Environmental Health Perspectives
Vol. 78, pp. 139–155, 1988

Summary of Discussion Sessions: Symposium on Lead-Blood Pressure Relationships

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The International Symposium on Lead-Blood Pressure Relationships was held in Chapel Hill, NC, April 27–29, 1987, with sponsorship from the Councils on Hypertension and Epidemiology of the American Heart Association; the Department of Epidemiology, University of North Carolina; the International Lead Zinc Research Organization; and the U.S. Environmental Protection Agency. The program was structured so as to first present an overview of theories and findings in the general area of human hypertension and then to have speakers review the extant literature on lead and blood pressure relationships, including papers on the human observational studies of lead and hypertension; related studies of lead and human hypertension; occupational studies of lead and hypertension; experimental studies of lead and hypertension; and papers presenting related information from work in progress. Invited discussants, invited speakers, and other workshop participants were encouraged to ask questions and to discuss needs for future research. This report summarizes key exchanges of information during discussions after individual papers were presented or during separate discussion sessions. It also summarizes presentations by several speakers who declined to publish in these proceedings full-length papers on ongoing work.

In the first plenary session, the three speakers (H. A. Tyroler, A. Chobanian, and C. Hennekens) gave overview presentations on the epidemiology of hypertension as a public health problem, mechanisms of hypertension, and the impact of reducing high blood pressure on more serious cardiovascular sequelae. These talks oriented the audience and participants to the types of studies and methods of analysis necessary to consider the possible influence of lead on blood pressure and other cardiovascular effects and reviewed the multiplicity of mechanisms that may influence the measured outcome of a change in blood pressure. Only limited discussion followed these introductory papers, with resulting clarification of certain key points concerning the relative role of various known or suspected risk factors for hypertension and associated sequelae. The next plenary session included a series of papers that discussed human observational studies of lead and hypertension, with special emphasis on additional analyses of National Health and Nutrition Survey II (NHANES II) data and further analyses of data from the British Regional Heart Survey. During discussions following these presentations, aspects of the NHANES analyses were clarified.

J. Schwartz (U.S. EPA) commented that he used P. Gartside's (University of Cincinnati) regression models with interaction terms for age and found none of the interaction terms to be statistically significant. Using somewhat larger age groups than Gartside did, he found that lead was statistically significantly associated with both systolic and diastolic pressure in all 30 age groups. He questioned whether or not the failure of Gartside to observe statistically significant effects was due to small sample size subgroups. Gartside doubted that the difference between the 20- and 30-year age groupings was meaningful. He noted that it was not infrequent for two individuals analyzing the same data set to come up with totally different results. Schwartz, although agreeing with this and noting its relevance to Fort's findings (Schwartz obtained statistically significant coefficients on regression analyses for both systolic and diastolic pressure including all 64 geographic sites in his regression), pointed out that an Expert Peer Review Panel convened by EPA, as well as a review committee of the EPA Science Advisory Board studying both his and the other NHANES analyses, accepted the Schwartz version. Schwartz added that

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inclusion of the 64 sites in his regression analyses reduced the magnitude of the regression coefficients by about 30%, not by the stated factor of three.

O. Carter (NCHS) questioned whether the Hispanic-NHANES analysis was restricted to Mexican-Americans. B. F. Fort (Ethyl Corporation) answered in the affirmative, but pointed out that the analyses presented to date were preliminary and that a corrected data set was to be analyzed in the future. Carter pointed out that the revisions involved only three persons and that should not change the analyses. Carter emphasized that others using the Hispanic-NHANES data should distinguish among Mexican-Americans, Puerto Ricans, and Cuban-Americans. Carter noted that acculturation, which may affect blood pressure levels, and birth place should be explored for their relationships to lead and blood pressure. K. Mahaffey (NIOSH) questioned whether there was a continuation in the decline of blood lead levels in the Hispanic NHANES. Schwartz responded that, although the blood lead levels in Hispanic-NHANES were lower than in NHANES II, one must acknowledge that there are population differences. Any attempt to separate out the Hispanics in NHANES II would be subject to the difficulties of small sample sizes. S. J. Pocock (University of London, UK) noted that the regression coefficient which Fort obtained for the relationship of lead to diastolic blood pressure was 1.96, a value quite similar to the coefficient of 2.1 in the British data. He also noted that when adjusting for site, the British coefficient moved from zero to slightly positive. The NHANES coefficients, when adjusted for site, were reduced to values that were still positive but of smaller magnitude.

There was a discussion regarding the reproducibility of results based on analysis of the same data set. Fort and Gartside reported that they were unable to reproduce Schwartz's results, whereas the University of North Carolina group obtained exactly the same results as Schwartz, using precisely the same subjects, variables, models, and analytic techniques.

P. Boscolo (University of Chieti, Italy) stated that lead exposure is associated with cadmium and other pollutant exposures and that interaction effects have to be considered.

L. Grant (U.S. EPA) opened the general question session by identifying several key issues: the significance of adjustment for site, for geographical location, analyses within different age groupings, and the implications of any blood lead-blood pressure associations for major morbidity and mortality cardiovascular outcomes, such as strokes or heart attacks.

D. Roxe (Northwestern University) inquired about the measurement techniques used for lead and blood pressure, whether subsets of the populations had had recent acute exposure and what environmental sources are considered the major sources of lead. Schwartz reported that NHANES blood lead measurements were taken in specially loaded vacutainers that were treated to be trace element-free. Quality control indicated a coefficient of variation of blood-lead levels of approximately 15%, equivalent to a confidence interval of approximately ± 2 μg/dL on the blood-lead determination. W. R. Harlan (University of Michigan) commented that blood pressure in NHANES II was taken on three occasions, seated at the beginning, supine midway through, and a second seated blood pressure near the end of the examination. Systolic pressure was recorded as the initiation of Korotkoff sounds and diastolic pressure as cessation of sounds (K-5). There were a large number of observers, trained to record blood pressure in a standard manner. Regarding acute exposures to lead, the only historic information was the 24-hr dietary recall. Those people who have had a significant number of calories on the day prior to examination were also the people reporting the highest intakes of alcohol as their habitual consumption. Schwartz remarked that the half-life of lead in the blood was typically 30 days and that a single, higher-than-average exposure dose is not going to have major perturbing effects on adults' blood lead levels. Individuals who work for lead exposure industries, as classified by NIOSH, were excluded from the sample. Exclusion of these individuals resulted in a slightly higher regression coefficient, which was still significant.

