor for chronic obstructive pulmonary disease (COPD), and silica dust is one of the most important occupational respiratory toxins. Epidemiological and pathological studies suggest that silica dust exposure can lead to COPD, even in the absence of radiological signs of silicosis, and that the association between cumulative silica dust exposure and airflow obstruction is independent of silicosis. Recent clinicopathological and experimental studies have contributed further towards explaining the potential mechanism through which silica can cause pathological changes that may lead to the development of COPD. In this paper we review the epidemiological and pathological evidence relevant to the development of COPD in silica dust exposed workers within the context of recent findings. The evidence surveyed suggests that chronic levels of silica dust that do not cause disabling silicosis may cause the development of chronic bronchitis, emphysema, and/or small airways disease that can lead to airflow obstruction, even in the absence of radiological silicosis.

79. SMITH KR
Inaugural article: national burden of disease in India from indoor air pollution.
Proc Natl Acad Sci USA 2000;97:13286–13293

80. CHURG A, WRIGHT, CA. JL

Airway wall remodeling induced by occupational mineral dusts and air pollutant particles
Chest. 2002 Dec;122(6 Suppl):306S–309S
COPD has been reported in workers exposed to particulates, and there is increasing evidence that high levels of ambient particulate pollutants may also be associated with COPD. The studies here investigate the hypothesis that particulates, including air pollution particles, can induce airway wall fibrosis, a process that can lead to COPD. DESIGN: Rat tracheal explants were exposed to various occupationally encountered dusts, air pollution particles, and model air pollution particles. In some experiments, iron was loaded onto the particle surface. Gene expression and nuclear factor (NF)-kappaB activation were measured after 7 days of air culture. Adhesion to and uptake of dusts by the tracheal epithelium were also evaluated. RESULTS: Known fibrogenic dusts such as amosite asbestos produced increased gene expression of procollagen, transforming growth factor-beta, and platelet-derived growth factor, and increased hydroxyproline in the explants, and the addition of iron increased these effects. The addition of iron also converted nonfibrogenic TiO2 into a fibrogenic dust. Dusts with surface complexed iron activated NF-kappaB via an oxidant mechanism. However, an ultrafine TiO2 with very low iron was also fibrogenic. In separate experiments, exogenous tumor necrosis factor-alpha increased dust adhesion to, and exogenous ozone increased dust uptake by, tracheal epithelial cells. CONCLUSIONS: Mineral dusts can directly induce fibrosis in the airway wall. Exogenous inflammatory cells and exogenous agents are not required, but they probably exaggerate the fibrogenic effects. An iron-mediated oxidant mechanism underlies the fibrogenic effects of some, but not all, of these dusts. Particle-induced airway wall fibrosis may lead to COPD.

81. [716]
MACNEE, W., & DONALDSON, K.
Mechanism of lung injury caused by PM_{10} and ultrafine particles with special reference to COPD
Eur Respir J 2003; 21; Suppl 40, 47s–51s
Useful review of evidence for oxidative stress engendered by PM_{10} in causing damage. Notes evidence of metal content as contributing to toxicity, and summarises evidence from rat experiments indicating that ultrafine particles, when instilled, cause increased BAP neutrophils and hence an inflammatory response. Good diagram of hypothetical sequence of events leading from the contact of particles with the cell surface, to an inflammatory response. Interaction with effect of adenovirus also noted.

82. HODGKIN JE, ABBEY DE, EULER GL, MAGIE AR.
COPD prevalence in nonsmokers in high and low photochemical air pollution areas
Chest. 1984 Dec;86(6):830–8
The prevalence of respiratory symptoms, as ascertained by questionnaire, was evaluated in 6,666 nonsmokers who had lived for at least 11 years in either a high photochemical pollution area (4,379 individuals) or a low photochemical pollution area (2,287 individuals). Of these, 5,178 had never smoked, and none was currently smoking. The risk estimate for “definite” COPD, as defined in this study, was 15 percent higher in the high pollution area ($p = 0.03$), after adjusting for sex, age, race, education, occupational exposure, and past smoking history. Past smokers had a risk estimate 22 percent higher than never smokers ($p = 0.01$). Multivariate analysis showed a significant effect of air pollution on the prevalence of “definite” COPD which univariate analysis failed to demonstrate.

