UCI - Planning Colloquium on Epidemiology and Air Pollution

Final Report
Contract No. A833-114

Prepared for:

Research Division
California Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, CA 95812

Submitted by:

University of California, Davis
Irvine, CA 92717

Prepared by:

James L. Whittenberger, M.D.
Professor Emeritus
University of California, Irvine
Chairperson

December 1990

UCI-PLANNING COLLOQUIUM ON EPIDEMIOLOGY AND AIR POLLUTION

Sponsored by:

The California Air Resources Board

December 12 - 13, 1989

Chairperson:
James L. Whittenberger, M.D.
Professor Emeritus
University of California, Irvine

Co-Chairpersons for Planning:
Carl Hayes, Ph.D.
U.S. Environmental Protection Agency

William McDonnell, M.D.
U.S. Environmental Protection Agency

Dane Westerdahl
California Air Resources Board

TABLE OF CONTENTS

OBJECTIVES OF THE PLANNING COLLOQUIUM

DECEMBER 12, 13, 1989 WORKSHOP

The objectives of the workshop are to assist the California Air Resources Board in: 1) evaluating past and current field studies of air pollution health effects; 2) evaluating research approaches that seem most promising for future studies; and 3) identifying principal investigators in California who are qualified and interested in undertaking such studies.

Planning of the workshop is based on information provided by the California Air Resources Board that a commitment has been made to plan and undertake the support of studies aimed at evaluation, in human populations, of potential health effects from long-term exposure to community air pollutants. The Board desires a critical evaluation of strengths and weaknesses of recent or ongoing field studies, with a view to identify the most promising approaches to be used in new studies. Research protocols have not been developed for future studies and are therefore not available for peer review. Neither has the Board identified specific investigators for these new field studies of air pollution health effects. To facilitate and expedite the addressing of these important tasks, the Board has suggested a workshop or conference to be held at the earliest feasible date.

UCI-PLANNING COLLOQUIUM ON EPIDEMIOLOGY AND AIR POLLUTION

Sponsored by the California Air Resources Board

Location: Irvine Marriott Hotel
18000 Von Karman Avenue
Irvine, California 92715
(714) 553-0100

Date: December 12-13, 1989

Chairperson: James L. Whittenberger, M.D.
University of California, Irvine

Co-Chairpersons for planning:
Carl Hayes, Ph.D.
U.S. Environmental Protection Agency
William McDonnell, M.D.
U.S. Environmental Protection Agency
Dane Westerdahl
California Air Resources Board

AGENDA

Tuesday, December 12, 1989

Session 1 **Objectives and Background**
Chairperson: James L. Whittenberger

8:30	Objectives of the Conference:	*James Whittenberger* *Dane Westerdahl*
8:40	Current status of air pollution in California:	*Michael Kleinman*
9:00	Review Community Health and Environmental Surveillance System (CHESS):	*James Whittenberger*
9:15	"Six City" and "24 City" studies:	*Frank Speizer*
9:50	Chronic Obstructive Respiratory Disease (CORD):	Anne Coulson
10:15	CORD "follow-up study"	*Henry Gong*
10:30	**BREAK**	
10:45	Ahsmog I and II studies:	*David Abbey*
11:05	An on-going autopsy study:	*Russell Sherwin*
11:25	International and other U.S. studies:	*Morton Lippmann*
12:00	**LUNCHEON**	

Session 2 **Chairperson: Dungworth**
1:15 State of the Science - Toxicity and Mechanisms Studies

1:15	1)	Physiologic and biochemical aspects:	*Daniel Costa*
1:35	2)	Pathology perspectives:	*Donald Dungworth*
1:55	3)	Sensitive & susceptible population subgroups: gaps in understanding dose-response relationship:	*Steven Colome*
2:15		Implications of clinical investigations to design of field studies:	*William McDonnell*
2:45		**BREAK**	

Session 3 — Chairperson: Patricia Buffler
Co-Chairperson: Jonathan Samet

3:00 Concepts in design of human health effect studies of air pollutant exposures:

3:05 1) Populations to be studied (questions posed, numbers needed, outcome measures):

Panel: *William McDonnell*, *Jonathan Samet*, *Anne Coulson*

3:50 2) Design of study: (including type of study, control of biases and confounders, etc.)

Panel: *Patricia Buffler*, *Frank Speizer*, *Thomas Mack*, *Carl Shy*

4:35 3) Exposure characterization:

Panel: *Morton Lippmann*, *Steven Colome*

5:00 **ADJOURN**

Wednesday, December 13, 1989

8:30 4) Data acquisition, processing and analysis, including QA/QC:

Panel: *Hoda Anton-Culver*, *Charles Rossiter*, *Frank Speizer*

9:15 Discussion of Topics in Session 3

9:45 Summary of scientific sessions: *David Bates*

10:30 **BREAK**

Session 4 Chairperson: Dane Westerdahl
Co-Chairperson: James L. Whittenberger

10:45 Group discussions on assigned topics for planning future studies

A. Identification of leadership and participants in the needed research
Group Leader: *James Whittenberger*

B. Field test facility needs
Group Leader: *Jack Hackney*

C. Identification of knowledge gaps for pilot research efforts
Group Leader: *Dane Westerdahl*

12:00 LUNCHEON

1:00 Group discussions, continued

2:00 Planning session: group reports and discussion

3:00 Summary of Plans for Future Studies

3:30 ADJOURN

SUMMARY OF CONFERENCE

UCI-PLANNING COLLOQUIUM ON EPIDEMIOLOGY AND AIR POLLUTION

INTRODUCTION:

Dr. Whittenberger welcomed participants to this planning colloquium and thanked particularly Dr. Carl Hayes, Dr. Bill McDonnell and Mr. Dane Westerdahl for their major contributions to planning the colloquium. Dr. Whittenberger continued: We were very gratified by the level of interest expressed by the people that we invited to be on the agenda of this conference. It is clearly considered to be a very important topic by a great many people and we're looking forward to an excellent planning exercise.

OBJECTIVES AND BACKGROUND:

The objectives of the conference were stated in the letter which I sent to almost all of you. Those objectives are reflected in the agenda which first encompasses a review of some of the past and some of the on-going studies of health effects of air pollution; we then look at clinical investigations and animal toxicology as sources of ideas and information that's useful in epidemiologic studies. This is a two-way street; there should be a feeding of ideas in both directions. Then, some of the important concepts in the design of epidemiologic studies are reviewed and discussed. We're very grateful to Dr. Patricia Buffler and to Dr. Jonathan Samet for taking the lead in organizing that session of the planning colloquium. Finally, the fourth session will be an attempt to translate the content of this meeting into the first steps in an on-going program that ARB has committed itself to support over the next number of years.

Because we have a very tight schedule, I will turn over the podium at this point to Dane Westerdahl.

MR. WESTERDAHL:

First, I'd like to welcome you and thank you for attending the meeting.

What you see assembled here are experts in the fields it takes to design a well thought out epidemiologic study to look at the long term effects of air pollution. Jim has spent a great deal of his time over the last four months putting this group together. He's had help from Beverly Laskey, former colleague of his and a great deal of help from the rest of the UCI staff. Bill McDonnell and Carl Hayes have done a great deal in helping with the technical organization of the speeches and talks as well. I'd really like to thank Jim and the others for their help in this; without it, it wouldn't be possible.

The issue of concern for the next two days is, "How can we mount an investigation of the long term effects of ambient air pollution"? It's a huge problem; essentially, it involves millions of people that within 20-30 miles of here are exposed to air pollution for their whole lifetimes, or as long as they're in the South Coast air basin. We initiated a program at the Air Resources Board which is unique in that it has a long

term commitment to it. Most studies in the past have had a relatively short time focus, based on budgetary and practical questions of "well, we have two years worth; if we can spend this money, let's solve our problems in two years". In this case, we went through the budgetary process all the way to the governor to initiate a program with a minimum of a ten year time focus. So we have some certainty that we have a program that can now begin to address how long term exposures to air pollution are affecting people in Southern California and California in general. It's unique; neither the federal government nor the state government in the past has begun a research program with this long a focus. The closest attempt that I'm familiar with is the CORD study which we'll hear about from Anne Coulson. That project had a long focus, but it was done in bits and pieces; we don't want the bits and pieces approach again. We want to focus on the problem from beginning to end. Since it's a huge problem, dealing with the health status of millions of people over many years, there are many things we need expertise and advice on. That's one of the reasons you are here. There's no sure way to go about dealing with the question. No matter how nice it is to have a long term commitment, funding is also a limitation. We'll talk about that later. Finally, it's a source of some embarrassment that within the Southern California area or in California in general, we don't have identifiable centers of expertise in environmental epidemiology.

This is a unique opportunity, and quite a challenge since we don't know exactly how to proceed and we want to make sure we don't make serious mistakes. One shouldn't do a ten year study and find out in 11 years that one didn't ask the right questions or asked them incorrectly.

One of the ways we hope to proceed is to establish a core of environmental epidemiology in the academic community of California. There's no decision at this point on what study will be done, or who will do a study. When we have finished with this meeting, we hope we'll have a better understanding of the capabilities, interests and possibilities for this study. It is our intention to go forward relatively soon in our fiscal year process. This is an identified project we're ready to move forward.

We haven't identified the pollutant of concern. It may seem obvious to some people that the pollutant of concern should be ozone or the pollutant of concern may be toxics, or the pollutant of concern may be something else. But, one of the things we've intentionally not done is identify the pollutant; in part, because the expertise needed to help design this sort of study may help us pick the best combination of pollutants as well.

In forming a core of environmental research, we will probably initiate a core study. There are many reasons for this approach; one is because we have finite resources. We need to make sure that we get a good foundation that can be built on to deliver the products we need.

One of the things that may come from this meeting is a suggestion that we focus on oxidant-related atmospheres. We've done a lot of oxidant related studies in Southern California in the past. That's not to say we don't want to look at other pollutants and other effects, but we want to establish a core and that core may be focused around oxidants.

I have two more observations. One is that this is an unusual meeting for me (and I hope for you as well) in that we have not requested scientific papers; we don't want the normal academic presentation. Rather, we want your observations of where you think the strengths of different approaches are, where you think the weaknesses are,

where improvements can be made. So what we need are your thoughts and your communication and help as opposed to just academic papers.

If there is further information that's needed about the approaches, and about findings of studies, I think it's a good idea to talk to the authors during breaks, lunch time, dinner, what have you.

The charges to the attendees are several, but the main thing we want from you is your expertise, your experience, your guidance on those best ways to go forward.

Finally, how do we propose to follow-up this meeting? Essentially, we intend to have an advisory committee. It will be made up of peers in the relevant scientific community. Some of them are in the room. Findings will be summarized including identification of expertise, limitations, interests, what can be done. We'll be looking for identification of cooperative funding sources and we'll then go forward with solicitation of work in this area. These things we hope will occur over the next three or four months.

DR. WHITTENBERGER:

As Dane said, we have not given the amount of time to important topics which could be easily justified. We thought there ought to be a general introduction to the state of the air quality in at least Southern California as the first presentation in this meeting. We can expect only a broad brush treatment and to carry out that assignment, we asked Dr. Michael Kleinman to present some of the work which he has done in connection with Arthur Winer and others in a Southern California study.

Dr. Kleinman has an unusual background of environmental chemistry at NYU, a great deal of toxicology experience and also a lot of experience in human studies partly obtained with Jack Hackney at Rancho Los Amigos.

DR. KLEINMAN:

Thank you very much. I think that from the standpoint of atmospheric chemistry, Southern California in particular has some interesting characteristics which I hope to point out and I think some of those characteristics will bear heavily on the kinds of epidemiologic studies that need to be done.

What I want to do is very briefly touch on the sources of pollution and talk a little bit about what are the chemical constituents of air pollution in Southern California. I'd like to devote a fair amount of my time to talking about the distribution of exposures of people in Southern California and then just briefly touch on what we see as the possible future for air pollution.

SUMMARY OF DR. KLEINMAN'S PRESENTATION:

Sources of concern include mobile and stationary sources. A considerable amount of resuspended road dust is present. The "center of air pollution generation" is relatively near the ocean. Typically, the wind blows toward the ocean in early morning and away from the ocean from the late morning onward.

Major air pollution constituents include NO_x, organics, acids (including considerable organic acid), ozone, particulates, sulfates, nitrates, ammonium ion, hydrochloric acid, and hydrofluoric acid.