Pocock remarked that the methodology of blood lead was more important than the methodology of obtaining blood pressure in these studies. Blood lead was measured under strict quality control methods at the leading British laboratory. Blood pressure was recorded on the London School of Hygiene zero-muddler sphygmomanometer. There were three observers per town. In addition to training to correct for observer variation, observer differences were adjusted for in the analyses. Pocock doubted that single exposures to alcohol would have meaningful effects. It was his opinion that food and water sources would be important causes of blood lead levels in the general population, in addition to effects of heavy drinking and smoking. Lead is still in British gasoline and is being removed gradually and is lower than it was previously. This will influence the lead in dust, air, and food. He was not aware of any occupational or ambient environmental problems from lead smelters influencing his data. Schwartz commented that in the United States there was a larger amount of lead in the general population coming from gasoline than in England and lower amounts coming from water. He estimated that approximately half the lead in the general population in the 1970s was based on gasoline as the primary exposure, accounting for higher levels in urban areas.

M. Galvin (NIEHS) questioned the differences in sample size between the Schwartz and DuPont analyses. Schwartz responded that DuPont did not use the same covariates that he did and that given some missing covariate values there were resulting slightly different sample sizes. Grant added that there are also some differences in the subjects included or excluded.

R. Lilis (Mt. Sinai, NY) raised questions regarding

the comparability of the British and American studies on the distribution of the blood lead levels in the two populations, the existence of a similar secular trend in the United Kingdom and the United States, and information regarding trends in blood pressure levels in the United Kingdom compared to the United States. Mahaffey inquired about hypertensives receiving medication in the British studies, were they excluded, at what level of blood pressure would medication be prescribed, and regarding the distribution of blood lead levels, what information is available regarding quality control and intake of lead? Pocock thought there might be a slight tendency to higher blood lead levels in NHANES II but that in general the distributions would be similar. Schwartz indicated that the mean blood lead level in the NHANES population was approximately 17 μg/dL. Pocock indicated that it was 0.76 μmole/L (equivalent to 13 or 14 μg/dL) in the British studies. The proportion of individuals with values over 30 μg/dL was small, suggesting generally similar ranges of blood lead in the two studies. Pocock suggested that there are not good epidemiologic data at present on trends in blood lead levels in the British experience. Such data are being assembled now and for monitoring over time with the removal of lead from gasoline.

P. Elwood, Medical Research Council (MRC, UK) has assembled several different approaches to this question and he reported consistency among them of a fall of about 4% per year over the last 10 years in blood lead levels prior to reduction of lead in gasoline. Pocock commented that there are not good data on trends in blood pressure, but he suspected that there have not been substantial trends. He added that hypertensive medication is not as intensive in the U.K. as in the U.S. Further, it was his opinion that treatment was not initiated until relatively high levels of diastolic blood pressure were observed. Elwood concurred that blood pressure changes over time have been minimal and that there is no good evidence either in trends in blood pressure or antihypertensive treatment in Great Britain.

Lilis referred to data from Scotland relating levels of lead in drinking water to blood lead, kidney function, and hypertension, data which were not presented by Pocock in his formal paper. Pocock responded that he restricted his analyses to the blood lead-blood pressure relationship. Lilis remarked that Pocock's data suggested that the localities which had higher blood lead levels were the areas of soft water and that the source of lead, whether it comes from water, air, gasoline, or other sources, is actually of secondary importance in this discussion of the effect of lead on blood pressure. Pocock concurred and justified his discussion of the association of higher blood pressure with water softness in his presentation as of background descriptive interest only. Pocock added that he included individuals on hypertensive medication in his analyses since their exclusion could lead to a bias due to their higher than average blood pressure values. Fort commented on studies of two towns in Massachusetts in which an association was detected between sodium chloride content of the water supply and blood pressure levels of school children, controlling for other relevant variables. He questioned whether there were other variables depending on location, water supply, and sodium chloride specifically, which could affect blood pressure, and had not been controlled for in the data sets under consideration.

D.-L. Zhu (University of North Carolina) inquired about the relationship between erythrocyte protoporphyrin, body burden of lead, and blood pressure in the NHANES cohort. Schwartz noted that erythrocyte protoporphyrin did not correlate with blood pressure levels in the NHANES studies. He indicated that in the general adult population, erythrocyte protoporphyrin is dominated by iron status and is a poor predictor of lead status; this is in contrast to a child eating lead paint chips who has marked elevation of blood lead and marked elevation of protoporphyrin.

S. T. Weiss (Harvard Medical School) commented on the implications of adjusting for site by pointing out that site may in fact be a link in the causal chain of the blood lead-blood pressure association, because site is associated with water or air sources of lead and, consequently, is the major determinant of blood lead. It was his opinion that this distinction between whether site is a confounder or a link in the causal chain could not be resolved with cross-sectional data and that a longitudinal study of changes in blood lead and blood pressure was one potential way of resolving the issue.