83. SCHIKOWSKI, T., DOROTHEA, D., SUGIRI, D., RANFT, U, GEHRING, U., HEINRICH, J. WICHMANN,H.E., AND KRÄMER, U.
Long-term air pollution exposure and living close to busy roads are associated with COPD in women.
Resp. Rsch. 2005, 6:152

In consecutive cross sectional studies conducted between 1985–1994, researchers investigated 4757 women living in the Rhine-Ruhr Basin of Germany. NO_2 and PM_{10} exposure was assessed by measurements done in an 8 km grid, and traffic exposure by distance from the residential address to the nearest major road using Geographic Information System data. Lung function was determined and COPD was defined by using the GOLD criteria. Chronic respiratory symptoms and possible confounders were defined by questionnaire data. Linear and logistic regressions, including random effects were used to account for confounding and clustering on city level.
Results
The prevalence of COPD (GOLD stages 1–4) was 4.5 percent. COPD and pulmonary function were strongest affected by PM_{10} and traffic related exposure. A 7 $\mu g/m^3$ increase in five year means of PM_{10} (interquartile range) was associated with a 5.1 percent (95% CI 2.5%–7.7%) decrease in FEV1, a 3.7 percent (95% CI 1.8%–5.5%) decrease in FVC and an odds ratio (OR) of 1.33 (95% CI 1.03–1.72) for COPD. Women living less than 100 m from a busy road also had a significantly decreased lung function and COPD was 1.79 times more likely (95% CI 1.06–3.02) than for those living farther away. Chronic symptoms as based on questionnaire information showed effects in the same direction, but less pronounced.

84. Austin Bradford Hill, "The Environment and Disease: Association or Causation?," Proceedings of the Royal Society of Medicine, 58 (1965), 295–300.

This classic essay is reprinted below.

By Sir Austin Bradford Hill, CBE DSC FRCP(hon) FRS, Professor Emeritus of Medical Statistics, University of London.

Amongst the objects of this newly-founded Section of Occupational Medicine and firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized.'

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what might a particular environment do to man, and then see whether such consequences are indeed to be found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this observed

association to a verdict of causation? Upon what basis should be proceed to do so?

I have no wish, nor the skill, to embark upon philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymous preventive, medicine in mind the decisive question is where the frequency of the undesirable event B will be influenced by a change in the environmental feature A. How such a change exerts that influence may call for a great deal of research, However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of the research. The whole chain may have to be unraveled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) Strength. First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the enormous increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some feature of life that may go hand-in-hand with smoking—features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess of cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic 'you can't prove it, there may be such a feature.'

Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute difference between the death rates of our various groups and not the ratio of one to the other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (i.e. presuming causation), then obviously we must use the absolute differences between the death rates—0.07 per 1,000 per year in nonsmoking doctors, 0.57 in those smoking 1–14 and 2.27 for 25 or more daily. But is does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to etiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative. It does not, of course, follow that the differences

revealed by ratios are of any practical importance. Maybe they are, maybe they are not; but that is another point altogether.

We may recall John Snow's classic analysis of the opening weeks of the cholera epidemic of 1854 (Snow 1855). The death rate that he recorded in the customs supplied with the grossly polluted water of the Southwark and Vauxhall Company was in truth quite low—71 deaths in each 10,000 houses. What stands out vividly is the fact that the small rate is 14 times the figure of 5 deaths per 10,000 houses supplied with the sewage free water of the Lambeth Company.

In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause and effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harboring the meningococcus fall sick of the meningococcal meningitis. Relatively few persons occupationally exposed to rat's urine contract Weill's disease.

(2) Consistency: Next on my list of features to be specially considered I would place the consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

This requirement may be of special importance for those rare hazards singled out in the section's terms of reference. With many alert minds at work in the industry today many an environmental association may be thrown up. Some of them on the customary tests of statistical significance will appear to be unlikely to be due to chance. Nevertheless whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and the observations.

