STATISTICAL PROBLEMS AND STRATEGIES IN ENVIRONMENTAL EPIDEMIOLOGY

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1. Introduction and definitions

The purpose of this contribution is to outline a series of problems encountered mostly in work on air pollution health effects and to a lesser extent in studies on health effects of water pollution, and of noise, as well as in the field of chronic disease epidemiology. The presentation is in terms intended to help design statistically satisfactory studies of the association of environmental factors with the well being of human populations.

This report is in three parts, general problems in environmental epidemiology, prototypical problems, and statistical strategies. Emphasis is placed on problems and strategies, rather than on the critical evaluation of results. The critical evaluation of results in terms of well planned research is the essence of scientific analysis in the field, and not necessarily the introductory material which this article essentially treats.

"Environmental epidemiology" is a subdivision of epidemiology, deriving historically from chronic disease epidemiology. The derivation is traced in a previous paper [9]. The main fallout of significant contributions of chronic disease epidemiology to health appears to be in the identification and better management of environmental factors; it was this plus the experience with studying the components of chronic respiratory disease morbidity, including symptoms of cough, shortness of breath, and alterations in respiratory function, which led to the conviction that the association of environmental factors could be studied with such health parameters, even though the study of such parameters was not necessarily equivalent to the study of the epidemiology of disease. Accordingly environmental epidemiology does not depend only on the determination of the presence or absence of a disease, but may include the alteration of health associated with environmental exposures.

There are four essential requirements for the conduct of effective work in environmental epidemiology. These are: (1) a suitable set of statistical strategies; (2) the capacity to design, carry out, and report the necessary procedures for dependable research; (3) access to populations of sufficient size and appropriate characteristics for study; and (4) an adequate support base in resources and in personnel for carrying out the necessary work. This paper and this meeting are

primarily oriented to the problems of research capability and its dependence on statistical strategies.

It cannot be assumed that good study design is sufficient to assure good epidemiological studies because there are always factors of population accessibility and unestimated variables which influence results of work in the field.

Compared to experimental research on related problems, the epidemiologic studies of environmental effects tend to be expensive and hence there is a greater importance given to the planning and design of studies.

Most epidemiologic research deals with tests of association and almost never can a single epidemiologic study be interpreted with respect to causation. Thus, it is of great importance that precise language be used in order to make it clear that, for an identified problem, a statistical association is being sought and evaluated, and a necessary and sufficient cause is usually not approachable solely by a single epidemiologic study.

1.1. *Relation of epidemiological association to causation.* Causation is approached usually by convergence of many epidemiological studies or by convergence of evidence from experimental and epidemiological work. Convergence means here the tendency for different studies in different loci to support a similar association.

The steps which permit one to consider a verdict of causation when an epidemiologic association has been demonstrated have been reviewed by Sir A. B. Hill [15]. He describes the problem as follows. "Our observations reveal an association between two variables, perfectly clearcut 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?" He then lists nine yardsticks that are relevant. They are (with the author's interpretation) the following. (1) *Strength* of the association; primarily a statistical attribute. (2) *Consistency;* this is largely an epidemiologic attribute and related to the convergence mentioned above. (3) *Specificity;* a matter which is partly epidemiological and partly statistical in that if one has included all of the variables, an epidemiologic task, one could accept an inference of high specificity. (4) *Temporality;* how the possible exposure is related in time to the possible effect. This may be analyzed by statistical procedures and it may be the subject of epidemiologic strategies as well. (5) *Biological gradient;* this is predominantly an epidemiological observation couched in mathematical terms and may be analyzed for by statistical yardsticks, for example, the regression of blood lead on atmospheric lead or the increase in some effect with an increase in the number of cigarettes smoked. (6) *Plausibility;* particularly biological plausibility. This is neither an epidemiologic nor a statistical attribute but one based on knowledge of other data. (7) *Coherence;* the extent to which the proposed association fits with a large body of related information. (8) *Experiment;* its insight into causal mechanisms may be reflected in the convergence cited above. It is neither an epidemiological nor a statistical criterion. (9) *Analogy;* this yardstick does not require comment.

Hill makes the unqualified statement, "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."

2. Types of health effects and environmental exposures

Health effects. Environmental epidemiology deals with a broad array of disease and health states. Heading that array, of course, in terms of gravity, is mortality including case fatality rates; morbidity is estimated in a variety of ways, such as reported new cases of illness, aggravation of pre-existing illness, the occurrence of episodes of hospitalization or demands for medical service, the occurrence of accidents, the impairment of function or the production of symptoms.

Other less clearcut effects are also of importance, such as biochemical and physiological reactions which may not be easily understood in relation to long term implications [11], the occurrence of annoyance reactions [17], and the storage of potentially harmful material such as lead and pesticides in the human body [19], [12], [24].

Environmental exposures. Exposures to chemical or biological agents can occur to a given substance through inhalation or by oral ingestion or occasionally by absorption through the skin. Toxicity of the substance may vary considerably depending on the exposure mode. The location of exposures and the manner in which the given pollutant is introduced are also quite varied. In the case of radiation, exposures occur as a result of natural background levels which vary to some extent. There is the important contribution of medical diagnostic and therapeutic radiation, and there are occupational exposures and the possible community exposures in association with nuclear power development. Similarly in the case of exposure to pesticides, there is the incidental exposure of a few people who live adjacent to areas being sprayed, there is the residue in food, and occasionally a food chain gradient; there is the possibility of absorption through handling and occupational exposures of workers. Thus, the types of environmental exposures are quite varied, and they have a tendency to interact.