A. J. Vander (University of Michigan Medical School) questioned the relationship between decreases in lead and the time necessary for an associated decline in blood pressure, assuming that lead had contributed to a rise in blood pressure. In particular, he inquired about the effect on statistical associations if over a 4-year period when lead was decreasing, blood pressure did not decrease. Schwartz responded that the question did not relate to the observations, since controlling for all other factors, blood pressure did change over time with changes in blood lead. Vander was skeptical about the time changes in blood pressure, but, assuming that blood pressure actually did decline, did it do so for reasons other than lead? Schwartz responded that elaborate, detailed models, including control for many potential confounders, failed to eliminate the blood lead–blood pressure association. This included site- and time-related variables.

W. Kannel (Boston University School of Medicine) commented on blood pressure trends. It was his opinion that there was no way to know whether blood pressure actually changed in the general population. There has been a massive amount of treatment introduced over time, the indications for treatment have changed over time as well, and currently, physicians in the United States are treating people with lower blood pressure. Under these circumstances, it is difficult to determine whether the prevalence of hypertension has changed over time. Harlan noted that com-

parison of the distributions of blood pressure in NHANES I and NHANES II, i.e., between the early and the late 1970s, and suggested that the differences were primarily at the upper end of the blood pressure distribution and suggested that treatment is one of the major reasons for the decline and that there are only small changes in mean values. Schwartz indicated that this is one reason his group did analyses excluding people on hypertensive medication, although he acknowledged that this approach results in truncating the sample.

D. G. Beevers (University of Birmingham, Scotland) attempted to reconcile the apparent disparities between the U.S. NHANES and the British Regional Heart Studies. He suggested that participant selection may have been partially responsible in that there was oversampling of disadvantaged persons of relatively lower social class in NHANES and unintentional selection of higher social class individuals in the Regional Heart Study. Pocock indicated that an attempt was made to select a general practice that was representative of its community in each town in the British Regional Survey. However, there was only a 78% response rate of individuals coming in for screening. He noted that the distribution of manual to nonmanual workers in the sample was generally similar to that in Great Britain; however, there was a slight underrepresentation of unskilled manual workers and a slight overrepresentation of the professional classes.

Schwartz indicated that there was in fact an oversampling of lower social status individuals in NHANES, but this was done by design in advance and sample weights were created, so that by weighing these people less than others it was possible in a weighted analysis to get back to a sample representative of the U.S. population. Weights also were assigned to adjust for nonparticipation in examinations, based on the fact that 97% of the persons selected had demographic and medical history information obtained from a home interview.

Grant opened the question and discussion period of the panelists. H. Smith (Statistical Consultant) queried Pocock and Schwartz as to whether each had carried out regression analyses within each site, which would permit site-specific estimation of the blood lead-blood pressure association controlling for the other major covariates. Pocock indicated that his final model contained adjustments for body mass, age, alcohol consumption, social class, and smoking categories in addition to 23 dummy variables to adjust for differences between towns. The number of individuals within each site, approximately 300, were too few to permit site-specific detailed analyses with multi-covariables. Schwartz responded that he could not do site-specific regression analyses because for the 40 to 59 year olds there were 543 people in 64 sites, and the information available per site would be markedly limited. Smith inquired about separate analysis at each site and then a meta-analysis of the derived coefficient across all sites. Smith suggested this (which had not been done) would be similar to the Landis approach, which was a pooling using the Mantel-Haenszel statistic across subgroups. Smith reiterated that what he was interested in was the magnitude of the regression coefficient across the groups and not the significance level. The magnitude of the estimated change in blood pressure per unit change of blood lead was of primary interest to see if any association detected was of importance. He stated that inference was the issue, not the test of hypothesis. Further, he argued that the selection criterion for admitting variables in a stepwise procedure, which mandates establishing a significance level to admit or discard a variable, is something that ought to be avoided or used only with caution. Schwartz responded by indicating that he had adopted a model with variables generally agreed to be associated with blood pressure, i.e., sex, age, body mass, and race, and then, since blood pressure has been hypothesized to be a multifactorial outcome, to have included a large number of dietary, serum micronutrient, demographic, and other factors which have been found associated with blood pressure in some studies. His approach was to see how stable the blood lead coefficient was, including or excluding these variables and under that circumstance using the stepwise regression analysis approach. Schwartz emphasized that this approach was not used to establish a model for blood pressure, but rather to test for the stability of the blood lead-blood pressure relationship as he expanded from the biologic model that included universally accepted variables to models that included variables that others have speculated about.

Smith queried R. Landis (University of Michigan) regarding the rationale for adopting the procedures he had used and which are discussed in detail in his formal paper. His response was that the expected value and variance in each subtable is computed conservatively under a fixed margin assumption. It can be viewed as a randomization model in which the beta coefficient at each site can be estimated. Given the expected value and the variance for that component based on the fixed margins of a conservative Fisher exact kind of hypergeometric framework, you can see whether or not the observed cross-product tends to exceed its expected value on average across very small subgroups of individuals. In the extreme, this would be the matched pair design adjusting for all the covariates; although not done yet, it could be done and to determine whether on average, the matched pair tends to favor the elevated level of pressure being associated with elevated level of lead. Landis prefers this to a multiple-regression model with 63 site parameters. Additionally, the procedure permits adjustment for the role of 64 sites without incorporating the site effects into the estimation of the partial beta coefficient. All the statistical power is focused on estimating one beta coefficient adjusted for all the other covariates. That beta coefficient has a test statistic that is nearly identical to the Mantel-Haenszel. In response to a question from Grant, Smith responded that he had never seen the

Mantel-Haenszel procedure applied this way before and he was not certain whether the application was appropriate.