Human air pollution exposure varies with location, population subgroup, and activities. Dr. Kleinman's research group has devised an exposure model which considers population subgroup, living mode (indoors, outdoors, or in transit), exercise, and dose delivered to the lower respiratory system. Response to ozone varies not only with total dose, but also with dose rate. Young children, college-age people, and outdoor workers are subject to the highest exposures.

Exposures in Orange County are relatively low. Those in Los Angeles are relatively high.

An ozone dose of 250 micrograms over 2 to 3 hours can induce a 2 to 3 percent decline in FEV_1. Many people in the Los Angeles Basin receive such a dose. The ozone standard of 0.12 ppm may not be totally protective. In southern California, the present ozone standard may possibly be attained in about 25 years.

DR. WHITTENBERGER:

Review of EPA's Community Health and Environmental Surveillance System (CHESS):

In 1974 the US Environmental Protection Agency (EPA) issued a monograph entitled "Health Consequences of Sulfur Oxides: a Report from CHESS, 1970-1971".

CHESS constituted a rapid expansion of work begun by EPA's predecessor, the National Air Pollution Control Administration (NAPCA). CHESS was the first major national field study of air pollution health effects, and its participants had a high level of epidemiologic and statistical competence. Biomedical endpoints included persistent cough and phlegm prevalence, acute respiratory illness prevalence and incidence in children, spirometric lung function in children, and exacerbation of asthma and cardiopulmonary symptoms.

CHESS was splendid in concept as a long-term surveillance system, but it did not fulfill its promise. Problems included unduly rapid financial and substantive expansion with resultant loss of quality control, insufficient standardization of questionnaires, spirometers, and test procedures, difficulties with exposure assessment, a mid-course change in computer system, delays in OMB clearance of questionnaires (and, finally, denial of such clearance).

The CHESS monograph cited above was prepared under considerable intramural pressure and real or perceived Congressional pressure. There was considerable concern that some results had been over interpreted in the monograph. In November 1976, a report entitled "The Environmental Protection Agency's Research Program with Primary Emphasis on the Community Health and Environmental Surveillance System (CHESS): an Investigative Report" was prepared for the Congressional Committee on Science and Technology. The "Rall Committee", after reviewing the CHESS program, recommended increased university participation in air pollution health effects research. The "Rall Committee" reviewed the CHESS program in 1973 and recommended increased participation by university scientists in air pollution epidemiologic research.

Dr. Whittenberger approached Dr. B. Ferris and Dr. F. Speizer at Harvard regarding the possibility of their conducting air pollution health effects research; the "Six City" study was subsequently begun, in some respects as a follow-up to the CHESS studies.

(During the discussion period following this presentation, it was suggested that persons interested in the investigative report cited above read Chapter 6 as well as the Executive Summary.)

DR. SPEIZER:

"Six city" and "24 City" studies:
The goals of the "Six City" study include: 1) determining the relationship of air pollution exposure (primarily sulfur oxide and particulate exposure) to symptom rates and lung function, and 2) charting the growth and decline of lung function in the population. Originally, the study examined children annually and adults every three years. Diaries were subsequently added.

Measured pollutants included sulfur dioxide, NO_2, 0_3, particulates (including size fractions), and hydrogen ion. Study cities, selected to exhibit a pollution exposure gradient, include (in rough descending order of exposure) Steubenville, OH, Kingston-Harriman, TN, St. Louis, MO, Watertown, MA, Topeka, KS, and Portage WI. The study includes an original cohort of 14,000 schoolchildren and 9,000 adults, as well as a second cohort of 6,200 children. Children are followed through high school graduation.

There is wide variation in the decline of smokers' lung function, and 20 to 30 % of smokers develop clinically significant chronic respiratory disease (not including lung cancer).

The investigators hypothesize that the level of lung function in childhood predicts the level of lung function in adulthood, and that slow growth of lung function in childhood may predict rapid decline in adulthood. A major study goal is thus to investigate the role of factors, such as active and passive smoking, acute respiratory illness, and air pollution exposure, which may influence level and rate of change in lung function.

Findings to date reveal an association of particulate exposure with chronic bronchitis in adults and with cough in children. Little association of pollution exposure with children's lung function has been observed. Comparison of results from the first and second children's cohorts will allow internal checking of inferences.

Long-term longitudinal studies like the "Six City" study may not be maximally cost-effective for the study of air pollution health effects.

Airborne acid levels are usually higher in summer than in other seasons. The "24 City" study was initiated largely to study airborne acid health effects. Eight cities, four selected in spring and four in fall, were to be studied each year. An assumption inherent in the study design is that acid measurements over one year are a reliable index of long-term acid exposure. To date, a limited association of acid level with chronic bronchitis prevalence has been observed. The presence of wheezing or whistling in the chest with colds has been reported for about 30% of study children.

MS. ANNE COULSON:

Chronic Obstructive Respiratory Disease (CORD) study:
The CORD studies began in 1972 and carried into the early 1980's. Study cities (with expected exposures) included Glendora (high oxidants), Long Beach (sulfur oxide exposure), Burbank (moderate exposure), and Lancaster (low exposure). The lung function (spirometry, plethysmography, single-breath nitrogen washout, helium-oxygen curves) of persons aged 6 and older was measured. Enrollment of all residents of demographically-matched census tracts was attempted. The response rate was about 70% for first-round data collection. All subjects lived within one mile of an air monitoring station. Most subjects were non-Hispanic white. The study included a 5-year follow-up in all cities and a 10-year follow-up in one city. In the 5-year follow-up, data were collected from about 70% of first-round participants, for a response rate of about half (0.70 x 0.70) of all possible participants.

Problems included persistent funding instability, loss to follow-up, probable but unmeasured self-selection of follow-up samples, and lack of simultaneity of data collection in the different cities.

It was suggested that long-term study be undertaken, and that study of panels might be preferable to study of entire census tracts.

DR. HENRY GONG:

CORD "follow-up" study:
This study was designed to test whether the rate of observed long-term decline in lung function in Glendora, where ambient oxidant levels are substantial, is associated with acute response to experimental ozone exposure. In Glendora, the lung function of a cohort of Caucasians aged 25-59 years was measured in 1978 and again in 1983. The mean annual decline in FEV_1 in non-smokers was about 50 ml.

The investigators invited 208 non-smokers who had been tested in 1978 and 1983, who were 30 to 40 years old in 1978, and whose mean annual decline in FEV_1 between 1978 and 1983 was 51 ml., to participate in 1986 field testing. A total of 164 persons participated. These persons showed a mean 30 ml. annual decline in FEV_1 from 1978 to 1986; their mean lung function had risen slightly from 1983 to 1986.

A total of 27% of all eligible persons was then experimentally exposed to 0.4 ppm ozone for 2 hours, with alternating 15-minute periods of rest and exercise. Ozone response varied neither with pre-exposure methacholine sensitivity nor with long-term loss of lung function.

Studies like this one, which combine epidemiologic and clinical elements, are feasible. Factors to consider in study planning include age, sample size, baseline health status, location, measurement schedules, biomedical endpoints (possibly including biochemical measures), and issues related to follow-up.

DR. DAVID ABBEY:

Ahsmog I and II studies:
The Adventist Health/Smog (Ahsmog) study started in 1977. Subjects were non-Hispanic white non-smoking Seventh Day Adventists, aged at least 25 years, from San Francisco, San Diego, South Coast Air Basin. A group of 862 SDA's from throughout California was also included. Data analysis was constructed to be of relevance to environmental decision makers. Health outcomes were assessed against the number of hours (or days) per year that exposure concentrations exceeded sets of discrete levels. "Families" of relative risk curves were developed for selected pollutants, plotted within a grid whose horizontal axis is exposure concentration and whose vertical axis is number of hours or days exceeding that concentration.

The investigators also assessed the appropriateness of geographic interpolation of exposure levels by interpolating measurements from different sets of stations to the same geographic point. Both high and low correlations were observed, suggesting that geographic interpolation is subject to uncertainty.

To date, the investigators have observed an association of total particulates with a measure of airways obstructive disease, and a limited association of ozone with respiratory cancer.

The geographic diversity of the study population lends difficulty to the interpretation of results. Distinguishing the effects of specific pollutants has also proven difficult.

DR. RUSSELL SHERWIN:

An on-going autopsy study:
The investigators view their efforts to date as a feasibility study. To date, 155 lungs from southern California decedents, many of them homicide cases, have been obtained for pathological study. "Classical" and immunopathological examinations are conducted. The investigators concentrate on three types of lesions, centri-acinar, bronchiolitis, and bronchiectasis. An unexpectedly high level of lung pathology (including cellular infiltrates, "withering" of bronchial glands as shown with PAS stain, and bronchiolectasis) has been observed. Observed changes may be related to air pollution exposure, but the effects of important covariates, such as smoking and drug use, have not yet been assessed. Frozen blood samples are available for many cases. The investigators wish to conduct cotinine analysis and to investigate other covariate effects.

DR. MORTON LIPPMANN:

International and other U.S. studies:
The observed associations of mortality with very high particulate levels, and of wheezing with SO_2, were reviewed. SO_2 and sulfates may be surrogates for hydrogen ion. In Ontario, Canada, respiratory admissions were more strongly associated with sulfates than with other pollutants. In 1985, Dr. W. Holland observed decrements in children's lung function in connection with short-term elevations in particulates and sulfur oxides; these decrements lasted several weeks. These observations were not dissimilar to those in Steubenville, OH, in the "Six City" study.

In Japan, Kitagawa observed an increase in allergic lung disease following an industrial release of sulfuric acid; disease rates declined when a cleaner was put on the factory. The effects of acute acid exposure may persist for a week. Thurston is now studying New York State hospital admissions. Informative studies can be conducted with available data.

The studies at children's summer camps were reviewed. To facilitate study of secondary pollutants like ozone, study sites were chosen to have low levels of primary pollutants. Three studies (two in PA, one in NJ) were conducted. Lung function was inversely related to ozone levels even below 0.12 ppm, the current ozone standard. In 1985, the investigators studied adults exercising outdoors at Tuxedo, NY, and obtained comparable results.

In the camp studies, morning lung function sometimes varied with the previous day's ozone level, suggesting an unexpectedly long duration of effect.

Ozone-related effects observed in the field are generally larger than observed in the laboratory. This raises the question whether pollutants act synergistically in the field. (However, investigators at Rancho Los Amigos Hospital have observed little difference between the change in lung function resulting from exposure to ambient air and the change resulting from laboratory exposure to ozone at a level identical to that measured during the ambient air exposure.)

In southern California, particulate acid levels tend to be low, but substantial gaseous acid levels have been observed.

SESSION 2

STATE OF THE SCIENCE - TOXICITY AND MECHANISM STUDIES

NOTE: The order of speakers had to be changed from the published agenda because Dr. Dungworth had a conflict with a simultaneous ARB meeting; he also was unable to chair this session, so the original purposes of the session were not satisfied - to show the important linkages between animal toxicology, clinical investigation and epidemiologic studies in assessing health effects of air pollution.

DR. DUNGWORTH:

Dr. Dungworth indicated his intent to highlight findings and concepts from pathology and pathophysiologic studies that should be kept in mind in the design and conduct of epidemiologic studies. He focussed on findings in animal studies of exposure to ozone, including short- and long-term exposures, and including studies of sub-human primates. Attempts to use time-response profiles in different species must be interpreted with a high degree of caution.

For acute exposures to ozone, a "no observed effect" level by biochemical and morphological criteria is about 0.08 parts per million. At 0.15 parts per million in exposure of Rhesus monkeys there is a lesion in the transitional epithelium of the nose, with a shift toward a more secretory population of cells. It is doubtful that any use of this information could be made in the design of human studies, although similar changes in human nasal epithelium might explain some of the short-term exposure symptoms.

A more important area affected by low levels of ozone exposure is at the junction of terminal conducting airways and alveolar parenchyma. Inflammatory changes at this point are readily apparent in the monkey after long-term exposure to levels of ozone around 0.64 parts per million. These changes would be expected to produce decrements in pulmonary function.

Some changes can be detected in respiratory bronchioles of the monkey after 8 hours per day exposure at 0.15 parts per million ozone. Further research is needed to determine the full nature of these cellular changes and their possible significance in terms of disease. Some of the epithelial changes in chronic exposures are conceivably pre-carcinogenic - obviously further studies are needed.

DR. DANIEL COSTA:

<u>Physiologic and Biochemical Aspects of Ozone Toxicity</u>:
Dr. Costa's presentation related to acute effects, possible mechanisms of adaptation, and chronic effects of ozone exposure. Acute effects from one hour to 8 or 10 hours of exposure are important to regulatory objectives, specifically, is one hour averaging appropriate for monitoring purposes, or would 6 to 10 hours averaging be more appropriate?