3. General logic and strategy for environmental epidemiology

In a review of the statistical aspects of air pollution medical research, Massey, Hopkins and Goldsmith reported [4] that the problems generally fell into three classes. There were (a) the problems of multiple factors influencing the single reaction and the corollary of multiple reaction from a single exposure *multivariate problems;* (b) the problems of complex interrelationships in time and space *time-space series;* and (c) problems which were best described as *systems problems*

because they were so complex that existing single methods did not seem appropriate for them.

Beyond these, there is a further set of problems which have been recognized more recently. In the first place, there is the problem of *nonspecificity;* most environmental exposures do not produce reactions that are only produced by such exposures, but may change the probability of occurrence of other diseases (coronary heart disease) or reactions (increased air way resistance). In general, it is best to assume that an environmental exposure will only *unusually* be related to a single clearly defined clinical entity or alteration in health status. It is prudent to assume that environmental exposures may alter health status in nonspecific ways.

Secondly, there is the problem of the interaction of agents within biological systems and within the environment. For example, factors which impair oxygen transport function may include oxides of nitrogen, carbon monoxide, and altitude. The presence or absence of respiratory infection can affect the oxygen transport function. The interaction of cigarette smoking with exposure to radiation in uranium miners, produces a massive potentiation as judged by the joint association of these exposure with lung cancer.

Factors which interact in the environment include the complex, and not entirely understood photochemical reactions, the association of atmospheric radioisotopes to whatever the particulate matter may be in the atmosphere, and the importance of particulate matter in carrying sulfur oxides into the lungs in relationship to the long term respiratory disease reactions from sulfur oxide and particulate pollution. However, there are many other interactions in the environment, and they include actions which either remove pollutants, neutralize pollutants, or produce more harmful effects of pollutants.

There are a number of biologic processes which affect the strategy of environmental epidemiology. They include, for example, the processes of adaptation. With the first exposure of mice to a given level of ozone there may be very substantial toxicity, but if, at a lower level, there is pre-exposure then the toxicity to the given subsequent level is reduced by some mechanism as yet unknown. Whether this occurs in humans is not known [33]. The adaptation to heat by physiologic mechanisms is well known and well studied. Alterations in respiratory patterns as a result of inhaled irritants are well known. Changes in the rate and nature of red cell production as a result of exposure to altitude, to carbon monoxide, or to hemorrhage are also well known. Unfamiliar or sudden noises can produce vascular reactions but familiar or continuous noises do not. Many such reactions occur and there is always the question whether a reaction which is wholly adaptive is deleterious in some way. In general, experienced workers in this field assume that there is always a health cost to be paid for adaptation, but this may require years of follow up to demonstrate. Sensitization also can occur, for example, to inhaled allergens or to plants such as poison ivy or poison oak.

Another phenomenon in environmental epidemiology, is the phenomenon of

avoidance. If living in a certain place produces uncomfortable symptoms people may leave; therefore, if one studies that population on a cross sectional basis alone, one may not find the unusually susceptible individual. Nevertheless, it is the unusually susceptible individuals, provided they can be defined in terms of age and medical status, which are of the greatest relevance, for example, to air quality standards. One must therefore take into account the potentiality for avoidance. This is of particular importance in occupational exposure to irritating materials or to materials which will produce allergic reactions (Ferris) [7].

In prospective study of mortality, there are competing risks; persons who are exposed to a dose which may in fact be carcinogenic, may not have the expression of cancer because the duration of time necessary for its manifestation is insufficient, and they die of other causes. For example, studies indicate that the exposure to cigarette smoking for 20 years is necessary to produce lung cancer [30]. Nevertheless, 20 years of observation is not always possible in a realistic population, and therefore one must not presume that the phenomena could not occur if a young population were exposed and studied for a sufficient period or if the rate of mortality were lower due to other causes which are "competing."

4. Prototypical problems

For purposes of brevity, the classes of prototypical problems are presented in schematic form in a series of tables. The tables include the identification of the particular health variable, and the environmental variables. In these entries, stress is placed on what has been published and not necessarily on what is conclusive, or what ought to be investigated. A crucial column deals with other variables, variables which are not thought to be directly relevant to environmental epidemiology but the control of which is essential for any reasonable interpretation of an association. Columns are also provided to reflect a judgment on the availability of data and a code is inserted as a crude estimate. The code ranges from 0 to 4 according to the relative availability of data.

0—Implies that a method needs to be developed and validated for obtaining the data.

1—Implies that data are accessible by available methods but are not compiled, organized, or collected.

2—Implies that data exist but will require considerable screening, review or reorganization before they are applicable to an epidemiologic study.

3—Implies that the data are in proper form for many purposes but need to be selected and extracted.

4—Implies that the data are well organized and are regularly published and widely available.

The references are not exhaustive and represent only a superficial selection. The question marks indicate a possible or doubtful relation.

Special comment is necessary for several problems. First, hospital morbidity, as well as requests for medical attention, represent a type of morbidity data

which can be strongly biased by medical care practices which in turn may reflect economic factors which in turn may be interrelated with environmental factors.