Kannel commented that it was necessary to return to basic epidemiologic principles and to evaluate whether or not a causal association is present. He set out the following criteria: to determine whether the observed relationship was found consistently, whether the association is strong, whether it is dose related, if it is biologically plausible, whether it can be reproduced experimentally, and finally, if it is present when taking confounding variables into account. Based on the information presented, he believed the effect of lead on blood pressure appears to be modest; however, within a population context, given ubiquitous exposure, the population attributable risk can be large, and this has public health implications. However, he believes that more information is needed. The shape of the dose-response relationship of lead to blood pressure is not clear. Is there an effect on blood pressure at toxic exposures over the limit of 30 or 40 μg/dL? More information is required regarding mechanisms. Is the effect short term or long term and cumulative? Kannel noted that for hypertension in general, even for the strongest of known population risk factors such as obesity, mechanisms are unclear and so the absence of this knowledge is not unique to lead. In assessing the role of potential confounders, Kannel felt that, in place of "mindless statistical numerology," it would be preferable to have and test specific hypotheses as to how lead might affect blood pressure in a population. Finally, he noted that lack of knowledge is no excuse for inaction, if we know that there is a possible relationship and a modifiable population environmental exposure. However, Kannel did feel that there is a need to establish the nature of the association more precisely.

H. Dustan (University of Alabama) summarized her reaction to the materials presented by stating that she regarded the evidence as quite unclear whether lead has an effect on blood pressure in large populations. She agreed with Kannel that it was difficult to know which of the multitude of analyses with different results was correct.

The next plenary session was devoted to four related studies of lead and hypertension. Following D. Kromhout's (State University of Lieden) presentation on the Zutphen Community Study of elderly men, Boscolo commented that the effects of lead exposure are very different in young and old persons. He suggested that the effects of lead exposure in younger individuals would be mediated via mechanisms regulating blood pressure through the brain and kidneys. Pocock questioned whether Kromhout would have published his findings had they not been statistically significant (referring to the issue of publication bias). Kromhout answered that he would have published the findings regardless of the outcome, but would not have published the blood lead-blood pressure results separately. Lilis commented that removal of one outlier observation of an individual with high blood lead and very high blood pressure resulted in the absence of a significant relationship between blood lead and blood pressure in Kromhout's presentation. Kromhout responded that removal of the one outlier resulted on univariate analysis in a borderline statistically significant relationship between blood lead and systolic blood pressure and absence of an association of blood lead and diastolic pressure, but that the association no longer was statistically significant upon adjustment for body mass index and age.

Lilis further discussed the appropriateness of including or excluding the outlier in the final analysis. Smith commented that the decision rests upon the range of inference to be made. If, in fact, the outlier is in the range of inference, then obviously it has to remain in the study. Alternatively, if the range of inference is restricted to lower values, then it would be inappropriate to include it. Schwartz questioned the effect on the magnitude of the regression coefficient including and excluding the outlier. Kromhout responded that there was only a small change in the magnitude of the regression coefficient, but the p value became 0.06, i.e., no longer conventionally statistically significant. W. Lee (University of Manchester, UK) raised the possibility of a threshold response of blood pressure to blood lead levels. He interpreted the data presented as showing very little effect of low blood levels on blood pressure, suggesting a horizontal dose-response relationship with an upturn in blood pressure response at some threshold value. Recognizing the limitations in one observation, he suggested that perhaps the outlier might indicate where the dose-response curve for the blood lead-blood pressure relationship is beginning to turn up.

Landis disagreed with Lee's interpretation of the dose-response relationship. He interpreted the NHANES data as showing an association of blood pressure with blood lead down to levels of 5 μg/dL. He suggested that, if anything, there is evidence that the response of blood pressure may taper off at the higher levels of lead. Landis commented that if there is a threshold, it is for higher levels than those observed in the NHANES data. Schwartz reported that he had tried fitting a threshold model in the NHANES data and had failed to find evidence of a threshold. He disagreed with the characterization of an outlier in the Kromhout data, arguing that the single value does not change the slope of the relationship much while being influential with respect to the significance level, and therefore it was not an outlier in the sense that there is a different relationship at the observed level and at lower levels.

After T. Moreau's (INSERM) presentation, H. Gonick (Cedars Sinai, CA) requested some clarification of the conclusions regarding lead's effect on red cell membrane lead content and cation transport systems. If lead binding to red blood cells affects Na^+/K^+ ATPase, one would expect to see a positive correlation between the two. Since that did not occur, one could reverse the question and ask if the total blood lead or membrane-

bound lead is a reflection of an active transport abnormality characteristic of hypertension. Dustan also queried Moreau concerning the lack of correlation between membrane-bound lead and cotransport systems, in particular, how calcium may interact with lead. Moreau indicated that his group was disappointed in this particular finding, but there may be a positive relation of membrane lead and K^+ channels. He suggested that the sulfhydryl groups of the Na/K ATPase enzyme are probably reacting with lead, even though the enzyme activity was not affected.

A. Johns (University of Miami) asked if inhibition of this cotransport system could be responsible for the increased contractility in smooth muscle cells of blood vessels. Moreau replied in the affirmative. Johns said a similar pump exists in uterine smooth muscles that appears to be furosemide insensitive but it is still responsive to agonists causing contraction.

Following the presentation of the paper by Weiss, Schwartz questioned the findings over time and whether or not a single measurement of blood lead lost power as a predictor of blood lead levels in successive years. Weiss responded that in the context of this model, it was necessary to treat blood lead as a fixed covariate, i.e., the assumption had to be made that blood lead does not change over time. Landis asked whether lead was analyzed as a continuous variable, rather than categorically as intermediate and high. This was of importance, since there was a large representation in the upper levels, i.e., 22% of the men. Weiss indicated that this had not been done; the data were simply categorized at the start of the analysis.

Landis indicated that the Weiss study included a large proportion who would be in the upper end of the distribution of the general population, i.e., in NHANES II. Kannel questioned the associations of alcohol intake with blood pressure in the study and asked whether or not Weiss was implying that the alcohol-blood pressure association is entirely due to lead. Weiss responded that the distribution of reported alcohol consumption in his sample was similar to that reported by the average American. He suggested his findings may reflect reporting bias. Regarding the association with blood pressure, he pointed out that all men in the study were normotensive and that the findings might result from a relatively small study of limited power. He did not believe any of his results vitiated any of the earlier studies regarding the relationship of alcohol to hypertension or alcohol to blood lead levels. It was just that the alcohol association with blood pressure was not demonstrable in his (small) cohort.