Returning to my more general example, the Advisory Committee to the Surgeon General of the United States Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries (US Department of Health, Education and Welfare 1964). The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words, we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guards against that.

Take, for instance, an example given by Heady (1958). Patients admitted to hospital for operation for peptic ulcer are questioned about recent domestic anxieties or crises that may have precipitated the acute illness. As controls, patients admitted for operation for a simple hernia are similarly quizzed. But, as Heady points out, the two groups may not be in pari materia. If your wife ran off with the lodger last week you still have to take your perforated ulcer to hospital without delay. But with a hernia you might prefer to stay at home for a while—to mourn (or celebrate) the event. No number of exact repetitions would remove or necessarily reveal that fallacy.

We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively.

Once again looking at the observed of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions. The experience of the nickel refiners of South Wales is an outstanding example. I quote from the Alfred Watson Memorial Lecture that I gave in 1962 to the Institute of Actuaries:

'The population at risk, workers and pensioners, numbered about one thousand. During the ten years 1929 to 1938, sixteen of them had died from cancer of the nasal sinuses. At the age specific death rates of England and Wales at that time, one might have anticipated one death from cancer of the lung (to compare with the 16), and a fraction of a death from cancer of the nose (to compare with the 11). In all other bodily sites cancer had appeared on the death certificate 11 times and one would have expected it to do so 10–11 times. There had been 67 deaths from all other causes of mortality and over the ten years' period 72 would have been expected at the national death rates. Finally division of the population at risk in relation to their jobs showed that the excess of cancer of the lung and nose had fallen wholly upon the workers employed in the chemical processes.

'More recently my colleague, Dr. Richard Doll, has brought this story a stage further. In the nine years 1948 to 1956 there had been, he found, 48 deaths from cancer of the lung and 13 deaths from cancer of the nose. He assessed the numbers expected at normal rates of mortality as, respectively 10 to 0.1.

'In 1923, long before any special hazard had been recognized, certain changes in the refinery took place. No case of cancer of the nose has been observed in any man who first entered the works after that year, and in these men there has been no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century.

'No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any clue or any support to this wholly statistical evidence. Yet I wonder if any of us would hesitate to accept it as proof of a grave industrial hazard?' (Hill 1962).

In relation to my present discussion I know of no parallel investigation. We have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so.

(3) Specificity: One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider. If as here, the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favor of causation.

We must not, however, over-emphasize the importance of the characteristic. Even in my present example there is a cause and effect relationship with two different sites of cancer—the lung and the nose. Milk as a carrier of infection and, in that sense, the cause of disease can produce such a disparate galaxy as scarlet fever, diptheria, tuberculosis, undulant fever, sore throat, dysentary and typhoid fever. Before the discovery of the underlying factor, the bacterial origin of disease, harm would have been done by pushing too firmly the need for specificity as a necessary feature before convicting the dairy.

Coming to modern time the prospective investigations of smoking and cancer of the lung have been criticized for not showing specificity—in other words the death rate of smokers is

higher than the death rate of non-smokers from many causes of death (though in fact the results of Doll and Hill, 1964, do not show that). But here surely one must return to my first characteristics, the strength of the association. If other causes of death are raised 10, 20 or even 50 percent in smokers whereas cancer of the lung is raised 900–1000 percent we have specificity—a specificity in the magnitude of the association.

We must also keep in mind that diseases may have more than one cause. It has always been possible to acquire a cancer of the scrotum without sweeping chimneys of taking to mulespinning in Lancashire. One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answer we might get back to a single factor.

In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.

(4) Temporality: My fourth characteristic is the temporal relationship of the association—which is the cart and which is the horse? This is a question which might be particularly relevant with diseases of slow development. Does a particular diet lead to disease or do the early stages of the disease lead to those particular dietetic habits? Does a particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment—or, indeed, have they already contracted it? This temporal problem may not arise often, but it certainly needs to be remembered, particularly with selective factors at work in the industry.

(5) Biological gradient: Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. The comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause and effect hypothesis. The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light.

The same would clearly be true of an alleged dust hazard in industry. The dustier the environment the greater the incidence of disease we would expect to see. Often the difficulty is to secure some satisfactory quantitative measures of the environment which will permit us to explore this dose-response. But we should invariably seek it.