Of importance is the fact that for study of some of the prototypical problems an extraordinary large volume of data is necessary. This is particularly the case for the analysis of mortality by day for which a population base of several millions is desirable and for the longitudinal study through survey methods of chronic respiratory disease morbidity, which may require a base population as great as a hundred thousand.

The references for each table appear at the end of the paper.

TABLE I

EFFECTS ON MORTALITY

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
A. On mortality by type and area	deaths per year for cancer, infant mortality, heart disease, respiratory disease, leukemia—various locations	air pollutants, dust fall, SO_2, ozone per station —average per month radiation, mr per year (in food, water, soil, and air)	meteorological conditions demographic conditions diagnostic facilities socioeconomic factors cigarette smoking occupation	4	1	Winkelstein Sternglass ABCC (Bizzozero) Graham Reid Stewart McMahon Court-Brown and Doll Lillienfeld Setlser and Sartwell
B. On mortality by type, by trend	deaths per year for cancer, infant mortality, leukemia, chronic respiratory disease, for a series of years	same as A.	same as A.	4	1	Sternglass Deane Gilliam Hesse
C. On mortality by day	deaths per day in large metropolitan centers with age break or cause break	air pollutants, SO_2, particulate matter, NO_x, CO weather variables	"heat and cold spells" natural and technological disasters time of year	2	2	Bradley Greenburg Watanabe Hexter and Goldsmith Hechter and Goldsmith Cassell
D. On Case-fatality rate	deaths as proportion of ill persons (coronary disease)	pollutants (CO) indoors and outdoors weather smoking of cigarettes	day of week facilities and staff	1	2	Cohen, Deane and Goldsmith

TABLE II

MORBIDITY

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
A. Hospital morbidity	hospitalized illnesses per time period by broad cause	air pollution—SO_2, particulate, CO, oxidant	time of year temperature availability of beds, insurance survival of acute episode	3	2	Breslow State of California Sterling
B. Sickness absence	sickness absence rate per period per school or plant	suspended particulates sulfur oxides and black suspended matter	fog weather holidays socioeconomic factors time of year	3	3	Dohan Reid Ipsen *et al.* Anderson Paccagnella Gocke
C. Demand for medical care	request for medical service per day per type of chief complaint (asthma clinic visits)	oxidant, CO, SO_2, suspended particulates temperature	day of week time of year availability of alternative care socioeconomic factors	3	3	State of California Greenburg Weill *et al.*
D. Respiratory disease morbidity (cross sectional)	survey data on respiratory disease prevalence	black suspended matter, SO_2, oxidant	cigarette smoking socioeconomic factors occupation ?housing	1	3	Boudik *et al.* Wahdan Reid Holland Deane *et al.* Petrilli *et al.* Schoettlin Ferris Anderson Goldsmith McKerrow
E. Respiratory disease morbidity (prospective)	prospective incidence of respiratory disease in children or adults	air pollution indices by location (fuel consumption, and so forth)	socioeconomic factors occupation smoking of cigarettes crowding nutrition	1	1	Douglas and Waller Buell, Dunn and Breslow Lunn McCarroll

TABLE II, (continued)

MORBIDITY

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
F. Disease aggravation	Aggravation of preexisting illness (asthma, bronchitis) by symptom by pulmonary function	oxidant, black suspended matter, SO_2, Nitrogen Oxides, CO	weather pollens time of year cigarette smoking	2	2	Lawther Schoettlin and Landau Schoettlin Remmers and Balchum Ury *et al.* Rokaw and Massey Shephard and Fair Carnow

TABLE III

IMPAIRMENT OF PERFORMANCE

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
A. Diminution of pulmonary function in presumably normal subjects	$FEV_{1.0}$ airway resistance maximal expiratory flow diffusion capacity	suspended particulates SO_2 (Sulfation) oxidant	temperature and humidity time of day ?respiratory infection	1	3	Wright *et al.* Discher Toyama Lawther and Waller
B. Occurrence of motor vehicle accidents per hour per day of week	number of accidents	oxidant carbon monoxide nitrogen oxides	traffic density weather conditions of road and auto ?cigarette smoking ?drugs holidays alcohol	3	2	Ury Goldsmith, Perkins and Ury Clayton
C. Impairment of athletic performance by day	proportion of secondary school athletes whose performance improves	oxidant carbon monoxide	weather ?cigarette smoking ?motivation	2	2	Wayne and Wehrle McMillan

TABLE IV

PHYSIOLOGICAL AND BIOCHEMICAL EFFECTS INCLUDING STORAGE
(See also Table III,A, Diminution of Pulmonary Function)

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
A. Growth and development (height, weight, skeletal age)	height by age, or increase in height per year by sex, by parents' height	sulfur oxide and suspended particulate ?sunshine ?oxidant ?CO ?water constituents	nutrition socioeconomic factors heredity	3	2	Kapalin and Novotna
B. Red cell indices	hemoglobin, hematocrit, RBC, WBC with differential methemoglobin (infants or ? adults)	suspended particulate SO_2 radiation nitrate in water or NO_2 in air	nutrition pregnancy parasitism ?hereditary hemoglobinopathy age of infant and formulae	2	2	Kapalin Petr and Schmidt Goldsmith, Shearer and Kearns
C. Biochemical indices	cholinesterase activity, ALA and heme metabolism indices	pesticide (Parathion, etc.) lead levels in paint, food, air, water	age nutrition hereditary factors	2	1	Selander and Cramer Nikkanen *et al.* California State Department of Public Health
D. Storage of potentially harmful pollutants	blood lead Carboxy-hemoglobin Radio-isotope burden	atmospheric lead levels atmospheric CO levels radio-isotope levels, air, water, food	lead in food and water cigarette smoking occupational exposures	1	2	Goldsmith and Landau Goldsmith and Hexter Tipton and Schroeder Goldsmith, Ury and Perkins Morgan Curphey *et al.* Butt *et al.*