Gonick asked the first question about R. Wedeen's (V. A. Medical Center, E. Orange, NJ) presentation; it concerned whether the EDTA lead mobilization test or the X-ray fluorescence bone lead measures of lead burden had been correlated with any blood pressure measurements. Wedeen responded that the limited number of subjects did not make such analysis suitable. A follow-up question from Gonick asked the relationship of these two measures of lead to that in the postulated target tissue for hypertensive effects, e.g., vascular tissue. Wedeen did not feel this was likely to be the target tissue. He plans to examine platelets and their calcium metabolism further, as well as endothelial repair. Moreover, lead concentrations may not be perceptibly higher in any target tissue. Gonick asked Wedeen to consider as toxic, the lead in the ionized form circulating in extracellular fluid, platelets or vascular tissue. Wedeen agreed that lead in bone (while being the best measure of past exposures) was unlikely to be indicative of damage to the bones; however, it is available for exchange with extracellular fluid and consequently to other tissues.

P. Grandjean (Odense University, Denmark) brought up various concerns about the use of X-ray fluorescence for lead burden measurements; the technique involves use of X-rays, it is expensive, and the measurement obtained varies with bone type. In addition, in renal failure dialysis patients, the serum level of aluminum is elevated. Aluminum binds to and affects bone hydroxyapatite, especially its ability to respond to homeostasis of serum calcium by parathyroid hormone. Therefore, bone metabolism of lead may be considerably altered in those patients with concomitant bone disease. Wedeen (in collaboration with scientists in the Netherlands) has histomorphometric evidence that the amount of lead in bones of renal disease is not altered.

Dustan queried if there is a difference between races with regard to renal disease. According to Wedeen, blacks are overrepresented in dialysis units; in spite of small numbers, he found these blacks had higher lead levels. Unfortunately, in clinical research, the number of patients studied is necessarily limited.

Vander asked for clarification on the ability of the X-ray fluorescence method to detect low level lead exposure. Dr. Wedeen indicated at present that detection limits are approximately 10 ppm with an error of 10 to 20%. Values in the general population are expected to be 6 ppm; therefore, the technique may be useful in selecting high risk groups. Vander was actually more concerned about the lack of correlation in the bone lead content with respect to the constant amount of lead measured in the EDTA mobilization test. Wedeen stated that the total number of patients has been rather limited when compared to the numbers in epidemiologic studies.

The next plenary session consisted of three presentations on persons who were occupationally exposed to lead.

Following the presentation of W. C. Cooper (physician-consultant) on his lead mortality study, there was a question from P. Pontzer (Federated Fry Metals Company) as to whether Cooper had attempted to correct for incompleteness of data on the death certificates used in the study. Cooper responded in the negative because he felt that the same correction could not be done for the comparison groups. Kannel then questioned why lead battery workers were separated from smelter workers, since he felt that if you combined the

data of lead-exposed workers and compared these data to the general population, a level of statistical significance would be achieved for some of the outcomes. Cooper indicated that he had carried out such an analysis, but it did not alter the results enough to be justified. Furthermore, these two groups of workers are in different plant operations and thus have different possibilities for confounding exposures which are important for assessing relationships with various types of cancer, specifically lung cancer and stomach cancer. Cooper suggested that if the age distributions and different hire distributions of these populations were examined, one would feel more comfortable seeing these two groups separated.

J. Bosch (George Washington University) asked whether there was any knowledge of workers that developed chronic renal failure and then died, to which Cooper indicated that he did not know about such cases. Lilis suggested to Cooper that since higher exposure levels were found in the smelters as compared to the battery plants and higher mortality rates for chronic renal disease were seen in the smelters, this would indicate that there is a dose-response relationship. Cooper responded that the data appeared consistent with that hypothesis.

Smith then asked what the total population of workers available to exposure was in the smelter and battery plants and their person-years experience. Cooper stated that battery plants had roughly 100,000 person-years and the smelters had 50,000 person-years.

After S. Selevan's (U.S. EPA) paper, Gonick asked a question concerning Selevan's designation of high lead vs. high lead/low other for exposure levels in her study. Gonick felt that the high lead/low other designation might be different for chronic nephritis than for cancer. For example, arsenic does not have an adverse effect on kidney function, but is presumably carcinogenic. On the other hand, silicon, copper, cadmium, and perhaps gold and silver do have an adverse affect on the kidney. Gonick suggested that a regrouping of the high lead/low other classification looking specifically for the silicon and cadmium effects on chronic nephritis might give a somewhat different insight to the current groupings in the study. Selevan responded that there would only be fairly minor differences, since the expected and observed were so low. Selevan suggested that NIOSH take a look at Gonick's suggestion.

R. Goyer (University of W. Ontario, Canada) then questioned whether the use of autopsy material, as well as information from death certificates, might give a better view of the nature of the renal disease and possibly the incidence of renal tumors in the study population. Selevan agreed and indicated that NIOSH had recently collected some pathology reports for such a purpose. Dustan then noted that there was no increase in hypertension-related deaths, but wondered whether there was an increase in hypertension in the overall cohort. Selevan indicated that there was no information on this because the mortality study only included those things which find their way to the death certificate. Dustan suggested that this information might be found through annual physical examination records. Selevan stated that this was not necessarily so since there was not a lot of information on blood leads in the older medical records and since annual physical exams were not carried out at the plant.