Animal toxicity studies may also identify endpoints for clinical and epidemiologic studies, and may help to clarify relationships between pulmonary function abnormalities and biochemical or pathophysiologic disturbances.

Broncho-alveolar lavage is used to study protein leakage into alveolai almost immediately after exposure of animals (0.2 to 0.8 parts per million for 2 to 7 hours). Another method used in rats and guinea pigs is a simulated forced vital capacity maneuver. Combining these approaches permits correlation of alveolar protein leakage with reduction of forced vital capacity.

An animal model has also been developed for studying adaptation to ozone, a phenomenon studied in humans by Folinsbee and others. After exposure for 2 hours daily to ozone at levels of 0.25, 0.35, or 0.5 parts per million, the changes in respiratory frequency and tidal volume are most marked in the first two days, are reduced almost to control levels on the third day and are absent at day 5. These adaptive functional changes are not paralleled by lavage fluid protein change, so absence of pulmonary function change does not indicate an absence of injury.

The EPA Health Effects Research Laboratory at Research Triangle Park, North Carolina has conducted an 18 month exposure study of rats to a profile simulating diurnal oxidant concentrations in the South Coast Air Basin. The purpose was to see if rats developed chronic lung disease from chronic exposure to ozone. Ozone varied from 0.06 to a peak of 0.25 parts per million with an integrated value of 0.19 PPM. Exposures were on 5 days weekly, with intervals of 1 week, 3 weeks, and 3, 12 and 18 months. After the longer periods, animals were observed for up to 4 months post-exposure.

A large battery of tests was applied to these animals, including lung morphometry and a large number of biochemical measurements, including tests of lung and liver metabolism. Results were generally negative, except that the longer duration exposures were associated with signs of a "restrictive" kind of pulmonary disease, with significant reductions of residual volume, total lung capacity, and forced "vital capacity". Excess protein in lavage fluid continued throughout the exposure. Signs of injury disappeared and functional recovery took place during the four months post-exposure period of observation; however, the fibrotic changes in the interstitium did not disappear.

DR. STEVEN COLOME:

Sensitive and Susceptible Subgroups in a Population:
Dr. Colome described what might be called a holistic approach to assessing the possible health effects of air pollution on a heterogeneous population. Although the numbers are mind-boggling, one can conceive the application of a host of dose-response relationships between a very complex environment and a very wide range of sensitivity among individuals in the exposed population. Keeping in mind this continuum of exposures and sensitivities, it is difficult to conceive of clinical studies or epidemiologic studies that would have a sufficient statistical power. Nevertheless, one must address this puzzle, and the studies of William McDonnell and Henry Gong have given provocative leads.

In repeated study of the same subjects, McDonnell showed that strong responders tend to remain strong responders, rather than regressing toward the mean. The reasons for the variability in normals and in asthmatics are mostly unknown, but McDonnell's studies show the need to identify "responders" and "non-responders". This is a potential benefit of the kind of study Henry Gong has done, taking subjects who have participated in an epidemiologic study and characterizing their responsiveness to air pollutants under controlled laboratory conditions.

DR. WILLIAM MC DONNELL:

Implications of Clinical Investigations of Air Pollutant Effects:
I'm going to describe a number of acute effects that we have measured in humans in chamber exposures. It's pretty well accepted that dose-response curves have been generated for a number of effects; I'm not describing them as a suggestion that we study these particular effects in the field, rather I'm reviewing them to the extent they may suggest or give us clues as to what other types of effects should be studied in the field and that we can't study in the chamber. Most of the things that I'm going to talk about occur at levels as low as .12 parts per million (PPM) with heavy exercise for two hour exposures and at levels even as low as .08 PPM, if we look at prolonged exposures, six or eight hours, again with very heavy exercise. The first effects are acute respiratory symptoms such as cough, shortness of breath, and pain on deep inspiration. Pulmonary function decrements initially are an inability to take a deep breath, manifested by reduction in inspiratory capacity. We also see a small amount of broncho-constriction manifested by increases in airway resistance. Individuals develop a more rapid, shallow pattern of breathing. We see increases in non-specific airway reactivity in response to methacholine or histamine challenge.

Something that we didn't pay much attention to when we noticed it is that one study in our laboratory and one in Dr. Hackney's laboratory suggested that individuals with chronic obstructive disease had very small reductions in hemoglobin saturation as measured by oximetry following recent low level ozone exposures with mild exercise. So in thinking about what are some of the more important events, I think that's something we might want to keep in mind.

We know that response is a function of concentration of ozone, duration of exposure and ventilation during exposure. An important observation that Colome alluded to is the marked individual differences in response, from no response to 0.4 PPM to a 30 or 40 percent decrement in FEV_1 following a .180 or .24 PPM ozone exposure. These are very reproducible. We don't know what the predictors of these differences are, but they are substantial. And when we talk about sensitive sub-groups or responsive sub-groups at least as far as the things we are able to measure in the laboratory and in these acute exposures the major variability in response in the population that we studied doesn't come from differences between asthmatics and people with chronic lung disease or normal individuals. Rather it's differences within groups, including asthmatic groups; all the groups that we've studied show large ranges of responses, not that the mean responses are very different or the distribution of responses are very different among these different groups.

SESSION 3

INTRODUCTION:

The Planning Committee decided in July 1989 to have a session of the Planning Conference devoted to the principles, approaches, difficulties, and other considerations which are important to the design and conduct of field studies of health effects of air pollution. The agenda for Session 3 at the Conference was the result of this decision, but a considerable evolution of topics took place before the final agenda was determined.

One principle remained firm - that the Conference should not attempt to design a specific protocol for a study that the ARB would support. The alternative agenda was arrived at by selection of a chairperson and co-chairperson, and by subsequent discussions that led to selection of panel members and panel topics.

There was general agreement on the primary importance of the questions posed for possible research projects. Each person developed a set of possible questions based on their own experience and on reading of such documents as the NAS-NRC monograph on air pollution epidemiology. The flavor of the planning process is suggested by the content of the following documents - the letter submitted by Jonathan Samet, on Questions and Possible Study Designs, and the letter which Patricia Buffler sent to each Panel Member.

QUESTIONS AND POSSIBLE STUDY DESIGNS FOR PLANNING CARB SYMPOSIUM DECEMBER 12, 1989

Jonathan M. Samet, M.D.

QUESTIONS:

What are the questions of policy makers? The public?

- Generically, the overall question to be answered is: Does breathing air in Southern California adversely affect health?
- The component questions are:
  - Is excess mortality associated with peaks of air pollution?
  - Are there chronic effects of air pollution in Southern California on lung function?
  - Are susceptible populations adversely affected by air pollution? Populations of obvious interest include persons with chronic respiratory conditions (asthma and COPD), cardiac disease (coronary heart disease and angina), the elderly, and infants.
  - Is exercise safe at times of high pollution?

What are the scientific hypotheses to be tested?

Lung Function:

1. Lung growth is reduced by residence in an area with high oxidant pollution. The hypothesis requires quantitative specification. Involuntary smoking reduces maximum FEV_1 achieved by perhaps 5%. Should an investigation be designed with this value as the minimum effect to be detected?

2. Residence in an area with high oxidant pollution accelerates lung function decline with aging.

   Animal studies indicate the potential for changes in the small airways at concentrations observed in Southern California. Analogous human effects might be observed as increased decline of FEV_1 or of V_{50} or V_{75}, which more closely reflect function of "small airways". This hypothesis also merits quantitative specification. The effect is likely to be small; in relation to annual decline of 20 to 30 ml, a 10% excess is only 2 to 3 ml additional.

3. Short-term response to oxidant pollution predicts long-term response.

   Short-term decrements of lung function have been well documented in normal persons with exercise. A range of responsiveness has been demonstrated among normal persons; the degree of responsiveness seems to be an individual characteristic. This hypothesis, like hypothesis 2, would require

large populations for assessment. The distribution of responsiveness must be described along with the anticipated increase in decline assumed to be associated with hyper-responsiveness.

Exacerbation of chronic respiratory disease:

1. Persons with asthma are adversely affected by oxidant exposure.

   Relevant outcome measures include reduced level of PEFR*, increased symptoms, and increased medication requirement.

2. Persons with chronic obstructive pulmonary disease are adversely affected by oxidant exposure. Relevant outcome measures include increased symptoms and clinical deterioration as manifested by functional limitation or requirement for medical care.

Respiratory Morbidity:

Other effects can be postulated:

1. Increased respiratory infection: not readily approached. Is temporal variation of interest? How assess exposure?

2. Increased respiratory symptoms: acute or chronic?

Study Design:

The following listing of study designs is not exhaustive, but intended to illustrate the types of investigations that could be feasibly undertaken.

1. Cross-sectional surveys of children or adults: Compare lung function, symptoms, and disease rates in persons residing in more or less polluted communities.

2. Panel studies of persons with asthma or COPD: Monitor clinical status with PEFR, symptom diaries, or other indicators.

3. Panel studies of exercising persons: Follow PEFR or spirometry and symptoms in persons who exercise maximally out of doors.

4. Community indicators of morbidity: Assess relationship of community measures (hospital admissions, ER visits, HMO visits) with pollution concentrations.

5. Longitudinal studies of lung function growth and decline: Prospective follow-up of populations of children and adults.

*PEFR = Pulmonary Expiratory Flow Resistance

DR. BUFFLER'S LETTER TO DR. ANTON-CULVER:

We have been asked to address a set of specific questions in Session 3 of the UCI Planning Colloquium on Epidemiology and Air Pollution. These questions related to the possible adverse effects of air pollutant exposure on human performance, growth, morbidity and mortality. It is anticipated that most of these questions can be addressed by well planned and well conducted epidemiologic studies.

Specific attention is being given to epidemiologic studies because of the particular relevance of the results from such studies to the setting air quality standards. With reference to ozone as a specific example, vast amounts of toxicologic information is available, and numerous excellent human investigations to study acute effects have been done under controlled conditions, but the health consequences associated with the episodic high exposures to ozone that occur in large parts of the country are still uncertain.

The Panels are not expected to design specific study protocols, but rather to outline some of the most important remaining questions in air pollution epidemiology, and to outline the principles of the epidemiologic method that provide a basis for sound research planning.

The Planning Committee, along with Dr. Samet and myself, proposed to accomplish the above by asking the panelists in Session 3 to consider the relevant research questions (as outlined in the attached document), and to evaluate the possible research approaches to these study questions by addressing a number of criteria, issues or principles. (A number of possible study approaches are also outlined in the attached document.)

The criteria, principles, or issues relevant to research planning may include the following considerations:

* What is the best study design? (Longitudinal, cross-sectional, case-control, hospital or ER admissions, panels of exercising and sensitive subjects, e.g., asthmatics). For mortality studies these options may be ecological, case-control, time-series, etc.

* How can individual exposure to pollutants be quantified? Are personal samplers and indoor samples necessary? What chemicals and particulates need to be identified and quantified?

* Can "susceptible" or "sensitive" groups be identified?

* What outcomes measurements are most reliable, sensitive and feasible for community studies? Are any new biomarker systems for tissue damage validated and available?

* Have sources of bias and confounding been avoided insofar as possible?

* Are resources adequate for acquiring, processing and analyzing data with high standards of quality control?

* Is the proposed study reasonably assured of being feasible and cost-effective?

* How will results of the study contribute to standard setting and regulations?

The above list is not presumed to be complete, but is offered to stimulate critical and creative evaluation of proposed research approaches for the epidemiologic assessment of the adverse health effects of air pollution. In preparing your comments, I encourage you to augment these criteria, as well as the research questions and possible study approaches indicated.

The four panels in Session 3 will be established as indicated in the second enclosure with the persons indicated being asked to chair the panels. I hope this information is helpful in preparing for your participation in the Session. If you have further questions about the Session, please do not hesitate to contact Jonathan Samet ([505] 277-5541), Jim Whittenberger ([714] 856-7240) or myself ([713] 792-4638). Thank you so much for your anticipated contribution to this important colloquium. I look forward to your input and working with you.

With best regards,

Most sincerely,

Patricia A. Buffler, Ph.D.
Ashbel Smith Professor

SESSION 3

SUMMARY OF PRESENTATIONS AND DISCUSSIONS

DR. PATRICIA BUFFLER:

It was indeed a pleasure to work with such an outstanding planning committee and an outstanding number of panelists. The charge to the committee was quite broad. We were not charged to design a specific study, but to outline and discuss some of the issues that would be involved in designing epidemiologic studies of air pollution. This session, as you will note in the program, is outlined in terms of the four panels focusing on different aspects of these questions with overall concepts in mind.