TABLE V

TERATOGENIC, MUTAGENIC, AND AGING EFFECTS

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
A. Fertility and sex ratio of newborn	relative number of successful pregnancies by sex	radiation exposures to gonads of parent or during gestation	age of parents nutrition ?occupation smoking complications of pregnancy	3	1	Jablon and Kato Meyer and Diamond
B. Birth defects physical and biochemical	birth defects	drugs (thalidomide) viruses (Rubella) ?parental radiation	time of year ?smoking	0–1	1	Macht and Lawrence
C. Leukemia (see also Table I,A)	leukemia onset by age, by cell type	radiation exposure (diagnostic, therapeutic, occupational) infectious agents	socioeconomic status other diseases competing risks	3	1	Graham *et al.* Stewart *et al.* McMahon Court-Brown and Doll
D. Spontaneous abortion	proportion of conceptions resulting in spontaneous abortion proportion of genetic defects in abortuses types of chromosome aberrations	drug use in parents radiation exposure heavy metal exposure infectious agents	nutrition age of parents other health factors ?socioeconomic factors	0	0–1	Bateman
E. Aging	age specific mortality	pollutants, CO, SO_2 and black suspended matter ozone and oxidants radiation	medical care nutrition infectious disease exercise cigarette smoking	4	0–1	Strehler and Mildvan Jones

TABLE VI

ANNOYANCE AND NONSPECIFIC HEALTH IMPAIRMENT

Effects	Health data	Environmental data	Other variables	Availability of data H	Availability of data E	References
A. Odor or noise annoyance	annoyance and response awareness of odor ?somatic reactions disturbed rest or enjoyment	olfactometry measured odorants or noise level	age, sex socioeconomic factors attitude or relationship to source air conditioning health status acoustic privacy	Odor 2 Noise 1	0–1 1	Jonsson Deane Goldsmith Lindvall
B. Residential instability	history of change of residence community dissatisfaction	oxidant odor visibility impairment noise level	socioeconomic status recency and basis for moving to area affected employment opportunities recreational opportunities	0–1	3	Hausknecht

5. Statistical strategies

Many of these prototypical problems have been tackled by a variety of strategies. This section outlines some of these strategies. In each case an example is cited and, if the results have been published the reference is given.

5.1. *Two-community strategy for maximizing one out of a set of environmental variables. The problem.* In Los Angeles there is an elevation of the photochemical oxidant level that is particularly marked during unusually hot weather. Thus in looking for the possible effects of oxidant on mortality the interaction of high temperatures is inevitable. In an attempt to maximize the contribution of oxidant while controlling for or stabilizing the effect of temperature we have developed the following plan.

Available data. The data available are for deaths by day by census tracts for Los Angeles County along with measured values of maximal temperature and measured values of photochemical oxidant and carbon monoxide. The number of monitoring stations is much smaller than the number of census tracts.

Strategic plan. The plan was to select artificial communities which had a common pattern of maximum temperatures for the month of September, but which had contrasting levels of photochemical smog and to carry out a difference analysis in order to maximize the difference between oxidant as an independent variable which might explain the difference in mortality for these two artificial

communities. The work has been reported by Massey, Landau and Deane but has not been published.

Analytical process and results. The first problem in analysis was to allocate census tracts to monitoring stations. This was done by nearness, assuming the absence of physiographic barriers. The second problem was to obtain some idea of the homogeneity of the two communities which were being compared, that is whether they had similar demographic characteristics, for example; unfortunately they did not. Nevertheless, the analysis, when carried out, failed to show that the difference in oxidant was associated with a difference in mortality by day.

5.2. *Poisson strategy for testing for nonhomogeneity of the distributions of dependent variables with extreme value distribution of independent ones. The problem.* The problem dealt with whether or not extreme values of temperature and pollutants might contribute, and if so how much to the mortality of persons in nursing homes in Los Angeles County. For many years data was collected from nursing homes as a monitoring technique.

Available data. Data available were deaths per day from all nursing homes in Los Angeles County with 25 or more beds, maximum oxidant values, maximum daily temperature and values for other pollutants as needed from the available monitoring stations.

The strategic plan. This consisted of selecting days which had extreme conditions; for example, the days which had both temperature values in the upper 10th percentile and the oxidant values in the upper 10th percentile and to them adding the population of days which had extremely low values for both temperature and oxidant. The plan was then to test whether the daily mortality from the combined distribution for the extreme positions of environmental factors could be or could not be described by a simple Poisson distribution. If it is assumed that the number of deaths of people in nursing homes per day is a Poisson variable, the work of Tucker [29] made it possible to test whether for a given population of days the assumptions of Poissonnous were valid for a simple Poisson or whether there was more then one λ value. If this were so it would indicate a mixture of such distributions.