H. A. Tyroler (University of North Carolina) then asked whether Selevan examined multiple cause coding and whether or not in proportionate mortality terms or in relationship to high exposures, there were more instances of hypertension and hypertension-related conditions as secondary causes of death. Selevan indicated that a secondary analysis was not done except for silicosis. Tyroler suggested it might be informative to do a secondary analysis.

Boscolo noted that Selevan's cohort consisted of a peculiar population of workers exposed not only to lead, but also to cadmium, arsenic, copper, and other elements, not only at work, but at home. He felt it would be difficult, therefore, to compare the data of this study to other data on people exposed only to lead. Selevan agreed with this observation, remarking that it was difficult to know what type of interactive effects may be occurring and what effects may be caused by other kinds of exposures. It is extremely hard to determine definite conclusions from this type of work.

Following W. L. A. M. de Kort's (Ministry of Social Affairs and Employment, the Netherlands) paper, Dustan noted that an increase in the average arterial pressures for both systolic and diastolic blood pressures was observed. Also, among the lead workers as opposed to the controls, there was a bit of an age difference between the two groups with the workers being a little older than the controls. Dustan noted that this age difference becomes very important in regard to blood pressures. Dustan then asked whether there were people with real hypertension, people with diastolic pressures greater than 105, or was this just part of the aging process. de Kort responded that mixed pair analyses had been done and consistently a difference in systolic blood pressure was found. The diastolic blood pressure was not statistically significant in the mixed pairs analyses.

de Kort noted that there were problems in obtaining exposure levels at the plant. There was an indication that the time-weighted averages appeared lower than the threshold limit value, which was 105 $\mu g/m^3$ at the time, but peak values often exceeded 10-fold this threshold limit value.

Lilis stated that she thought that not adjusting for body mass in a hypertension study was such a drawback that one could not possibly draw any conclusions. de Kort disagreed with this, stating that he had not seen studies where body mass index and blood leads were highly correlated, and, furthermore, if body mass index had been included, there would have been a risk of overmatching in such a small group which would be very serious. de Kort then noted in response to another question by Smith that the time frame of his

data collection was one month.

Lee noted from listening to all papers presented so far at the conference that there appeared to be a very slight rise of blood pressure over a range of blood leads, something like a 2-mm Hg/10 μg Pb/dL blood. Yet, in the first two mortality papers, there were observations of people dying from renal disease and perhaps hypertensive disease, from some rather ill-defined but generally accepted very high blood lead levels. Lee suggested that perhaps something was occurring at higher levels of exposure or that lead was having an effect in higher doses and producing renal disease without producing marked hypertension. de Kort responded that when people are exposed to high lead levels, effects will show up that will not necessarily show up at lower levels. Also, de Kort stated that he disagreed with the theory put forth by Wedeen that the kidney is of importance in the hypertension relationship. He believes it is the vascular wall that is important. However, if one is exposed to insoluble lead components, most of the material remains in the lungs. So, perhaps the lung is the target organ where the angiotensin converting enzyme plays a role in generating vasoactive agents.

Schwartz remarked that he was disturbed by hearing people talking about very small effects and called the audience's attention back to the original comments made at the beginning of Monday's session on attributable versus relative risk. He stated that he did not believe that anybody who has done work on lead and blood pressure thinks that lead is the principal determinant of blood pressure. Furthermore, everyone agrees that the slope of the relationship with body mass is much bigger and more stable than blood lead. The problem is that it is very difficult to change people's body mass index. It is even more difficult to change their age, and that goes in one direction as far as we can tell. In terms of a slope of 2 mm for a 10 μg/dL change in blood lead, Schwartz felt that that was roughly in the ballpark of the results that he found in his study and that Pocock found in his study. To put that into perspective, Schwartz noted that there had been almost a 10 μg/dL change in the average blood lead level of American adult males since the mid-1970s. If, in fact, 10 μg lowered the average systolic blood pressure in the United States by 2 mm Hg, then everything we have seen from prospective cardiovascular disease studies suggests that while it would not produce dramatic changes in the relative risk of the largest cause of death in the United States, it might have some important public health consequences, which is the real issue here.

Tyroler then expanded on Schwartz's point by stating that there had been a mean difference of only about 5 mm of diastolic Hg between the treated and the control group in the Hypertension and Detection Follow-up Program (HDFP). That was attended by almost a 20% reduction in all-cause mortality among middle-aged adults and so a seemingly small mean difference, 2 mm Hg, at the population level would be associated with as much as an 8 to 10% decrease in all-cause mortality. It is not trivial in terms of its public health impact. Schwartz then remarked that a relative risk of 1.08, while important for public health consequences, is rather hard to find in studies looking at specific mortality ratios.

Vander noted that there appeared to be some unanimity. He agreed with Lee that there may very well be a difference in the dose response for renal disease and for hypertension in experimental animals. Most of the published work on experimental animals shows certain doses of lead will produce high blood pressure and as one goes higher, the high blood pressure vanishes. Given the difficulty of doing epidemiology studies, Vander felt that what he had heard so far was in pretty good agreement. In fact, Vander felt that there was a remarkable agreement in terms of the expected rise in blood pressure that would occur for a given rise in blood lead. If one uses those doubling doses, the value that one comes up with from lowering blood lead from 16 down to 4, and 4 is still quite a high number for preindustrialized societies, is in the ballpark of 5 mm Hg. That is a very large reduction in blood pressure for the general population. In terms of what was heard on Monday, Vander noted that approximately 40% of people would go from being labeled hypertensive to being labeled normotensive. He felt that these very small changes in blood pressure are extraordinarily important.

J. Rosen (Albert Einstein Medical School, NY) then clarified some statements concerning the K X-ray fluorescence instrumentation that Wedeen spoke about. He noted that his instrumentation at Brookhaven, at Einstein, and at Montefiore Medical Center was completely different from the instrumentation used by Wedeen in East Orange, NJ. Rosen's instrumentation, which is based upon soft L X-rays of lead, has a minimum detection limit of 2 ppm. It also has the capability of exposing children as well as pregnant women to virtually no radiation other than what one would anticipate on a trip to Denver, CO. Rosen believes his instrumentation is widely applicable to the general U.S. population and noted that he would be presenting his data on 66 children using L X-ray fluorescence at an open meeting following the conference.