The first panel deals with questions to be posed: "Study Design Issues" are to be addressed by the second panel; "Exposure Characterizations and Exposure Related Issues" will be addressed by the third panel; and lastly, but certainly not least important, issues of Data Management and Data Quality. Each panel will have its own chairperson. The first panel will be headed up by Dr. Jon Samet and will include Ms. Anne Coulson, Dr. William McDonnell and Dr. Frank Speizer. Before we start the panel discussions, I want to outline the broad array of questions that were posed to all four panels. The questions cross over the topics that will be addressed by each of the panels.

Most importantly, what are the most important unresolved questions in air pollution epidemiology, with particular relevance to California? What are the best study designs to address these questions? Are the proposed studies reasonably assured of being feasible and cost effective? What outcome measures are most relevant, reliable, sensitive, and feasible; how can individual exposures be quantified? What exposures in a particular study need to be measured or assessed? Is it possible to identify susceptible and sensitive population groups relevant to a particular problem? And additional questions, such as are there any new bio-markers of tissue damage, susceptibility or exposure that are available for incorporation in the study design to improve precision? Are these bio-marker systems available now? Specifically, are they validated and ready for application in field studies? Many of them, as we know, are being reported but are they really ready for application in epidemiologic study? Are there adequate resources for acquiring, processing and analyzing the data? (An enormous amount of data are usually collected in epidemiologic studies of air pollution.) And lastly, how will the results of the proposed studies contribute to standard setting and pollution control, one of the ultimate criteria in terms of looking at the relevance of epidemiologic studies of air pollution. So with that brief overview, I would like to turn the chair over to Dr. Samet for the first panel discussion.

DR. JON SAMET:

What I plan to do is set up a few general issues related to questions and hypotheses that anyone will need to face in trying to address these problems. The members of the four panels had lunch together today and we came up with some of our own issues and questions that we recognize that we could not answer. We began to talk about the public's questions and its concerns, the regulators, the policy maker's questions and concerns, and the scientific hypotheses that could be tested. We felt

that studies must be designed with the expectation of answering the questions from the public and the regulators if the scientists were to be successful in doing their job. We felt that there needed to be a dialogue between the scientists who might undertake studies and those who would be posing questions to the scientists to be answered in those studies. And if this dialogue was not explicit, there is a very real chance of a mismatch at some point down the line when the scientists crank out their point estimates and confidence limits and the regulator asks what have we learned here? One thing that our luncheon group wanted to know was, first of all, how do we know what the public is worried about and can those who are asking scientists to do studies with the idea that they are going to get some data to do something with, give us some explicit direction. I think that's one issue that should be discussed.

Putting all that aside, I was brave enough to sit in Albuquerque and decide what the public's questions were. Of course, in Albuquerque we don't worry about air quality (we actually do). There's a general question that I think we can all recognize that might be put by a member of the public, does breathing this air that I can see, it's visible, it's brown, does it adversely effect my health, is it bad for me? If I were a man on the street, that's the question I would ask. That's the question that was asked in Albuquerque because we have our own brown cloud. When people call me up and ask, "Is that bad for me", of course, I say, "I don't know".

We can identify some component questions and earlier participants have pointed to what those components should be, for example, is mortality increased? Are there chronic effects, are susceptibles affected and is exercise safe? This is a generic question that might belong to those of the public and the regulators and is the most obvious of components as we begin to break it down.

We've heard earlier about scientific hypotheses and I think we can begin to frame a number of explicit hypotheses that might be posed as null hypotheses in developing study design and sample size and sample size aids. I've listed some of these here. We've heard these threads through all of today's presentations. It has been suggested that lung growth might be adversely affected, that the age-related decline of lung function might be accelerated, that there might be a relationship between short-term response and long-term response. However, we've not said how tight that relationship might be. We're concerned that exposure to pollution might exacerbate, or might increase the incidence of asthma. We've heard that it might exacerbate Chronic Obstructive Pulmonary Disease (COPD) and I suppose by linking up to this hypothesis it could possibly contribute to the incidence of COPD. We've heard concern about respiratory symptoms and increased risks of respiratory infections; so if nothing else, we can certainly frame a set of scientific hypotheses.

What I'd like to do is talk about a few of these in more detail so you can see some of the problems that we're up against. It goes back to what I said originally. Let's take Frank Speizer's suggestions about lung function during growth and decline and think this through a bit. Lung function, let's say FEV_1, grows from birth to somewhere in the age range of 18 to 24 years. Somewhere between 24 and 30, FEV_1 reaches a plateau in non-smokers and then begins to drop off at about 24 ml a year. Frank's hypothesis that lung growth might be affected suggests that perhaps there's a different trajectory of growth for those who are pollution-exposed; it's lower than what it could have been. In adulthood, the decline may be steeper than it would have been. Let's think about this. What are we concerned about from the standpoint of biology? What magnitude of effect might be plausible? How steep is this curve going to be or how depressed will this one be.

From a public health perspective, what's important? What effect do we want to protect against and what should we design regulations to guard against? In thinking about specifications of the hypothesis related to lung function growth and decline, we have to have these three sets of issues in mind.

Now, let's think about decline. Consider just the age-related decline. Let's assume that from about age 35 FEV_1 normally declines by 25 ml a year and let's talk about a 40 year loss through age 75. If the annual loss is 25 ml, there would be a 1,000 ml total loss across that span of time. A 10% effect on FEV_1 roughly means that the annual rate of loss goes from 25 ml to 28 ml, and there's an additional total loss of 120 mls. Ten percent sounds like a big effect. Will we accept a 10% effect? Do we want to design a study to detect a 10% effect because we think that's important from a regulatory point of view?

From a biological perspective, is this additional 120 ml loss at age 75 very important? Probably not as an average rate of loss, but if there are some who are more susceptible, instead of losing 1,000 ml they have now lost 1,500 or 1,600 ml. So perhaps we are talking about something significant, but we don't know the distribution of responses. You can see then what happens as we go up to 20%, 40% excess loss, etc. What in fact is important and what level of effect can we detect? I haven't done formal sample size calculations, but I'll give you some guesses. At the 5% level we're probably talking about 10's of thousands of subjects if we are honest about our ability to measure exposure and to measure outcome. I think that somewhere in the 40% range we come down to the thousands of subjects. I think of one example of a study design on a five or seven year basis which could detect an effect in this range; this is the nationwide lung health study which I think has 6,000 or 7,000 persons who are at risk of rapid decline randomized. So if we're worried about a 10% effect, we're talking about a massive undertaking. We need to decide how much of an effect we're worried about and why. This gets down to whether we want to do a study that can rule out large effects that are unacceptable. We're probably never going to very precisely quantify the rate of lung function loss as we come into the range of 10% - 20% as a point, with wide confidence limits around it. That's a limitation of the method, but that's not to say that we can't begin to design studies that rule out effects that we might be concerned about.

We also need to think about how tightly we want to predict response. I'll take asthmatics as an example of a susceptible population. We might design studies to look at a number of different indicators, short-term, perhaps variation of peak flow rates, symptoms, medication use, outpatient department, or ER visits. Death is so unusual in asthma that we would not pick as an indicator mortality rates.

Again the same issues come up, what magnitude of effect are we concerned about and do we want to precisely quantify the effects on individuals or groups? How carefully do we want to describe the distributions of responses that we wish to study?

There's one more set of problems that plague environmental epidemiology that I think we should always deal with up front although we often fail to do so. An overriding problem is always mis-classification. When we measured our health outcome, whether it be lung function decline or visits to emergency rooms, there's always some degree of misclassification. Things aren't what we think they are. In some cases that's quantifiable. Exposure is inherently subject to misclassification and we know it. Misclassification most often occurs at random and we know that for tracking personal exposures to pollutants that its magnitude can be relatively great. We also know that

there are consequences for the statistical power of our investigations to detect effects. I want to remind you that the sample size game we play when we write our grant applications does not assume any misclassification, it assumes that exposure is measured without error.

In this case, we know that is not true. So we're going to have to use help from the exposure side to decide just how much misclassification there is and what its consequences are. And we might want to look for strategies that minimize misclassification. Like looking for extremes of exposure.

The other issue that I put forth is "what are we really interested in"? And I think this goes back to the regulators. Do we want to describe exposure response relationships -- the slope of the line between dose or exposure and response or are we interested in designing studies that maximize the contrast between groups and then look at response. Are we interested in proving there's an effect because we think that's the information that's needed by the regulatory policy side or are we interested in describing exposure-response relationships?

Are we smart enough to know what those relationships might look like when we design investigations? This is probably the best use of any given set of funds or resources if we can do it. I think I've heard a lot of talk through the morning that perhaps we should be focusing on exposure-response relationships. Again, obtaining very precise relationships from epidemiological data is usually a problem. Are we interested only in describing an effect or do we want to know about these quantitative relationships? I put these issues out as issues that need to be addressed as we design studies. They'll certainly influence sample size calculations, and the kinds of studies that we might want to follow. They're issues that there are tools to deal with but now is the time to begin thinking about them. Having posed these questions that don't have easy answers, but that we need to think about, what I'd like to do is give each panel member a chance to add his or her thoughts to the discussion.

DR. FRANK SPEIZER:

I agree about the necessity of defining the questions very clearly. To the extent that is possible, we should choose susceptible individuals, the ones most likely to experience an effect or the ones most likely to have some adverse outcomes from an effect. We maximize our ability to define the effect or to define some dimension of the public health problem. When I think of occupational diseases, the most likely people in which to detect an effect of an occupational exposure are cigarette smokers - the hardest people to study. I wonder whether that may be the case with air pollution too, particularly ozone and what we know about the lesions in both cases - small airway inflammation and obstruction associated with cigarette smoking. I think that's a question we need to deal with and it can make studies much more difficult, but it may be necessary.

Jon asked me to comment on outcome measures. What sorts of things should we be measuring in these studies? Again, a lot depends on the questions we're asking. I think that measures should have properties such that whatever we measure should be a predictor of the actual outcome that we're interested in. A good predictor, as sensitive and specific as possible.

The method should be a precise, accurate, non-invasive technique that can be taken into the field. For example, after hearing about the pathophysiology of ozone toxicity, I think that one should be interested in small airway disease and physiology, and one would want to then design some sort of outcome measures to assess the physiology of the small airways. From a scientific point of view, we might use some measures that may not be direct predictors of morbidity, but that might contribute to our knowledge of pathogenesis of whatever disease process is going on. One can divide outcome measures into several levels., to look at mortality and morbidity rates, hospital visits, or exacerbation of disease symptoms. These are effects that the public and regulators can relate to. Another level down would be markers of disease. Some of the obvious ones are things like FEV_1 -- very few people suffer respiratory disability with a normal FEV_1. Whether we talk about measuring changes of FEV_1 cross sectionally or longitudinally is a different story. When we go to the next levels of complexity, we're talking about such things as single breath nitrogen wash-out, looking at small airways functions. There's a question, I think, what does that tell us. Are changes in wash-out curves a predictor of longer time morbidity or mortality? There are reports in the cigarette-smoking literature that these tests are predictive, but the evidence is not conclusive.

When we go one step further, it would be very nice to have some markers, biological or biochemical markers of lung disease or pathologic process. I'm not convinced that we have any of those that are satisfactory to be taken into the field. It comes down to the aerosol bolus technique which hopefully we'll talk about later. This technique shows some difference between smokers and non-smokers, but we're not quite sure what it means and at what level we'll be ready to take that into the field. Those are my initial thoughts.

MS. ANNE COULSON:

I'd like to address the question of numbers. It isn't the highest priority question, but maybe it is because it may be a question of what can you afford.

I was interested in the mention of the national lung health study; I'm involved with the Los Angeles chapter of the lung health study and I would like to point out some of the attributes of the study. They want 6,000 people -- 4,000 assigned to the smoking cessation group (two groups of 2,000) and another group for usual care with the non-intervention on the smoking. Starting with that number, 6,000 is a useful place to start because they have a limited age range of 35-59 years. Their pulmonary function levels are between 50% and 75% of predicted FEV_1; they are all smokers by definition. There are no questions about pollution, there are a few about occupational exposure, but we're not putting all those things together into these humongous regressions or multiple logistics or this or that or stratifying which leads us to no people in a cell almost immediately. In the CORD study which I discussed this morning, I neglected to mention that we had more than 15,000 people in the study. By the time we divide into four pollution areas and to smokers, non-smokers, former smokers, men and women who are very different in their smoking experience and kids and grown-ups and all the rest of this stuff, with 15,000 people we are down to cells of only 1, 2, and 3. So clearly the question of numbers is an extremely serious one. It probably can be best resolved by very judicious sampling, which

would cover the range that we want in much the same way as the lung health study has taken a specific age group. But unless we do sampling on each time we pick up something, we either lose generalizability or we lose the power in the number that we've got.