Analytic process and results. The analysis carried out failed to detect any effect of seasonality on nursing home mortality, an effect which could have been observed in general daily mortality as the work of Hechter and Goldsmith [13] has shown. It also failed to show any effect of extreme conditions on the distribution of daily mortality. Possibly this is due to the precarious state of health of these elderly people and the very high variance in daily mortality which reflects this.

5.3. *Fourier strategy for minimizing time of year effects in multiple regression analysis of mortality. The problem.* Mortality by day is a statistic which varies seasonally. Also environmental temperatures and pollutant values vary seasonally. We face a dilemma trying to see whether there is an association between pollutant values and daily mortality in that if the period of the approximately

sinusoidal fluctuations is similar there will be a significant association using a sufficient set of data, regardless of whether there is any dependence of mortality on pollutants. For example Hechter and Goldsmith have shown that carbon monoxide levels are unusually high in the winter and mortality is unusually high in the winter. Both these are out of phase with maximal temperatures and maximal oxidant values (see Figure 1, [14]). So regardless of any biologic or physical processes, these data would produce a positive association between mortality and carbon monoxide and a negative association between mortality and oxidants.

Strategic plan. The plan was to add a sufficient number of Fourier terms according to the scheme of Bliss [2] to account for the seasonal variability of the underlying associations and then after adjusting for long term trend, test to see whether there were significant associations between pollutants and mortality among the residuals. The initial application [13] used simple cross correlation analysis with lagging and a weak association was observed, the statistical significance of which was not formally tested.

Analytic process and results. Hexter and Goldsmith [14] have applied a more complete Fourier strategy to a more recent set of daily mortality data for Los Angeles and have shown that there is a small contribution of carbon monoxide variation to the variation in total daily mortality, when trend, seasonal fluctuations and the effect of temperature are controlled for.

5.4. *Death clearance strategy for longitudinal study of cohorts. The problem.* The relationship of pollution to chronic disease problems has been a prominent political and public health problem but experience indicates that a longitudinal study is often necessary for a valid assessment of the effect of environmental factors. It was desired to study a cohort over a period of time but funds were not available for the repeated examination of a sufficiently large sample. Accordingly Buell, Dunn and Breslow [3] have developed the following approach.

Available data. Smoking, occupation, and residence history from a population of military veterans in California and from their spouses, a total of nearly two hundred thousand people, was obtained in 1957 and information is subsequently obtained as to when and from what cause they die, based on registration of deaths.

Strategic plan. To collect data on smoking, occupation and residence of a group of people in 1957 and then by checking the rosters of such individuals with those persons who die from lung cancer and from chronic pulmonary disease to find out whether these exposure variables are associated with the occurrence of these conditions.

Analytic process and results. These data have been analyzed in several reports and results indicate that there is no evidence of increased incidence of lung cancer occurring among persons in Los Angeles County, when compared to residents in other parts of California.

5.5. *Temporo-spatial strategy for reducing effects of location and time when environmental factors vary over both. The problem.* A large number of the studies

referred to in Section 4 on Prototypical Problems are comparisons of morbidity or mortality between different locations with different environmental conditions or between different periods of time *in the same location*, when environmental conditions change. The weakness of spatial comparisons are that populations are often self-selected for living in a certain location and therefore two different locations almost invariably, have populations which differ in attributes which usually are important to the health reaction. The temporal comparison strategy has the weakness that a large number of factors may change over time including meteorological, cultural, and other environmental variables, and there may be changes in structure of the population as well so that these comparisons may be inappropriate because of inadequate control of these other variables.

The combined testing of the more complex hypothesis of the health reaction being more frequent or stronger *in the relatively more polluted place at the relatively more polluted time* seems intuitively to be a great deal more powerful. Therefore, following the example given by Toyama [28], and the two community strategy by implication, we prefer to cast each problem that is at all suitable into a combined temporo-spatial hypothesis testing framework rather than into a simple spatial or temporal hypothesis testing framework.

Data available. The data available for the example which we will cite were data on the myocardial infarction case fatality rate at hospitals in two parts of Los Angeles County, one of which was thought to have more pollution from carbon monoxide than the other on the basis of aerometric and monitoring data [6].

Strategic plan. The correlation of carbon monoxide values with case fatality rate within a given day of week for the total area was undertaken but has been treated as of lesser importance than the application of the temporo-spatial strategy. In this strategy, the question is asked whether the portion of the basin which has higher carbon monoxide compared to the other portion has a higher case fatality rate, during weeks of the year when carbon monoxide levels are high.

Analytical process and results. With the advice and suggestions of Hans Ury, the data were compared by a sign test in which four quartiles of weeks of the year were determined on the basis of a ranking of the average carbon monoxide value. We then scored a plus for each week when the higher area had a higher case fatality rate and a minus when the higher polluted area had a lower case fatality rate.

The sign tests showed that in the high quartile of the year there were twelve out of thirteen weeks in which the case fatality rate was higher in the more polluted area. On the other hand, during the other three quartiles, there were no differences between areas in the case fatality rate. We therefore feel that while a number of the variables were not controlled, for example the relatively polluted area is in the interior of the basin as opposed to the lesser polluted coastal area, and therefore the population may differ between these two areas, it seems unlikely that population variables would have their greatest effect during periods of high air pollution. However, these and other variables, for example cigarette

smoking, should certainly be studied. We have drawn no causal conclusion from this study.