(6) Plausibility: It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

> '…no biological knowledge to support (or to refute) Pott's observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19 that led to a prize essayist writing on the value and the th fallacy of statistics to conclude, amongst other "absurd" associations, that "it could be no more ridiculous for the strange who passed the night in the steerage

of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected." And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against th rubella.'

In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr. Watson, 'when you have eliminated the impossible, whatever remains, however improbable, must be the truth.'

(7) Coherence: On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease—in the expression of the Advisory Committee to the Surgeon-General it should have coherence.

Thus in the discussion of lung cancer the Committee finds its association with cigarette smoking coherent with the temporal rise that has taken place in the two variables over the last generation and with the sex difference in mortality—features that might well apply in an occupational problem. The known urban/rural ratio of lung cancer mortality does not detract from coherence, nor the restriction of the effect to the lung.

Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agents, the lack of such evidence cannot nullify the epidemiological associations in man. Arsenic can undoubtedly cause cancer of the skin in man but is has never been possible to demonstrate such an effect on any other animal. In a wider field John Snow's epidemiological observations on the conveyance of cholera by water from the Broad Street Pump would have been put almost beyond dispute if Robert Koch had been then around to isolate the vibrio from the baby's nappies, the well itself and the gentleman in delicate health from Brighton. Yet the fact that Koch's work was to be awaited another thirty years did not realy weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day—both just and unjust.

(8) Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed.

(9) Analogy: In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe—and this has been suggested¯ that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other

answer equally, or more, likely than cause and effect?

Tests of Significance

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.

Nearly forty years ago, amongst the studies of occupational health that I made for the Industrial Health Research Board of the Medical Research Council was one that concerned the workers in the cotton-spinning mills of Lancashire (Hill 1930). The question that I had to answer, by the use of the National Health Insurance records of that time, was this: Do the workers in the cardroom of the spinning mill, who tend the machines that clean the raw cotton, have a sickness experience in any way different from that of the other operatives in the same mills who are relatively unexposed to the dust and fibre that were features of the card room? The answer was an unqualified 'Yes'. From age 30 to age 60 the cardroom workers suffered over three times as much from respiratory causes of illness whereas from non-respiratory causes their experience was not different from that of the other workers. This pronounced difference with the respiratory causes was derived not from abnormally long periods of sickness but rather from an excessive number of repeated absences from work of the cardroom workers.

All this has rightly passed into the limbo of forgotten things. What interests me today is this: My results were set out for men and women separately and for half a dozen age groups in 36 tables. So there were plenty of sums. Yet I cannot find that anywhere I thought it necessary to use a test of significance. The evidence was so clear cut, the differences between the groups were mainly so large, the contrast between respiratory and non-respiratory causes of illness so specific, that no formal tests could really contribute anything of value to the argument. So why use them?

Would we think or act that way today? I rather doubt it. Between the two world wars there was a strong case for emphasizing to the clinician and other research workers the importance of not overlooking the effects of the play of chance upon their data. Perhaps too often generalities were based upon two men and a laboratory dog while the treatment of choice was deducted from a difference between two bedfuls of patients and might easily have no true meaning. It was therefore a useful corrective for statisticians to stress, and to teach the needs for, tests of significance merely to serve as guides to caution before drawing a conclusion, before inflating the particular to the general.

I wonder whether the pendulum has not swung too far—not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the USA where, I am told, some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary—because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the table diverts attention from the inadequacies of the fare. Only a tithe, and an unknown tithe, of the factory personnel volunteer for some procedure or interview, 20 percent of patients treated in some particular way are lost to sight, 30 percent of a randomly-drawn sample are never contracted. The sample may, indeed, be akin to that of the man who, according to Swift, 'had a mind to sell his house and carried a piece of brick in his pocket, which he

showed as a pattern to encourage purchasers.' The writer, the editor and the reader are unmoved. The magic formulae are there.

Of course I exaggerate. Yet too often I suspect we waste a deal of time, we grasp the shadow and lose the substance, we weaken our capacity to interpret the data and to take reasonable decisions whatever the value of P. And far too often we deduce 'no difference' from 'no significant difference.' Like fire, the chi-squared test is an excellent servant and a bad master.