The panel of invited discussants then gave their views on the session. Kannel made some general comments on the occupational epidemiology studies. He felt the studies seemed to rely heavily on death certificate evidence of outcome and that these can be imprecise, particularly in respect to the hypertension end point depending upon whether one uses multiple cause certification, underlying cause of death, or stated causes of death. Kannel also felt that the studies relied upon external controls, or comparisons; that is, standardized mortality ratios which he felt rather uneasy about. He also noted that the healthy worker effect can often appear in epidemiologic studies because investigators often use the general population expe-

rience as an external control. There is also a lack of adjustment or information on major confounding variables such as relative weight, alcohol intake, cigarette smoking, and factors related either to lead or to hypertension. Kannel felt there was an imprecise measurement of the actual exposure to lead in these studies. There are arbitrary decisions as to where cut points are made when the exact dose-response relationship is poorly defined. There also seems to be low power to detect some of the excess mortality for some of the uncommon causes which are being sought after making it very difficult to draw conclusions about the relationships. When one finds an excess of perhaps 30 to 40% which is significant, the significance test merely tells you that you cannot place much confidence in your estimate. It is always troublesome to find a major excess that would be significant from a public health standpoint, but not be able to say whether your estimate is precise enough to judge whether it is true.

Smith felt that one should be careful about saying that the papers presented were moving in the same direction. He noted C. Henneken's (Harvard Medical School) paper on the combination of clinical trials that pointed out very clearly the difficulty of combining information from across a wide variety of experiments. Henneken threw out half of the trials and ended up with a very small set because the investigators did not adhere to strict protocol and strict collection of information. One must, therefore, be very careful with a combinational type of inference when comparing groups of studies.

Dustan then gave her comments. She stated that the evidence presented so far suggested that there is a relationship between blood lead or lead exposure and blood pressure. She noted that there was no information about the mechanism of this relationship; the relationship seemed to be of relatively low power, but could be significant. Dustan asked whether there is an experimental model for the effect of chronic lead intoxication on blood pressure, and if such a model exists, whether that model is different than acute intoxication. If it is not different in terms of its determinant, then Dustan suggested using acute intoxication for a further study. Dustan remarked that this is one of the major issues that needs to be addressed because it is the influence of lead on the blood pressure of the population that seems to be so subtle and that is very difficult to determine. Dustan noted another confounding factor. As we reduce the lead in the environment through the reduction of lead in gasoline, are we then going to see an important decrease in the mean blood pressure of the population. Dustan felt that if it does happen, it would be nice to know what the decrease is due to and questioned whether we would ever know what it is due to. Dustan suggested that in the discussions that followed later in the morning and afternoon perhaps one would get some idea as to whether there are experimental models of chronic lead intoxication that suggest lead having a role in producing hypertension.

Investigators who have performed research in experimental settings on the effects of lead on the cardiovascular system spoke at the subsequent session. W. Victery (U.S. EPA) presented a short overview of chronic exposure protocols, using both high and low exposure levels, which were evaluated for blood pressure effects. Vander reviewed findings of a lead effect on the renin angiotensin system, and R. Webb (University of Michigan) discussed the effects of lead exposure on vascular reactivity. These talks were followed by S. Kopp's (Chicago College of Osteopathic Medicine) findings on cardiotoxic effects of lead; the final presentation by Boscolo was on neurohumoral effects of lead exposure.

Following the presentation of Kopp on cardiotoxic effects of lead, there was a question from de Kort on the effect of anesthetics on the blood pressure and cardiac effects observed in the experimental animals. Kopp indicated that they no longer use pentobarbital because it tends to blunt the measured effects of lead or cadmium on the cardiovascular system but have found that a mixture of Ketamine and Xylozine are effective. In addition, pentobarbital depresses the cardiovascular system responses of lead-exposed animals more than those of control animals so that the differences seen between the groups is an underestimate rather than an overestimate.

There was a question directed to the speakers regarding any evidence that the high renin levels observed in the lead-exposed animals were related to sodium or fluid imbalance. Vander responded by indicating that in other published reports from the Michigan group, animals with similar lead exposure had a subtle defect in sodium reabsorption by the kidney. The animals initially responded to a sodium-restricted diet by excreting more sodium than control animals. There were no differences in steady-state sodium balance. Whether this finding was correlated to the renin level was not determined, e.g., by using blocking drugs for the renin angiotensin system to determine the causal role of renin.

Lilis asked for clarification regarding Boscolo's remarks about a possible genetic component to susceptibility to blood pressure changes related to lead exposure. The two agreed that this hypothesis would require further study. Wedeen indicated that humans with essential hypertension may have excess body burdens of lead that are not remedied by chelation therapy. On the other hand, patients with elevated blood pressure during an acute lead poisoning respond to chelation therapy by reduction in blood pressure. Vander pointed out that there is no experimental evidence that removal of lead from the animals will lower blood pressure. There were additional comments by the speakers who indicated that we should recognize that the data are quite different when animals are exposed to chronic low levels of lead compared to acute effects of higher level lead exposure. This appears to be the case in animal experiments but is probably also the case in the two types of human expo-

sure. Kopp explained that the cardiac effects seen with acute versus chronic exposure are clearly different (with acute or high-level chronic exposure being cardiodepressive while low level exposure produces enhanced contractility).