5.6. *Concordance sign strategy with classification for singling out contribution of dependent variables in a complex time series. The problem.* We wish to study whether or not there was an association between motor vehicular pollution and motor vehicle accidents. It is obvious that such pollution concentrations in Los Angeles are, in any event, highly dependent on motor vehicle traffic intensity in that the more the traffic the greater the emissions of primary pollutants. Further, the more the traffic the greater the population at risk of motor vehicle accidents. Thus an association of motor vehicle accident frequencies with pollution is greatly affected by the "hidden variable" of motor vehicle traffic. The fluctuation in traffic density is complex and difficult to describe by a simple mathematical relationship. We therefore look for a strategy for determining whether there was an excess of motor vehicle accidents during periods when the pollution concentration was higher.

Available data. Data were available for pollution measurements at the monitoring stations in Los Angeles and for the frequency of occurrence of motor vehicle accidents from the Los Angeles City Police Department. Other data such as whether visibility was normal, whether there was drug involvement or whether there was spillage of material on the roadway were also recorded.

Strategic plan. The plan was to compare adjacent weeks by hour of the day within day of week, with the assumption that for the same day-hour combination, traffic density at intervals of one week, would show only random differences. This plan would yield a large number of pairs of data sets for which both pollution concentrations could be defined and the number of accidents defined. We will test whether the differences between weeks go in the same direction (are concordant), tie, or go in opposite directions (are discordant). In the case of the pollutant carbon monoxide, the useful data extend over nearly all of the 24 hours. In the case of the pollutant oxidant, only the hours of daylight are used since the oxidant concentration drops to a very low value at night. Corrections are necessary for daylight saving time and a decision is needed as to whether the maximum value observed in the basin or the basin average value for a pollutant ought to be used. Ideally, one should use the pollution concentration nearest the place of occurrence of the accidents but the scarcity of the data and the small number of the monitoring stations makes such an analysis unattractive.

Analytic process and results. Ury [34], and Ury, Goldsmith and Perkins [35] have reported that, summing the sign test applied to the concordance or discordance of variation between pollutant and accidents in sets of pairs, there is a statistically significant association of photochemical oxidant and accidents. So far the results do not provide evidence of an association with carbon monoxide.

5.7. *Nonparametric correlation and trend strategy in the dual matrix trace metal problem. The problem.* The problems associated with the body burden of trace metals is one which presents some unusual problems we have worked with but on which we have not yet published. The analysis is based on a set of data made

available through the courtesy of Dr. Edward Butt, formerly Director of Laboratories of the Los Angeles County hospital, on the levels of 14 metals in nine organs of 154 persons who had died at the hospital. The determination was made by emission spectroscopy. The analysis of the biologically important trace metals is usually carried out by dividing these metals into those which are called "essential" and those which are called "nonessential" and such an approach has been used, for example by Tipton and Schroeder [22], [27].

The distribution of any given metal concentration in any given organ is, in general, but not invariably, skewed. A log transformation would have been one possibility for analyzing the organ-metal combinations using normal distributional tests for associations. However we preferred a nonparametric approach through which we obtained medians and 95 per cent confidence intervals followed by a rank correlation analysis in which the concentration of metals in each organ was ranked for the 154 subjects.

Available data. The data consist of, except for the occasional missing item, the concentration of 14 elements in each of nine organs for 154 persons. The data are represented in units of milligrams per 100 grams of dry tissue for soft tissue organs and micrograms per gram of ash for rib and calvarium.

Strategic plan. The plan was to see how many inter organ correlations by metal could be explained by a small number of clusters. Rank correlation analysis yielded correlation coefficients for each pair of metals within an organ and for each pair of organs with respect to the same element. This therefore gave us two sets of correlation matrices, the interaction of the metal ranks within each of the organs and the interaction of organ ranking for each metal. From the analysis we selected those correlations which were statistically significantly different from zero by conventional yardsticks and then have described the clusters of correlations which occur both in the metal by metal matrix for organs and the organ by organ matrix for metals. The nonparametric trend test is then applied to see whether cancer patients or cigarette smokers have an unusual set of patterns.

Analytic process and results. Work has not been completed on this problem. It is premature to give results. We were also able to carry out a nonparametric trend test for deaths due to cancer, deaths due to heart disease and to study the association of smoking with metal-organ distributions. There are, only four correlation clusters for organs and similarly there are apparently three for metals. We are able to define at least four general mechanisms by which the correlations might occur: (1) those due to measurement methods; (2) those due to common population attributes; (3) the differences in exposure of subgroups of the population to several elements (which can be studied by trend tests); and (4) common biological mechanisms of distribution of an element between organs.

5.8. *Day of week replication for reducing autocorrelation. The problem.* In the study of daily mortality, one must start with the assumption that successive environmental measurements or successive mortality frequencies for adjacent

days are not independent estimates of a random variate but are dependent to the extent that autocorrelation exists. Hechter and Goldsmith [13] have shown that there is significant autocorrelation and so the problem becomes one of treating this in carrying out a systematic analysis.

Available data. The data available are pollution measurements and mortality by age and cause, by each day in a period of over a year.