One of the most important things I have learned from the lung health study and from other collaborations is the necessity for an excellent and detailed protocol. For those of you who are not familiar with the Lung Health Study, I brought along the protocol book which is a thick notebook that has at least a 1/2 inch of modifications (or did in the early days of the study) coming through every month or two. Because of the necessity for all doing exactly the same thing in ten places around the country we were obliged to write the things that many of us take for granted we'll remember. And then the institutional memory quits, and a tremendous amount of information is lost.

This might lead us to the thought of what is the irreducible data set, the standardized data set that all participants should be getting so that we can make comparisons between studies in Los Angeles and between Los Angeles and Houston or other places, the "Six Cities" or the "24 Cities" or whatever. A lot of things have come up today that I have become very interested in over the last year in my own epidemiologic thinking about host characteristics. I think epidemiologists are not paying enough attention to this. We are not paying enough attention to exposure assessment. The idea of identifying the most susceptible hosts and protection of those individuals, we've done a little bit about. My attention has been drawn to this problem by some AIDS studies and some earthquake studies, both of which have quite a lot of host factors involved. I think that the closer we are to a free-living population, such as we used in the CORD Study, the more generalizable our results are going to be - but the larger the sample size we are going to have to have. On the other hand, the closer we get to controlled chamber studies, the smaller the sample size that we can deal with and the less generalizable is what we can talk about.

SPEIZER:

In thinking about what contribution can be made by studies in California, it seems to me we ought to be looking at children. They are a cleaner, less "contaminated" pool of subjects to work with and studies in children can answer some very specific questions. It might appear to be a sort of a leap of faith to say that if we found something in children that it relates to chronic respiratory disease in adult life. This is really a part of a bigger effort going on in the country in terms of trying to understand the natural history of disease. So, we really ought to focus the hypotheses on something that is very tangible and is very circumscribed, to answer one, two, or three questions that are very specific, and that we believe are responsive to the public's concerns. From my perspective that would be studying children. I have some specific ideas as to what and how to do that, but that should come later. At this point we ought to focus on what those hypotheses are and whether they are answerable in a relatively short period of time. Ten years is a relatively short period of time.

BATES:

Accepting Frank's point about the children, which I will say something about tomorrow, I'd like the panel to answer this question. If we assume that the longitudinal measurement of FEV_1 is too difficult, let's say, or too expensive because

of sample size requirements and other problems, what other indicator might tell you whether there had been what might be loosely termed premature aging? Would, for instance, the age at death from pneumonia be of any interest to you? What other things can you extrapolate that might indicate that indeed there was a total effect on the population, and what other kinds of data can you suggest which might get at that?

SAMET:

I'll give one answer and then let everybody else comment. For one, I don't want us to dismiss carefully thought-through cross-sectional studies too quickly, because there may be some answers there. As Frank says, we do know a lot about lung functions in populations and we have the potential if we think creatively about subject pools who might be accessible by virtue of their employment and might have had higher exposures, who might have been consistently employed in one location. Perhaps we could identify such populations, study them cross-sectionally and begin to understand if in relationship to appropriate reference groups there are or are not important changes of lung function in the population. Your suggestion that we need to think creatively is true. I feel like I'm going back to the old ways, but I think maybe we can use some creativity.

COULSON:

I think that the concept of looking at age at death from pneumonia is an excellent one.

ROSSITER:

I have here the 1971 Mahoney paper on standardization of mortality rates in Los Angeles. The author clearly anticipates the beginning of a long series of studies of mortality in relation to Los Angeles air pollution, none of which, so far as I'm aware, ever appeared. Looking at the Mahoney data as initially reported in 1971, can you see building on that in any intelligent way to answer some of these questions?

COULSON:

The Mahoney report was not followed up, but there has been considerable analysis of mortality data in various areas of different pollution and for different days of the week. In general we found very little.

ROSSITER:

Could I as an outsider to this continent make a few comments -- I've just spent a week at WHO in Geneva working at a conference on occupational epidemiology in developing countries. One observation was that no developing country believes any developed country's epidemiology is particularly relevant to their own country without pre-testing or testing in their own country. Another comment concerns the issue of longitudinal vs cross-sectional studies; they address very different questions, one being a prevalency issue and the other concerned about the incidence of effects.

The question then is to decide which gives more useful information. As to longitudinal studies, I believe they have tremendous importance, but in children they become rather difficult, especially when you start with 8 or 9 year olds and come up to 14 or 15, where the peaks of growth come. Is there a way of studying 8 and 9 year olds, 14 and 15 year olds, and 20-31 year olds to build a picture for Southern California of what the whole lung function pattern is in a series of cross-sectional studies in the state?

SPEIZER:

That's the pattern that I would very much favor. When I said I favored a study of children, I did not mean that we should do a longitudinal study of children.

SAMET:

Someone asked the question, why does the Air Resources Board want more studies? Maybe we should ask for a response to some of the questions that we posed and begin the dialogue that we need to start a scientific planning process. We've been posing questions about lung growth and lung decline because those are the scientific questions, but let's ask the Air Resources Board to respond to questions on some of these issues.

HOLMES:

We have our own system of establishing air quality standards in California and EPA is responsible for federal standards; for ozone, both standards are one hour standards. We on the staff are concerned, our Board is concerned, our Governor and the Legislature are concerned about the question of whether or not there are long-term consequences of exposures to toxics, ozone, NO_X, acids, and respirable particulates. So they've appropriated us a sum of money to continue funding over ten years to get at the question of the consequences of long-term, life-time exposure to smog. So that's what was set up -- with the idea that we learn whether or not our standard is going to provide adequate protection. If it doesn't, what standard would provide satisfactory protection?

UNIDENTIFIED SPEAKER:

Maybe I could paraphrase. I think what you said was that you wanted to know has the one-hour standard for ozone provided protection against any health effects, and then the second part of that, if not, what level would provide protection? Is that what the scientific community needs to keep in mind in proposing research protocols - that studies must respond to those two specific items: has the standard provided protection and if not where should you set a number? Isn't that what we are aiming for?

WESTERDAHL:

I think there is one additional point. We worried about many things, for example ozone standards for acute effects versus chronic effects. We also have uncertainties about how other portions of the environment, whether they be acids or other

pollutants, may affect health after a lifetime of exposure. That's a very specific focus. The other focus is on the health consequences of other pollutants and obviously combinations of these pollutants, so it's more than just ozone.

SPEIZER:

To throw a question back, I'm unclear about what is meant by chronic effects. If indeed, one could demonstrate that children living in the South Coast Air Basin, aged 8, had 10% lower levels of lung function than children living outside the basin, would you consider that a chronic effect?

WESTERDAHL:

I think we're back at the level where we were 20 years ago when we asked that question: is a 10% change in FEV_1 due to a one-hour exposure to ozone a problem? We are not talking now about one study to resolve the issue within our lifetime, but if we don't start, we certainly won't get the answer. So this is a beginning. The answer to the question, is the 10% decline in parameter X in a child of concern, I think it's too early to answer that question. The panel could help answer that question. I guess part of the problem is comparable with ozone twenty years ago or even to some extent today, what do the changes that we measure mean.

LIPPMANN:

It seems to me that there's good reason to also study adults because there are preliminary indications that oxidant exposures contribute to earlier death or disability. On the other hand, adult studies are much more difficult because of the mobility of adults; they work in a different part of the community than they live, they move around, you can't define their lifetime exposure and its chronic effect, you need to know their cumulative exposure. The children offer much advantage, not only can you address the cumulative lifetime exposure from the extensive monitoring data that you have combined with their residential history, but they don't have the commuting issue, they presumably haven't smoked, presumably they haven't used hard drugs, they haven't done a lot of things that you would find much more of a problem in the adults. So if you would be willing to make that leap of faith that a slower rising of lung growth has the implication of a like probability of greater loss of function later, then studies of children can be surrogates for studies of adults. There's so much advantage to doing that that I think it makes sense, it makes it practical to do a study. Among the other advantages is it's easy to get children in groups to study. They go to school and you can monitor at the school, in and outside their homes in a limited area and use certain children as sentinels to get good personal exposure data on a larger population. You can in the kind of funding timetable that's been proposed, do at least two cuts in time between the age, say of eight, where you find that you get good data, and three, four, five years later when you can get data points to establish a slope on their growth. So if chronic disease is the focus, this has so many advantages in terms of feasibility of getting scientifically defensible outcome that I would certainly recommend doing that. You would also have the option of picking different communities. As I understood the CORD data, the effects are as great or greater in Long Beach than they are in Glendora, which suggests that while ozone is probably necessary, it isn't strictly the amount of ozone, but that the SO_X and NO_X pollutants are playing a contributory role toward the effects. I suspect these effects

wouldn't happen without as much ozone as there is in Long Beach, but you don't need more, so you can, considering the geographical diversity of this basin have highly targeted school populations with different gradations of ozone alone and gradations of mixtures. There are characteristic mixtures such that they can be considered a two component study and still be manageable, whereas if you look for a large number of pollutants the search could be infinite and you'll never get any resolution. So it seems that there's much in favor of a limited longitudinal study in children. Initial answers will come from the cross sectional first analysis, and more definitive answers presumably will come from the follow-up study when they're approaching their adolescent growth spurt. There's no other choice that seems anywhere near as feasible for getting you where you want to go.

BUFFLER:

Just one quick question directed at Dr. Speizer. It would seem that there is some information forthcoming from the studies that you're involved in that might provide an indication as to the long-term significance of this reduction in amount of growth in children before this ten year period is over. Am I being too optimistic about that?

SPEIZER:

I think that's correct. We'll have tracked these children, at least through high school and indeed linked them up with results that can be examined. It's pretty clear that we're not going to see something that will get written down on a death certificate as COPD in these people we're studying. In fact, we have evidence already that those with reduced levels of lung function from 1974 to 1976 predict excess mortality from COPD. I think that the data that will come in over the next few years would suggest that this tracking phenomenon is real and that it persists and indeed other exposures in adult life do affect it. We have seen some indication of this and Dr. Chapman could comment on what we've both seen in China with indoor exposures affecting children and adults. Certainly you see a lot more disease in women who are non-smokers, COPD, in women who are non-smokers in the developing world which must relate to exposures that happen earlier in life or perhaps throughout life from indoor exposure. The question though has got to come back to the Air Resources Board in what they have to respond to in the political sense: if everybody was absolutely convinced that a 10% drop in lung function in eight year-olds was a real phenomena, would that satisfy your needs for demonstrating a chronic effect?

DR. BOSTON:

I've listened to this kind of discussion for quite a while and I agree with a lot of what was said, but I'd like to put it in a little different perspective. As one of the fellows sitting on the Board, I really don't need to hear anymore about future studies of ozone and chronic bronchitis. I want some hard facts. I want some numbers. We're doing everything that we can right now to reduce the pollutants in the air over the basin, trying to bring pollutants down to a standard level. We're asking our citizens to make a lot of sacrifices, and industry is going to have to chip in; it's going to be very, very expensive. And when we sit on the Board and ask you to do these things, we ask for some hard numbers - where do we have to bring the ozone levels down to. How can we ask our citizens to make the sacrifices if we really don't have the facts. Dr. Sherwin put some pictures on the board to show that people between 14 and 20

years old are having a lot of changes in their lives. We know that that's due to air pollution in lieu of something else. Where do we go? How do we compare animal studies to human values? We have this come up all the time during toxic substance discussions. You can show us how a rat responds to .02 parts per million. How do we know that that does anything to the humans. We want some guidance on that type of thing in the various pollutants that we're forced to regulate right now.

SAMET:

I think we understand the pressures that are on the Board. Maybe one more comment and then I think we'd better move on to the next panel and give it a shot.

DR. BOSTON:

I think that we need to consider whether just because they're children, that they're non-smokers. We need to choose non-smoking groups, whether this be church members or some other way, so that we know these children are not only non-smokers, but also are non-secondhand smokers. Only in this way can we really look at air pollution, because tobacco smoke, even secondhand, has a lot of possibility of confounding the issue.