The Case for Action

Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgement (in that sense) should be utterly independent of what hangs upon it—or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action. If this be operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

While that is a commendable ambition, it almost inevitably leads us to introduce differential standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.

On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on 8:30 the next day.

85. Areas Designated Nonattainment for $PM_{2.5}$: Atlanta, Baltimore, Birmingham, Canton-Masillon, Charleston, Chattanooga, Chicago-Gary-Lake County, Cincinnati-Hamilton, Cleveland-Akron-Lorain, Columbus, Dayton-Springfield, Detroit-Ann Arbor, Evansville, Rome, Greensboro-Winston Salem-High Point, Greenville-Spartanburg, Harrisburg-Lebanon-Carlisle, Hickory-Morganton-Lenoir, Huntington-Ashland, Indianapolis, Johnstown, Knoxville, Lancaster, Libby, Liberty-Clairton, Los Angeles-South Coast Air, Basin, Louisville, Macon, Martinsburg, WV-Hagerstown, New York-New Jersey-Long Island, Parkersburg-Marietta, Philadelphia-Wilmington, Pittsburgh-Beaver Valley, Reading, San Joaquin Valley, St. Louis, Steubenville-Weirton, Washington, Wheeling, York, Source: U.S. EPA

http://www.epa.gov/airtrends/pdfs/pm25dv20050824.pdf

86. WOODRUFF, T.J., PARKER, J.D., & SCHOENDORF, K.C.
Fine Particulate Matter ($PM_{2.5}$) Air Pollution and selected causes of postneonatal infant mortality in California Environmental Health Perspectives: website posting: doi: 1289/ehp.8484 (available at http://dx.doi.org/)
On line 13th January 2006 ^(6b) Studies cover years 1999 and 2000 in California. Maternal addresses had to be within 5 km of a $PM_{2.5}$ monitor. Each postneonatal death was matched to 4 infants surviving to one year of age, by birthweight category and date of birth (within 2 weeks). For each matched set, average $PM_{2.5}$ exposure was calculated over the period of life for the infant who had died. 788 postneonatal infant deaths matched to 3,089 infant survivors with 51 and 120 postneonatal infant deaths due to respiratory causes and SIDS (Sudden Infant Death Syndrome), respectively. After all corrections, for a 10 $\mu g/m^3$ increase in $PM_{2.5}$, there was a 1.07 risk for overall mortality, a 2.123 increase for respiratory-related postneonatal mortality; and a 0.82 or nonsignificant risk for SIDS. Review of what has become quite an extensive literature for this age group, which began with observations in the Czech Republic, but now cover other locations.

87. BOBAK M, LEON DA.
The effect of air pollution on infant mortality appears specific for respiratory causes in the postneonatal period.
Epidemiology. 1999 Nov;10(6):661–2.
To examine the association between individual lifetime measures of mean exposure to air pollution and postneonatal respiratory deaths, we have conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. For each case of infant death, we have randomly selected 20 controls from infants of the same sex born on the same day and alive when the case died. Exposure was assigned as the arithmetic mean of all 24-hour air pollution measurements in the district of residence of each case and control for the period between the birth and death of the index case. We used conditional logistic regression to estimate the effects of suspended particles, sulfur dioxide, and nitrogen oxides on risk of death in the neonatal and postneonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. There were 2,494 infant deaths with exposure data on at least one pollutant, 133 of them from respiratory causes. The effects of all pollutants were strongest in the postneonatal period and were specific for respiratory causes. For these, rate ratios for a 50 $\mu g/m^3$ increase in particles, sulfur dioxide, and nitrogen oxides were 1.95 [95% confidence interval (CI) = 1.09-3.50], 1.74 (95% CI = 1.01-2.98), and 1.66 (95% CI = 0.98-2.81), respectively, after controlling for all covariates. Only particles showed a consistent association when all pollutants were entered in one model. We found no evidence of a relation between any pollutant and mortality from other causes. These results indicate that the effects of air pollution on infant mortality are specific for respiratory causes in the postneonatal period, are independent of socioeconomic factors, and are not mediated by birth weight or gestational age.