Strategic plan. The plan was to carry out calculations of correlations of pollutant measurements, including lags, trend, and Fourier terms with the daily mortality separately for the phenomena attributable to each day of week. This would include lagged pollution and weather measurements for the preceding days as well as for the day of mortality. By carrying out such calculations, one obtains presumably an independent set of seven replicates. However, the independence is also qualified in these replicates of interpenetrating data sets as it was in the original autocorrelation problem but the values for the individual correlations do not reflect significant autocorrelation. This strategic plan depends on the use of some correction for seasonal variation and the Fourier strategy mentioned above was used for that purpose.

Analytical process and results. Hexter and Goldsmith (unpublished results) have carried out the calculations and find consistency between the significance tests for each day in the mean square error explained by regression, and the importance of individual variables. By using replicates on a seven day basis or on a 28 day basis it is possible to obtain presumptively (but not truly) independent estimates of regression coefficients and to apply a t type of test to determine the consistency of these values. This was used in the early phase of the study reported by Hexter and Goldsmith [14].

5.9. *Combined variable strategy for relating monitoring data to possible morbidity and mortality. The problem.* A measuring system for the intensity of pollution which is dependent on a single compound or element or on the results of a single instrument may not reflect the burden of a pollution exposure which occurs. The same phenomena would exist in the case of a radiation estimate which did not include both beta and gamma radiation from a nuclear source. One therefore wishes to combine the impact of several pollutants in some way or other by weighting them with respect to their possible contribution to morbidity.

Available data. The data are, in general, restricted to the measurements made of pollutant concentration and include, of course, the meteorologic variables as well as pollutant data.

Strategic plan. The strategic plan outlined by Ipsen [16] consists of first removing trend and seasonal effects and then summing the levels of smoke shade, sulfate and particulate matter. Then they use the sum of these variables to study the association with respiratory infection prevalence. The sum is significantly positively correlated, while no single pollutant estimator is. A similar approach was suggested by the results of Spicer [23] who studied the effects of total variability in weather and pollution on lung function among a population in Baltimore.

Analytic process and result. The analysis by Ipsen and Spicer does show that the total contribution of pollutants and meteorological factors is significantly associated with lung function and with prevalence of respiratory infection. Individual pollutants do not show such a consistent result.

5.10. *Convergence of epidemiological and toxicological data and its relevance to policy decisions. The problem.* Epidemiological studies, even well planned ones, often suggest but do not prove causation. Because of the long lead time necessary for determining such effects as genetic and chronic disease associations, studies can hardly be justified if they lead to delaying the adoption of policies to minimize the risk. Yet if it happens that experimental and epidemiological data converge on even an approximate dose response relationship, policies to avoid a given "response" are scientifically supportable. We choose, as examples, effects of airborne lead on storage of lead in the body and on the enzyme delta-amino levulinic acid dehydratase, and effects of carbon monoxide exposures on coronary heart disease.

Available data. "Three city" [33] "seven city" [25] and "freeway" [26] lead studies present data on blood lead in relationship to atmospheric exposure. Kehoe [18] has presented experiments with four subjects exposed an increasing number of hours per week to defined concentrations of lead in air. With increased blood lead biochemical effects on heme metabolism occur.

We have presented data on case fatality rate in myocardial infarction and on daily mortality in association with carbon monoxide exposures [6]. Ayres [1] has reported experimental and theoretical work on the impairment of oxygen extraction by the myocardium following human exposures to carbon monoxide. This is especially marked for persons with coronary artery disease. Forster [8], Coburn [5], and Permutt [21] have confirmed and expanded on the relatively greater effect of CO on organs and tissues with a high oxygen extraction ratio.

Strategic plan. To compare dose response relationships between experimental and epidemiological studies, to see if the two sets of data appear to converge on a similar relationship. If so, the relationship can be depended upon as one basis for policy decisions.

Analytic process and results. Goldsmith and Hexter [10] have presented the logarithmic regression for blood lead on estimated atmospheric exposure for a number of community studies and have plotted the experimental data of Kehoe on the same graph. A good agreement appears to be present. This relationship has been used by the California State Department of Health and the Air Resources Board of California as one basis for air quality standards.

The National Academy of Science-National Research Council Committee on Effects of Atmospheric Contaminants on Human Health and Welfare includes as one of eight tentative conclusions "a possible effect of increased ambient levels of carbon monoxide in coronary vascular disease" [20]. The Federal Air Quality Criteria for Carbon Monoxide [31] treat both epidemiological and toxicological results separately. However these citations [6], [1] are among the few cited in the Conclusions and Resume section of the report. We may thus conclude that the

convergence was influential in the Federal policy decisions on air quality standards for carbon monoxide. It is doubtful if either toxicological or epidemiological results alone would have been of comparable importance for these policy considerations. By contrast, Federal Air Quality Criteria for oxides of Nitrogen [32] are based primarily on epidemiological studies. They are currently being contested by representatives of the motor vehicle industry.

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Table V: Teratogenic, mutagenic aging effects

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[119] M. MEYER and E. DIAMOND, "Investigation of the effect of prenatal X-ray exposure of human oogonia and ooctyes as measured by later reproductive performance," *Amer. J Epidem.*, Vol. 89 (1969), pp. 619–635.

B. *Birth defects; physical and biochemical*

[120] S. H. MACHT and P. S. LAWRENCE, "National survey of congenital malformations resulting from exposure to roentgen radiation," *Amer. J. Roentgen*, Vol. 73 (1955), p. 442.