SAMET:

We've raised a lot of questions in this panel. I think there have been some answers. My suggestion is that this dialogue has to keep going on if the epidemiologists are to provide studies, that we know in advance can be responsive, and I think we all know that if funds are available for research, we'll all do research. We want to make sure that the research is answering the right questions. I'd hate ten years down the line for somebody to say, "See, epidemiology flunked again". I think we can avoid that if there's enough discussion now so that those designing studies and then carrying them out know what questions need to be answered. It's time to let the next panel have their shot.

BUFFLER:

We were talking about this at lunch -- we said that this was going to be one continuous panel discussion and I think it is. The issues are cross-cutting and with that, I would like to introduce the panel members for the next panel. First of all, our cross-cutting member who is Dr. Frank Speizer, who was willing to participate and will be participating on almost every panel. At my far left, Dr. Tom Mack, from the University of Southern California, and next to him, Dr. Carl Shy of the University of North Carolina and myself as a member of this panel.

I don't want to break the flow of discussion, but just redirect it a bit toward some study design issues. I've outlined some considerations that I want to pose and then we can continue right on with the discussion. The first issue was illustrated by the first panel, that specification of the research questions and the development of available research strategies needs to precede the development of a particular study protocol. We can't talk about designing a type of study in children unless we have a clear operational definition of the research questions.

The second issue I wish to emphasize is about the disciplines that should be involved. I've listed toxicology, clinical medicine and epidemiology, but there are even more disciplines that need to be involved and they must interact not just at the outset of a study, but all through the study informing each other and helping to redirect questions, reinforcing each other and overall complementing each other in addressing the research questions.

The remainder of Session 3 will not be summarized in detail. Each panel member had an opportunity to add comments to the panel chairpersons' summary, based on his or her personal experience.

Dr. Thomas Mack emphasized the principal sources of error which weaken the conclusions of epidemiologic studies. The two most important sources of problems are misclassification and lack of statistical power. He pointed out that only 1/3 of present day Californians are native born (large numbers are from Southeast Asia and from Mexico and Central America). Using "place of residence" is more a life-style factor than an index of present and past environmental exposures. Mack joined others in recommending the study of children, as a way of minimizing the influence of confounding factors such as smoking and occupational exposures. Even with children, one must be careful to make sure these confounding factors are truly excluded.

On the subject of Data Acquisition, Process and Analysis, Dr. Anton-Culver and her panel summarized their experiences in large scale studies such as multi-site cooperative epidemiologic studies or development of disease registries. These were discussed according to the following outline:

A. PUBLIC PRE-STUDY PUBLICITY

1. Professional Organizations
2. Community Newspapers
3. Press Releases

B. STAFF TRAINING

1. Field Workers
2. Data Coders
3. Data Entry Personnel
4. Data Processing Personnel

C. DATA COLLECTION

1. Development of Standard Diagnostic Criteria and Data Dictionary

2. Field Data Collection

   a. Interviews
   b. Abstracting of Records

3. Telephone Interviews

4. Computerized Data from Agencies

   a. Hospital Admissions and Discharges
   b. SSA
   c. Mortality

5. Non-Computerized Data from Agencies

   a. Network of Sentinel Medical Sites
   b. Family Practitioners
   c. Emergency Rooms

6. Procedures for Handling Missing Data

7. Establishment of Denominator Data

D. DATA COMPUTERIZATION

1. Software Selection and Development

2. Data Management and Tracking System

3. Data Coding (ICD9, DOT., etc.)

4. Data Entry

   a. Automated
   b. Manual

5. Data Linkage

6. Maintenance of Data-Base

E. QUALITY CONTROL

1. Visual Quality Control
2. Re-abstraction of Records
3. Re-entry of Data or Alternative Means of Entry
4. Re-interviews
5. Inventory of Records
6. Computerized Editing
    a. Out of Range Checks
    b. Valid Entry
    c. Consistency Checks

F. DATA REDUCTION

1. Linkage
2. Consolidation
3. Geo-coding
4. Data Extract Files
5. Standardized Descriptor Variables

G. IDENTIFICATION OF HYPOTHESES

1. Study Design
    a. Prevalence Studies
    b. Time-based Studies
2. Data Analyses
    a. Semi-automated Analytical Techniques

        Age-adjusted Rates
        Cumulative Rates
        P.I.R.
        S.I.R.

    b. Intelligent Interactive Analyses

H. FEEDBACK

1. Report to Funding Agency
2. Special Requests
3. Scientific Publications
4. Lay Publications

I. DATA ARCHIVING

1. Hard Copy Records
2. Electronic Data

J. ISSUES

1. Non-English
2. Homeless
3. No Telephone
4. Loss to Follow-up
5. Emigration and Mortality

REMARKS
BY
DR. DAVID V. BATES:

On July 31, 1968, Professor Whittenberger and I gave testimony before Senator Muskie's Committee of the U.S. Senate, which was then considering the form of the proposed Clean Air Act. He was asked a lot about how you set criteria for air pollution levels, and about interpreting animal data; and I was asked entirely about acute ozone effects, and I said it was high time we knew a great deal more about Los Angeles. Looking back, I think we both did a fair job in view of the very limited information at our disposal.

We have had a remarkable display of ideas, options, experiences, and expectations. At the start, I want to comment on the problem of expectations. It is a very natural tendency to expect that the kind of data which should drive public policy in respect of air pollution, is data like that on automobile accidents - "hard data" was the term used by one speaker. This is definitive, numerical and non-controversial. Certainly that kind of information can drive policy in relation to air pollution, but there are other kinds of information that should drive policy in this sphere, and these are the kinds you deal with when you deal with air pollution. They are not quantifiable in the same way as automobile accidents, unless you want to wait for a catastrophic episode, as occurred in London in 1952. Further, you cannot assess the benefits of alleviating air pollution in economic terms. If you thought you could, or have tried to do so, read the Report to Congress dated February 1989 *[1]* which contains a very good analysis of why those economic calculations cannot realistically be made. So that you cannot go to the policy maker and say, "We suggest that you spend 2 billion dollars alleviating air pollution because the economic benefit of doing this will be offset by reduction in health costs of 3 billion dollars". What occurs is that you derive information from a number of sources, subject these to detailed examination, and then make a judgement in relation to future policy. The pretence that such a process can be short-circuited by "hard data" has to be undermined at the start.

When we had a war every 25 years, we used to joke that the military was always ready to fight the previous war. I was reminded of this when I thought that epidemiologists, armed with the MRC questionnaire and the FEV_1 (with a satisfactorily low coefficient of variation), tools that were very effective in detecting the consequences of smoking and of acidic reducing air pollution, propose to use the same tools in respect of a quite different form of oxidizing pollution. Are they appropriate? Are these the tools we need to answer the questions about Los Angeles?

The expectations from epidemiologic data are often too high. This, I think, was one of the problems with the CHESS data, to which Professor Whittenberger referred in his introduction. It doesn't matter, if you are trying to get money for epidemiologic research, if you exaggerate the value of the study. Having sat on an epidemiology study section of NIH for four years, I can tell you that everyone does that. But when you come down to describing your findings, you have to be very careful indeed that you are not carried away by the rhetoric you used when you applied. The important thing about epidemiology, is that once the data are established, they stand on their own feet. I mention this because a conference organized by Batelle Northwest to examine animal data in respect of asbestos exposure and cigarette smoking, has recently been published *[2]*. The epidemiological data on this interaction in respect

of lung cancer, is unanimous, indisputable and definitive. In this volume, animal experimenters from around the world discuss what they have learned of the interactive mechanisms. You go all through that book and come out educated on one point, that animal data is in general a poor tool to explain that interaction. Many people talk as if animal data can drive (or confirm) epidemiological evidence. Although very occasionally, it can do this, in most instances, it is the epidemiological data that drives the search for mechanisms using animal exposure data.

The other problem we have touched on is the difficulty of measuring long-term effects. This is quite evident in relation to the old pollution data from Britain. If you go through the data comprehensively, you would conclude that FEV_1 decline was a consequence of cigarette smoking, and then an air pollution episode occurs and administers a "coup de grace" with relationships between mortality and accentuation of pollutants. And then you ask the question: "What effect did those pollutants have on those people over the period of forty or fifty years?". There is very little data on this; but it is biologically implausible, though conceivable, that the pollutants have no long-term effect leading up to the endpoint. The excellent book on the decline of FEV_1 of which Frank Speizer was a co-author *[3]* (it wasn't called that, but that is what it was about), does not mention the impact of air pollution. This is not surprising, because all the subjects studied were living in the same climate and atmosphere, and hence the effect would not be detectable.

In relation to ozone, there is one highly significant concordance. This is between the results of dosimetric modeling and the animal target site for the effect of ozone. Miller's elegant work *[4]* has shown that the regional 0_3 concentration rises as you descend the airway, reaching its highest level in the terminal bronchiole. Also, for the same inspired concentration, the transition from rest to exercise leads to a tenfold increase in delivered ozone to this region. The animal data, obligingly, shows us that this is precisely where the first lesions occur. That concordance cannot be accidental, and it should lead to an immediate consideration of human effects. It leads to the first question: "Does the human autopsy data we were shown, indicate that the human data is also concordant?".

I think that more needs to be done before one can draw that conclusion. The lung lesions obtained from autopsies on young people who had died violently, looked to me like a fairly severe respiratory bronchiolitis. We must recall that it was Niewohner's *[5]* work on the lungs of young smokers who had died of non-respiratory causes, that first demonstrated the lesion of respiratory bronchiolitis of smokers, giving us the morphological counterpart to the early derangement of terminal airflow velocity and closing volume (but, not FEV_1) that had been demonstrated in young smokers; so that we have a model. Is the magnitude of the respiratory bronchiolitis we were shown excessive in relation to the smoking of the individual? Small airway damage can be precisely quantitated, and Wright who has pioneered this effort, has recently summarized the data *[6]*. Furthermore, data from the same laboratory some years ago *[7]*, which was published in a highly respected journal but is rarely quoted, showed that if dilute hydrochloric acid aerosol is administered to dogs, and the resulting morphological changes in the airways are precisely quantitated, that significant function test changes accompany the earliest evidence of induced inflammation. We need more data on the individuals whose lungs are being studied, but I think that a very encouraging start has been made on what is an important endeavor. We would expect the effects of ozone to have an additive effect on the respiratory bronchiolitis of smokers; but, it may be difficult to prove that this is occurring.

The basic question that has been put to us a number of times is: "What is peculiar or distinctive about the population chronically or intermittently exposed to ozone?". In this connection, we heard some discussion about "irreversible endpoints". Let me caution you that these are very hard to define. Is increased airway responsiveness an irreversible endpoint? We know that acquired airway responsiveness, in those exposed to agents in the workplace that induce it, does not reverse after removal from exposure in about half the people affected. It should therefore be classified as an irreversible change. Irreversible cannot therefore be equated with "morphologically identifiable".

One problem with the very carefully conducted Seventh Day Adventist study is that it will tell us a good deal about that population, but cannot tell us about the interaction of the effect of ozone with tobacco smoke. I should note the importance of separating the symptoms of chronic mucus hypersecretion, with increased wheezing and possibly breathlessness, from Chronic Obstructive Airway Disease, which necessarily requires a measurement of the FEV_1 if it is to be rigorously applied.

Reviewing the range of options that have been presented to us, and remembering that several people made the point that no single study can answer the range of questions that exist, I would like to put to you four thoughts. Firstly, about studies on children. We have several reasons why studying 8 to 12 year-olds is a very attractive option. You may be predicting the later development of chronic obstructive lung disease, but this is not, for me the main reason. It is because any indication of damage in that age group would be a clear "dys-benefit". Furthermore, such studies do not suffer from severe sample attrition; and because the subjects can be studied in school, in the yard of which you can set up air monitoring, your estimates of exposure may be closer to reality; and pulmonary function tests can be done, several times if necessary, in the school setting.

There are already two cohorts of Californian children being studied in Monterey and in Livermore in the "24-Cities" Study. You could make six other California communities cities 25 to 30 in this study. It would be easy to have a future programme director involved for several months in the on-going study, seeing children tested in schools, and how the local community is involved, and how the data are handled. If such a course were followed, it would be important to consider adding tests more sensitive than the FVC and FEV_1 to small airway changes; possibly using the techniques applied by Ernst to epidemiological studies of children *[8]*.

The retired population might also be worth looking at. Dr. Tager, in Sonoma in Northern California, has access to a large bank of Veteran's data, and these subjects live in many different parts of California. Might a comparative study, being careful to get rid of occupational influences, tell us something about premature ageing? The possibility is worth exploring.