88. HA EH, LEE JT, KIM H, HONG YC, LEE BE, PARK HS, et al. 2003.
Infant susceptibility of mortality to air pollution in Seoul, South Korea. Pediatrics 111(2):284–290.
The susceptibility of target populations to air pollution is an important issue, because air pollution policies and standards should be based on the susceptibilities of those at particular risk. To evaluate which age group is more susceptible to the adverse health effects of air pollution, this group compared the effects of air pollution on mortality among postneonates, those aged 2 to

64 years, and those over 65 years of age.
Daily counts of total and respiratory death along with daily levels of meteorological variables and air pollutants were analyzed using generalized additive Poisson regression. The relative risks (RR) of mortality for interquartile changes of the levels of particulate matter <10 μm (PM_{10}) were calculated on the same day.
Results. For postneonates, the RR of total mortality for an interquartile change (42.9 $\mu g/m^3$) in PM_{10} (RR: 1.142; 95% confidence interval [CI]: 1.096–1.190) was greatest among age groups. Next were the elderly over 65 years of age (RR: 1.023; 95% CI: 1.022–1.024). Regarding respiratory mortality, RR for an interquartile change of PM_{10} in postneonates (RR: 2.018; 95% CI: 1.784–2.283) was also greater than those in the other groups.
Conclusions. These results agree with the hypothesis that infants are most susceptible to PM_{10} in terms of mortality, particularly respiratory mortality.

89. Reinhard Kaiser, R. Romieu,I., Medina, S., Schwartz, J., Krzyzanowski, M. and Künzli, N. Air pollution attributable postneonatal infant mortality in U.S. metropolitan areas: a risk assessment study. Environ Health. 2004; 3: 4
Based on exposure-response functions from a U.S. cohort study, the team assessed the attributable risk of postneonatal infant mortality in 23 U.S. metropolitan areas related to particulate matter <10 μg in diameter (PM_{10}) as a surrogate of total air pollution.
The estimated proportion of all cause mortality, sudden infant death syndrome (normal birth weight infants only) and respiratory disease mortality (normal birth weight) attributable to PM_{10} above a chosen reference value of 12.0 $\mu g/m^3$ PM_{10} was 6 percent (95 percent confidence interval 3–11%), 16 percent (95 percent confidence interval 9–23%) and 24 percent (95 percent confidence interval 7–44%), respectively. The expected number of infant deaths per year in the selected areas was 106 (95 percent confidence interval 53–185), 79 (95 percent confidence interval 46–111) and 15 percent (95 percent confidence interval 5–27), respectively. Approximately 75 percent of cases were from areas where the current levels are at or below the new U.S. $PM_{2.5}$ standard of 15 $\mu g/m^3$ (equivalent to 25 $\mu g/m^3$ PM_{10}). In a country where infant mortality rates and air pollution levels are relatively low, ambient air pollution as measured by particulate matter contributes to a substantial fraction of infant death, especially for those due to sudden infant death syndrome and respiratory disease. Even if all counties would comply to the new $PM_{2.5}$ standard, the majority of the estimated burden would remain.

90. [985]FISCHER, P.H., BRUNEKREEF, B., & LEBRET, E.
Air Pollution related deaths during the 2003 heat wave in the NetherlandsAtmospheric Environment 38 (2004) 1083–1085
An excess of 1000–1400 deaths occurred in the Netherlands during the very hot weather in the summer of 2003. An estimate was made that an excess of 400–600 deaths were attributable to ozone and PM_{10} levels. Authors conclude: “These calculations suggest that in the Netherlands, a significant proportion of the deaths now being attributed to the hot summer weather can reasonably be expected to have been caused by air pollution”. Average daily ozone levels for 8 hours were 61 $\mu g/m^3$ in 2000; 71 $\mu g/m^3$ in 2002: and 87 $\mu g/m^3$ in 2003. Weekly average PM_{10} levels were 31 $\mu g/m^3$ in 2000; 33 $\mu g/m^3$ in 2002; and 35 $\mu g/m^3$ in 2003.