C. *Leukemia*

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[124] W. M. COURT-BROWN and R. DOLL, *Op. cit.* [45].

D. *Spontaneous abortion*

[125] A. U. BATEMAN, "The use of spontaneous abortion in man for monitoring the mutation rate," Department of Cell Biology, New York University School of Medicine, multilith.

E. *Aging*

[126] B. L. STREHLER and A. S. MILDVAN, "General theory of mortality and ageing," *Science*, Vol. 132 (1960), pp. 14–21.

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Table VI: Annoyance and nonspecific health impairment

A. *Odor or noise annoyance*

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B. *Residential instability*

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Discussion

Question: T. Sterling, Department of Applied Mathematics and Computer Science, Washington University

With respect to the statement that sometimes we formulate public policy in order to avoid harm even though the data are poor, let me point out that such a policy entails a serious loss that largely is overlooked. Presuming to know what causes a disease, we stop (or slow down) further research. The classical case is smoking. Much of the acceptance of cigarette smoking as a cause of lung cancer has been based on this type of thinking, namely, "what does it harm if we discourage smoking?" But, as a consequence, the progression of work investigating the effects of particular pollutants, namely, soot, dusts, and so forth, on lung cancer has been seriously hurt.

We have learned that pollutants that occur in trivial quantities in the environment may, nevertheless, be concentrated in the food chain. John, how does this problem fit into your thinking on strategies?

Reply: J. R. Goldsmith

When epidemiological data are used to formulate and support the need to enforce a health policy, there are many considerations other than scientific ones in the strict sense. They include not only the convergence of the data from epidemiological studies and experimental ones, but the 'cost' of the existing pattern which a policy is to modify as well as some evaluation of the health harm which we seek to prevent. To use an example familiar to me, the Lindane vaporizer was widely used on the basis of certification by the Department of Agriculture as to its effectiveness as a household insect control system. With no or trivial effort, our department heard of some eight cases of blood dyscrasia in California associated with the use of the vaporizer in the home. We published them along with our views that since there were other ways to control insects, the certification should be removed since some of the cases were fatal and all were serious. After some delay, they have been taken off the market. On the other hand, it is reasonable to expect that a number of studies controlling many of the relevant (or possibly relevant) variables should be undertaken before we

ask to have major eating and smoking habits drastically affected by health policy decisions based on epidemiological research. I disagree with T. Sterling as to the comparative importance of data on particulate air pollutants and on cigarette smoking as regards their association with lung cancer (assuming I understand his question). The data on smoking and lung cancer is sufficient to convince me that there is a causal relationship. The data on particulate air pollution is much less impressive, and largely consists in the unequivocal and consistent demonstration that there is an urban factor in lung cancer, but the evidence that air pollution is that urban factor is not consistent, and my position is that the association of particulate air pollution and lung cancer is not causal because, among other reasons, it is not consistent. For example, there are no such associations in the British study of Buck and Brown (Tobacco Research Institute Report), nor in the study of W. Winkelstein, both of which did have other positive associations of a more convincing nature.

Decisions about health policy do have a massive impact on feasibility of further research, and this too should enter into the decision as to whether a policy is apt.

I have not included data on food chain effects on human health, since except for some radioactive compounds, there is little data of interest. The data on lead which were cited are associated with some food chain problems on which we are now working.

Question: R. J. Hickey, Institute for Environmental Studies, University of Pennsylvania, Philadelphia

(1) If I understood you correctly, regarding your reference to a report of Bradford Hill and the various statistical relationships mentioned (temporal, and so forth), and the association of environmental pollutant characteristics and health variables, you seemed to imply that if a number of related statistical relationships appear consistent, this increases confidence that a causal relationship exists. Was this implied?

(2) Since certain elements of public policy seem to have been determined on the basis of reported statistical associations, is this not an implicit acceptance of conclusion of causality from correlation? Further, is it not a commonplace of statistics that statistics can be used properly to reject a hypothesis, but never to establish that the hypothesis is true?

I find the nonrigorous use of statistics in determination of important matters of public policy quite disturbing. Perhaps in public policy matters it should be pointed out to the public and to legislators that statistics did not reject the hypothesis in question (if that is the case), and that public policy is, therefore, being determined on the basis of a hypothesis and not on the basis of a proven causality relationship.

Reply: J. Goldsmith

(1) Yes, this increases confidence, but it does not lead to a categorical conclusion. If the same relationship is found in different populations, using different

methods, this increases confidence more than a variety of statistical relationships. You should read Hill to obtain a more authoritative answer.

(2) Causality is a logical problem and public policy is a value problem. We often adopt policies in the face of uncertainty. We should participate in and encourage this, even though it precludes at times the opportunity for a definitive causal conclusion. This does *not* imply an acceptance of a causal relation on the basis of correlations. We agree on the use of statistics in hypothesis testing, and that the public and legislators should be informed as to the basis of recommended action.

Question: Alfred C. Hexter, California Department of Public Health

I agree with the previous discussants that these studies may establish association but the results do not show cause and effect.

Nevertheless, in many cases public policy depends upon such data. The health, or even the lives, of many people may depend upon decisions based upon such data. There may be many cases when we must *act* as though cause and effect is proven, because human safety requires that if we err, we err on the *conservative* side.

Reply: J. Goldsmith

I agree.