I may say that I am not convinced that the regional mortality and morbidity data in California has been carefully and thoroughly looked at. I quoted Mahoney's 1971 *[9]* study, showing an apparent relationship between and respiratory mortality. Enough aerometric data now exists for this question to be re-examined. I think it is important that this be done, and of course, it would be relatively cheap.

With regard to exposure data (which we all recognize is central in epidemiological studies) there is a very detailed description in the current issue of the Journal of Air and Waste Management Association *[10]*, in which a detailed computer programme is described for estimating individual pollutant exposures. It involves 56 subdivisions of personal category, from children to retired people; takes account of home conditions and personal habits; and using data on outdoor pollution levels, gives you an estimate of individual exposure. An example is given of the calculated ozone exposure in a child attending school in Los Angeles. It seems to me that this model should be validated by actual measurements using personal exposure monitors. If we could rely on it, it would add a great deal of power to future epidemiological studies, allowing a far more precise estimate of exposures without major cost.

If panel studies are being undertaken, it is essential to define very carefully the population that is being followed. This is the Achilles heel of the famous Whittemore and Korn study *[11]*, in which the elegance and originality of the statistical handling can be contrasted to the very sketchy description of the panel members to whom the data applies. Samet *[12]* has recently contributed a very useful review of this problem in connection with controlled chamber exposures. It is also important to recognize that asthma is such a diverse disease, that a large panel of subjects would be required. We are not talking of twenty or thirty subjects, but of the necessity for 200 or better 500, if meaningful data are to be secured. After all, in a population of 12 million in the Los Angeles basin, you would expect there to be 360,000 asthmatics from which to choose.

The question has been asked as to what happens in Los Angeles in acute air pollution episodes. I know exactly what happens because in Vancouver, I can see reports on television. The reporter is standing in front of a Hospital Emergency Department talking into a microphone, while ambulance attendants pass frequently in the background going into the automatically opening doors. This is great visual material, but it is not exactly data. In Vancouver, in a population of a million people, we have an average of ten emergency room visits to our nine hospitals for asthma each day, year round *[13]*. With a population twelve times greater, there should be an enormous data bank to be studied. Richards et al., *[14]* could find no relationship between ozone and children's visits to a hospital in Los Angeles; but the study only extended over a three month period, which is much too short; and older age groups may be more important than children in relation to air pollutant effects -- at least we have evidence in Vancouver that this may be so *[13]*.

But possibly, the impact of acute effects is not the most important question; indeed the first question you have to decide is whether it is or not. If it is not, then it can be disregarded; if it is, it must be done in sufficient detail to provide a definitive answer; it would be complicated to organize to ensure sufficient quality of input data; but, in theory it is not difficult to do.

We have heard a lot about the difficulty of longitudinal studies. I would like to draw your attention to the best of the early air pollution epidemiological studies, which was by Holland & Reid in Britain in 1965 *[15]*. In samples of postal workers, standardized for socioeconomic status, they determined smoking history, and studied groups in London and in English country towns, where pollution levels were generally about half what they were in London. The FEV_1's were different, and from that cross-sectional study, you can calculate that the London atmosphere probably accelerated the decline in FEV_1 by about -20 ml/year. You could do the same here; and it might be more attractive to plan a very careful cross-sectional study within the Los Angeles basin, and be able to deduce comparative function decline from it, than to try and

secure the data from a longitudinal study. Longitudinal studies not only have the ever-present difficulty of maintaining instrumental stability over a long period, but also the difficulty of comparing rates of longitudinal decline between populations, since often the SD of the rate of decline measured (in ml/yr) is as great as the rate of decline itself.

So I end up by concluding that to answer the many questions that have been put, you will have to adopt different and complementary approaches. There is no one study that could possibly provide a definitive and complete answer. You will recall the Chinese Proverb: "To walk ten miles, you must begin by taking one step". Some of the loose ends could be mopped up without major expense. This applies to the regional mortality and morbidity data, and also to the continuance and elaboration of the autopsy data, for which an excellent foundation has been laid. Pilot studies on children could be initiated, with training of the personnel needed to run it, and with careful forward planning in target communities.

Frank Speizer referred to the 'maturing process' in epidemiological studies after the data had been collected, based on his experience with the "Six Cities" study. You also need a 'maturing process' in thinking about the protocol. As a member of the NIH study section on epidemiology which regularly sent back at least 80% of the applications for reconsideration, I can confirm that the obligatory maturing process often led to the submission of an improved proposal. We liked to think that the applicant had also had time to mature (but, this consideration was rarely, for some reason, appreciated). So, I think I should express the hope that you will devote enough time to the generation of proposals -- ignoring specious 'political' deadlines, and refusing to be stampeded.

I have one last comment. I believe you have a responsibility, not only to the people of Southern California, but to all of us, to define the long-term effects of repetitive ozone exposure, or to prove that they don't exist. What, in 1968, could be described as a problem only in California, has in the interim, become a problem for millions of additional people elsewhere. In Southern California, the resources and expertise exist, if properly deployed, to provide answers to questions becoming important in many parts of the world.

REFERENCES

[1] BLODGETT, J.
Health benefits of air pollution control: a discussion
Congressional Research Service Report for Congress
February 27, 1989. Library of Congress

[2] Biological interaction of inhaled mineral fibers and cigarette smoke
Edited by: Alfred P. Wehner & Dvara-Lee Felton
Battelle Press, 505 King Avenue, Columbus, Ohio 43201-2693
ISBN 0-935470-44-1

[3] FLETCHER, C.M., PETO, R., TINKER, C., & SPEIZER, F.
The natural history of chronic bronchitis & emphysema
Oxford University Press, Oxford, 1976., pp 272.

[4] MILLER, F.J., MCDONNELL, W.F., & GERRITY, T.R.
Exercise and regional dosimetry: an overview
In: Susceptibility to inhaled pollutants, ASTM STP 1024, M.J. Utell and R. Frank, Eds., American Society for Testing and Materials, Philadelphia, 1989, pp 91-99.

[5] NIEWOHNER, D.E., KLEINERMAN, J., & RICE, D.B.
Pathologic changes in the peripheral airways of young cigarette smokers
New England J. Med. 291, 755-758, 1974.

[6] WRIGHT, J.L.
Small airway disease: structure and function
In: CLINICAL EPIDEMIOLOGY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE:
Edited by Michael J. Hensley & Nicholas A. Saunders
Volume 43 in Lung Biology in Health in Disease: Executive editor: Claude Lenfant.
Marcel Dekker, Inc., New York & Basel, 1989.

[7] BAILE, E.M., WRIGHT, J.L., PARE, P.D., & HOGG, J.C.
The effect of acute small airway inflammation on pulmonary function in dogs
Am Rev. Respir. Dis. 126, 298-301, 1982.

[8] ERNST, P., THOMAS, D., & BECKLAKE, M.R.
Respiratory survey of North American Indian children living in proximity to an aluminum smelter
Am. Rev. Respir. Dis. 133, 307-312, 1986.

[9] MAHONEY, L.E.
and respiratory mortality in Los Angeles
Arch. Environ. Health 22, 344-347, 1971.

[10] HAYES, S.R.
Estimating the effect of being indoors on total personal exposure to outdoor air pollution
J. Air Pollu. Control Ass. 39, 1453-1461, 1989.

[11] WHITTEMORE, A.S., & KORN, E.L.
Asthma and air pollution in the Los Angeles Area
Am. J. Public Health 70, 687-696, 1980.

[12] SAMET, J.M.
Issues in the selection of subjects for clinical and epidemiological studies of asthma
In: Susceptibility to Inhaled Pollutants, ASTM STP 1024, M.J. Utell & R. Frank, Eds., American Society for Testing and Materials, Philadelphia, 1989, pp 57-67.

[13] BATES, D.V., BAKER-ANDERSON, M., & SIZTO, R.
Asthma attack periodicity: a study of hospital emergency visits in Vancouver
Environmental Research (In press), 1989.

[14] RICHARDS, W., AZEN, S.P., WEISS, J., STOCKING, S., & CHURCH, J.
Los Angeles air pollution and asthma in children
Annals of Allergy 47, 348-354, 1981.

[15] HOLLAND, W.W., & REID, D.D.
The urban factor in chronic bronchitis
Lancet 1, 445-448, 1965.

SESSION 4

PLANNING OF FUTURE STUDIES
MEMORANDUM ON WORK GROUP ASSIGNMENTS

TO: Participants - Planning Colloquium on Epidemiology and Air Pollution

FROM: Dr. James L. Whittenberger

Please note the following information:

Plenary Sessions will be recorded and transcribed

Tuesday, December 12, 1989: Luncheon will be provided in the Berkeley/Anaheim Room

Session 4: Group Assignments are as follows:

Individuals not listed below can elect to attend the session of their choice

A - Meets: Los Angeles/Irvine Room
Chairman: Dr. James Whittenberger

Anton-Culver	Hayes
Collier	McDonnell
Coulson	Moore
Culver	Newill
Everson	Warren

B - Meets: Suite 208
Chairman: Dr. Jack Hackney

Colome	Ostro
Kleinman	Wilson
Linn	Winer
Lippmann	

C - Meets: Suite 212
Chairman: Dane Westerdahl

Abbey	Mack
Buffler	Menzel
Chapman	Rossiter
Costa	Shy
Gong	

SUMMARY OF PLANNING OF FUTURE STUDIES

This session was an attempt to direct the broad topical discussions of the first three sessions into specific suggestions for follow-up by the Air Resources Board. To facilitate input by as many attendees as possible, the participants were divided into three working groups, each with a specific assignment. The charge to each sub-group is given, followed by a summary of the discussions.

I. Working Group A: Identification of Leadership and Participants in the Needed Research

Charge to Group A:

The Air Resources Board is committed to the support of studies of adverse health effects from long-term exposure to outdoor air pollutants. Emphasis will be placed on epidemiologic studies because unusual opportunities exist in California to determine whether real world exposures are jeopardizing health in the case of pollutants which are known to have potentially adverse effects in short-term exposures under controlled conditions (ozone).

The success of ARB's research planning is dependent on identifying university-based researchers who are qualified and interested in undertaking the required new research. The nature of the planned studies should include epidemiologic field studies of the effects of prolonged air pollution exposures; these might be carried out by a team of investigators from a single institution or by a cooperating group of investigators from more than one institution. Although the studies should focus on California, they could be part of a regional (or multi-state) project.

In addition to well-planned epidemiologic studies, there is a need for additional laboratory studies which would be planned in close coordination, such that all parties would benefit from new information and new ideas obtained from animal toxicology, clinical investigation and epidemiologic studies.

Specific tasks of Group A are to:

1) Inventory present air pollution health effects research in California, including:
   a) field studies (CORD project and others)
   b) controlled human exposure studies
   c) animal studies which are most relevant to epidemiologic studies of chronic exposures to ambient pollution.

2) Identify individuals or groups in California universities that might be targeted to do the needed studies, as principal investigators or potential collaborators.

3) Identify on-going projects which are based outside of California, but which might be extended to California or expanded in California (such as the "24 City" study).

Summary, Working Group A

1. Air pollution health effects research not discussed in the conference:

   Dr. Lippett stated that the Department of Health Services was conducting mortality studies which attempted to relate mortality patterns to acid particle exposures.

   Three UCSF faculty members were said to be interested in air pollution health effects research: Paul Blanc, John Balmes, and Ira Tager. Tager has unusual access to veterans groups that might provide good opportunities for study.

   Drs. John Peters and Stephanie London at USC are interested in broadening their epidemiology research program into air pollution health effects. Most of their previous research has focussed on occupational exposures.

2. Other potential researchers:

   It was emphasized that ARB should not limit potential investigators to those who have previously been identified with air pollution health effects projects. Peters and London, just mentioned, have no past history of air pollution research and should be considered as potential recruits to the field. Going even farther, ARB should consider any group in California that has sufficient quality and strength in biostatistics and epidemiology and related biomedical sciences, independent of any previous association with air pollution-related research. Each group could facilitate development of multi-campus cooperative projects.

3. On-going activities that could be expanded or strengthened:

   Several people expressed the desirability of developing more and closer ties with research activities outside the UC system. Loma Linda and USC were identified specifically as places where there is already strength in relevant disciplines and on-going studies which could benefit from complementary disciplinary input from other campuses. Such associations would be mutually beneficial.

   The on-going "24 Cities" study was mentioned by several people as an opportunity for fruitful collaboration, which could add additional cities in California and perhaps new hypotheses to be tested.

   A specific example was given for a new study that would complement an on-going project:

   a) Choose a sub-sample of David Abbey's non-smoking population, including subjects living in areas of high and low O_3 and high and low total suspended particulates.

   b) Choose 1-4 neighbors of each subject identified in (a), who smoke and are otherwise matched with the subjects in (a).

c) Measure individual pollution and pulmonary function for (a) and (b).

d) Analyze results to separate smoking and air pollution effects.

(Apply for Proposition 99 research funds to support this research.)

II. Working Group B: Field Test Facility Needs

Charge to Group B:

As discussed at the conference, epidemiologic studies of long-term exposures to air pollution require sophisticated and expensive resources for quantifying the atmospheric environment to which the people being studied are actually exposed. Most atmospheric monitoring systems have been set up for regulatory purposes and have little value for epidemiologic purposes. Environmental assessment must take into account not only what chemicals and particles to measure, but where the measurements are made, how often and over what periods. In the past 20 years, it has come to be recognized that epidemiologic studies of air pollution must include total human exposure assessment - not only outside air, but indoor atmospheres, work-place exposures, and life-style factors such as physical activity and smoking.

The group should postulate some general principles about representative kinds of epidemiologic study, with examples of resources required for each. For example, what kinds of studies would require extensive characterization of indoor air?

I. The group considered whether to address exposure only or exposure and health effects; they elected to concentrate on exposure and to state appropriate caveats.

The group adopted a generic approach and sought to make some widely applicable statements about appropriate ways to assess exposure.

One major issue: What are appropriate shares of resources for exposure assessment and health assessment? Priorities are likely to differ between retrospective and prospective studies. But in this group's opinion, in prospective studies a 50/50 split between exposure and health assessment is not unreasonable.

Given budget limitations, range and complexity of scientific issues, a deliberate approach with careful pilot studies to validate <u>both</u> experimental methodology and exposure models is necessary.

II. Needed pilot research efforts.

A. Critical laboratory evaluation and field validation of personal monitors is needed (our consensus is that ozone, SO_2, acid aerosol and PM monitors need a great deal more development before use as definitive personal monitors).

B. Priorities must be set concerning which species should be monitored. Ideally, we should pay attention to non-criteria pollutants and size-resolved chemical composition studies of fine particulate matter. Again speaking ideally, we should not limit monitoring to "most suspect" pollutants as of today. Other suspects may be identified later.

III. Exposure Models

A. Prospective Studies: (1) The ideal is to predict individual exposures with minimal direct measurement. Models should be pre-validated by pollutant specific field monitoring, then re-validated in a sub-sample of the main study population. Shifts in outdoor as well as indoor exposure patterns must be anticipated over a ten year period; models may not be general enough to account for such changes; (2) Models designed to predict population exposures, e.g., NEM, Rehex, are not appropriate to predict individual exposures; (3) Additional field studies are needed to characterize time-activity patterns and influences of various occupational, residential and in-vehicle micro-environments on total exposure.

B. Retrospective Studies: (1) Exposure estimates are necessarily uncertain, therefore useful only when large health signals or large exposure differences are expected; (2) Non-specific, non-standardized monitoring methods make retrospective assessments highly problematical for periods before the 1970's.

Recommendation:

Because of the many dimensions of this problem (many pollutants and potential health effects), ARB needs to focus carefully on the highest-priority issues. Our consensus is that oxidants should receive highest priority.

III. Working Group C: Identification of Knowledge Gaps for Pilot Research Efforts

Charge to Group C:

It is unlikely that a large scale long-term study will result immediately from ARB's research planning efforts. Even though such studies may be in the planning stage, there will be many information gaps that need to be filled. For example, when the "Six City" study was planned, the primary focus was on sulfur oxide pollution; but, there was at that time no satisfactory method for measuring sulfuric acid particles in community atmospheres. Consideration was given to delaying the epidemiologic data collection until a satisfactory acid aerosol method would be developed.

Numerous gaps in formation were noted at the conference and many examples are given in the NAS - NRC report entitled: Epidemiology and Air Pollution (1985).

To the extent possible in the time available, the Group should develop an inventory of important information gaps, and indicate those that should be resolved by pilot studies before larger studies are undertaken.

No summary is available for the findings of this Working Group.

Conclusions from closing plenary session:

1. Dr. Holmes indicated that ARB would take the product of this planning colloquium and ask a small group to develop the best possible long-range plan for ARB - supported studies of effects of air pollutants on human health.

2. An advisory committee should assist ARB in identifying the most important questions to be asked and the hypotheses to be tested in the proposed long-term plan of studies. The committee could also assist in identifying the relevant expertise in academic institutions.

3. Such an advisory committee should include highly qualified statisticians and epidemiologists, but should not be limited to those disciplines. Members should be drawn from other states, in addition to California (for California members, conflict of interest issues need to be kept in mind).

4. ARB should continue to think about cooperative studies, involving multi-institutions, and should continue to seek co-sponsors of funding, such as EPA, NIH, and the Health Effects Institute. Specifically, ARB should explore the possibilities of co-funding by Proposition 99 funds (Tobacco Tax).

APPENDIX

CONFERENCE-DECEMBER 12, 13, 1989

INVITED SPEAKERS AND OTHER ATTENDEES

Abbey, David, M.D.
Evans Hall, #204
Loma Linda University
Loma Linda, California 92350
(714) 824-4959

Amar, Praveen, Ph.D.
Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, California 95812

Anton-Culver, Hoda, Ph.D.
Associate Professor, Epidemiology
Department of Community & Environmental Medicine
University of California, Irvine
Irvine, California 92717
(714) 856-6269
FAX: (714) 856-4773

Avol, Ed
Environmental Health Service
Medical Science Building, Room 51
Rancho Los Amigos Medical Center
7601 E. Imperial Highway
Downey, California 90242

Bates, David V., M.D.
4891 College Highroad
Vancouver, V6T 1G6
British Columbia, Canada
(602) 228-7144, 2722

Boston, Eugene, M.D.
510 West Commonwealth Avenue
Fullerton, California 92632

Buffler, Patricia A., Ph.D.
University of Texas, School of Public Health
Health Science Center at Houston
Epidemiology Research Unit
P.O. Box 20186
Houston, Texas 77225
(713) 792-4644
FAX: (713) 792-4407

Chapman, Robert, M.D.
MD 58
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Collier, Clarence, M.D.
6930 Casa Contenta Drive
Somerset, California 95684
(916) 621-1519

Colome, Steven, Sc.D.
Integrated Environmental Services
University Tower, Suite 1090
4199 Campus Drive
Irvine, California 92715
(714) 854-1167
FAX: (714) 854-1840

Coulson, Anne
Senior Lecturer
UCLA - School of Public Health
10833 Le Conte Avenue
Los Angeles, California 90024-1772
(213) 825-5417
FAX: (213) 206-6039

Costa, Daniel, Ph.D.
MD 82
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Culver, B. Dwight, M.D.
Southern Occupational Health Center
University of California, Irvine
Room 100 Whitby Research Center
Irvine, California 92717
(714) 856-6269
FAX: (714) 725-2070

Dungworth, Donald L., Ph.D.
Professor and Chairman, Department of Pathology
School of Veterinary Medicine
University of California, Davis
Davis, California 95616
(916) 725-1385

Everson, Richard, Ph.D.
Human Studies Division
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

Gong, Henry, M.D.
UCLA School of Medicine
Center for the Health Sciences
10833 Le Conte Avenue
Los Angeles, California 90024-1736
(213) 825-9235

Hackney, Jack, M.D.
Environmental Health Service
Medical Science Building, Room 51
Rancho Los Amigos Medical Center
7601 E. Imperial Highway
Downey, California 90242
(213) 940-7561

Hall, Jane, Ph.D.
Associate Professor of Economics
California State University
800 N. State College Boulevard
Fullerton, California 92634
(714) 773-2592

Hayes, Carl Ph.D.
U.S. Environmental Protection Agency
Health Effects Research Laboratory
HSD (MD-55A)
Research Triangle Park, North Carolina 27711
(919) 541-7739
FAX: (919) 541-4324

Holmes, John, Ph.D.
1102 Q Street
P.O. Box 2815
Sacramento, California 95812

Kleinman, Michael, Ph.D.
Department of Community & Environmental Medicine
Room 100 Whitby Research Center
University of California, Irvine
Irvine, California 92717
(714) 856-4765, 4651
FAX: (714) 856-4763

Laskey, Beverly
1923 Anderson Street
Manhattan, Kansas 66502
(913) 539-7908
FAX: (913) 776-0193

Linn, William, M.D.
Environmental Health Service
Medical Science Building, Room 51
Rancho Los Amigos Medical Center
7601 E. Imperial Highway
Downey, California 90242

Lippmann, Morton, Ph.D.
Professor, Institute of Environmental Medicine
New York University Medical Center
Long Meadow Road
Tuxedo, New York 10987
(914) 351-2396

Lipsett, Michael, M.D.
Department of Health Service
2151 Berkeley Way
Berkeley, California 94704
(415) 540-3322

McDonnell, William, M.D.
U.S. Environmental Protection Agency
Herl-Human Studies Division
Chapel Hill, North Carolina 27504
(919) 966-6220
FAX: (919) 541-4324

McKee, David
Ambient Standards Branch
MD-12
U.S. Environmental Protection Agency
Research Triangle, North Carolina 27711

Mack, Thomas, M.D.
Department of Preventive Medicine
2025 Zonal Avenue, PMB B105
Los Angeles, California 90033

Menzel, Daniel, Ph.D.
Southern Occupational Health Center
Department of Community & Environmental Medicine
Room 100 Whitby Research Center
University of California, Irvine
Irvine, California 92717
(714) 856-8642
FAX: (714) 725-2070

Miller, Paul, M.D.
Assistant Professor
Loma Linda University
Loma Linda, California 92350

Moore, John
Air Resources Board
1800 - 15th Street
P.O. Box 2815
Sacramento, California 95812

Newill, Vaun, M.D.
201 Channel Run
Washington, North Carolina 27889
(919) 946-8244 (Home)

Ospital, Jean, Ph.D.
Southern California Edison

Ostro, Bart, Ph.D.
Department of Health Services
Room 516
2151 Berkeley Way
Berkeley, California 94704
(415) 540-2669

Pitts, James N., Jr., Ph.D.
P.O. Box 669
San Clemente, California 92672
(714) 361-1132

Prasad, Shankar
Air Resources Board - Research Division
1800 - 15th Street
P.O. Box 2815
Sacramento, California 95812

Richmond, Martha, Ph.D.
Health Effects Institute
215 First Street
Cambridge, Massachusetts 02142
(617) 491-2926

Rossiter, Charles
London School of Hygiene
Department of Occupational Health
Keppel Street
London, UK WCIE 7HT
59 Warwick Avenue
Harrow, HA2 8RE England

Samat, Jonathan, M.D.
Professor of Medicine
Chief Pulmonary Division
Department of Medicine
University of New Mexico
Albuquerque, New Mexico 87131
(505) 277-5541
FAX: (505) 277-8572

Shy, Carl M., M.D., Dr. P.H.
NCNB Plaza Suite #32
CB 7400
University of North Carolina
Chapel Hill, North Carolina 27514

Sherwin, Russell, M.D.
University of Southern California
Department of Pathology
2011 Zonal Avenue
HMR 201
Los Angeles, California 90033
(213) 224-7475

Speizer, Frank, M.D.
Harvard Medical School
Channing Laboratory
180 Longwood Avenue
Boston, Massachusetts 02115
(617) 732-2275

Warren, A. Jane, Ph.D.
Director of Research
Health Effects Institute
215 First Street
Cambridge, Massachusetts 02142
(617) 491-2926

Westerdahl, Dane
Senior Air Pollution Specialist
Air Resources Board - Research Division
1800 - 15th Street
P.O. Box 2815
Sacramento, California 95812
(916) 323-1522
FAX: (916) 322-4357

Whittenberger, James L., M.D.
Department of Community & Environmental Medicine
Room 100 Whitby Research Building
University of California, Irvine
Irvine, California 92717
(714) 856-7240
FAX: (714) 725-2070 OR (714) 856-4773

Wilson, Katherine, Ph.D.
1011 Hayes Avenue
San Diego, California 92103
(619) 295-8084

Winer, Arthur M., Ph.D.
Director of Environmental Science and
Engineering Program
Department of Engineering Health Science
University of California Los Angeles
Los Angeles, California 90024
(213) 206-1278