The two invited discussants, Goyer and Johns, wrapped up the session. Goyer, a pathologist well known for his studies of ultrastructural and chemical changes in metal nephrotoxicity, indicated that from his viewpoint, blood lead levels resulting from lower doses of lead will not be reflected in renal lead concentration in rats of more than 2 to 3 μg/g. Pathological changes in the kidney are usually not observable until the renal concentration exceeds 10 to 15 μg/g. At the high levels of exposure, there are measurable changes in intracellular calcium that are so severe that the cells are unable to perform their functions. At this point, he would not expect to see any physiological response to pressor amines, changes in renin levels, or other regulatory systems. These levels of lead exposure are quite different from the exposure levels seen in the general population. For experimental studies, documentation of the range of blood lead associated with the range of observed blood pressures is needed. Finally, Goyer urged that researchers consider the essential metal content of the dietary regimen administered with the lead dose because the toxicity of a specific lead dose can vary 20-fold by reducing calcium content in the diet. Similar effects can be obtained by altering iron or zinc levels. Several other scientists indicated that the relative inconsistency between administered dose and blood lead level achieved should be considered when considering the effect or lack thereof on blood pressure. In addition, because the rat kidney accumulates much more lead for a particular blood level than do human kidneys, we need to determine lead concentration of other critical target organs (including vascular smooth and cardiac muscle, and juxtaglomerular cells) in order to determine which responds in parallel with blood lead.

Johns proposed a number of critical experiments to understand how lead may be affecting blood pressure and whether blood pressure changes can be reversed by removing lead from the diet. Inhibitors of angiotensin converting enzyme should be tried to determine if this prevents the pressure increase during lead exposure. Levels of intracellular calcium should be measured and calcium or potassium channel blockers might reduce the effects of lead.

The discussion of the last few minutes of this session delved into why some experimental differences in blood pressure were so much greater than seen by other investigators (for example, the 50 mm Hg increase seen by the Italian scientists). Are we actually dealing with a model that is analogous to the human situation, or do we need to determine an animal model that demonstrates only a few millimeters of mercury increase in blood pressure which is attributable to lead exposure?

There were two sessions devoted to mostly unpublished studies. Some of these are to be found elsewhere in this volume; the main findings coming from the other studies will be summarized here for sake of completeness.

H. Perry (Washington University School of Medicine, St. Louis) presented new findings on low-level lead exposure in experimental animals. He noted that in a pilot experiment they found that if lead exposure was terminated for 2 months after a 6-month exposure, the 0.1 ppm lead-exposed rats became normotensive while the 5 ppm did not, and 1 ppm were between the two. In response to a question from Goyer, Perry gave the specific trace mineral components of the rat chow used. Several audience members tried to evaluate these lead doses with respect to that seen in the human population. A calculation made by Wedeen illustrated the total amount the rat ingests is of the same order as the human body burden over a lifetime. Vander pointed out that the true lead burden in the rat is much lower because of the lower gastrointestinal absorption rate of lead in rats compared to humans. de Kort pointed out that when anesthetics are used to obtain blood pressures in animals, there may be an effect of lead on the effect of the anesthetic on blood pressure. Perry agreed and indicated that animals are currently studied without anesthetic (which results in higher control blood pressure measurements), but the levels seen in the metal-exposed animals are unchanged. In addition, there is more consistency in the readings and lower standard deviations.

In the discussion following Gonick's talk, it was noted that accurate and sensitive methods for measuring plasma lead as the important biological indicator of lead exposure are not available as yet.

C. Morris (Oregon Health Sciences Center) informed the audience about the findings in a clinical trial with calcium supplementation in patients who had their blood lead and erythrocyte protoporphyrin (EPP) measured and blood pressure monitored. They found that, in spite of modest blood lead levels, there was a positive correlation between blood lead, EPP, and diastolic blood pressure. In addition, they believe that the blood pressure response that occurs with calcium supplementation is probably independent of changes in blood lead concentration.

F. Hodgson (University of Pittsburgh) presented the paper originally expected to be given by Parkinson. Cross-sectional data from approximately 250 occupationally exposed U.S. workers and 170 controls were reanalyzed to examine the contribution of current, recent, and cumulative indicators of lead exposure to systolic and diastolic pressure. Only TWA (time-weighted average) lead exposure (which was collinear with age) was statistically significantly correlated with both systolic and diastolic blood pressure. None of the indices of lead exposure accounted for more than 2% of the variance. This regression coefficient is fairly similar to that derived in the NHANES data.

Schwartz queried Elwood regarding the blood pressure data from the Caerphilly Study in that the values were higher than those obtained in the rest of

Wales. Elwood noted that the data from the Welsh Heart Program are standardized to age 40, while the Caerphilly men had a mean age of 54. Their blood pressure values are appropriate for the age differences.

Grandjean reported on a study of blood lead-blood pressure relationships with alcohol consumption and hemoglobin values as confounders. The population studied was approximately 1000 men and women born in 1936 in 3.5 municipalities west of Copenhagen, Denmark, who were presumed to be representative of the entire country of Denmark. Blood lead was significantly associated with both systolic and diastolic pressures with a doubling of blood lead associated with an increase in blood pressure of 2 to 3 mm Hg. Among several predictors, only blood hemoglobin and alcohol intake were true confounders. When taken into consideration in the regression analysis, all statistical significance was lost. There was also an association of blood lead with smoking; smoking is also an important risk factor for increased blood pressure.

Kannel questioned the finding of a positive relationship between blood pressure and cigarette smoking, whereas most epidemiologic studies show an inverse relationship, i.e., those who smoke have somewhat lower blood pressures which may be attributable to lower relative weights among smokers.

Grandjean responded to Kannel's question by indicating that smoking was treated as a discrete variable, categorized into five different groups and that smokers who smoke between 15 and 24 cigarettes per day actually had a lower blood pressure than did nonsmokers. Dustan questioned Grandjean's interpretation of the hemoglobin, blood lead-blood pressure association and questioned whether or not it was not possible that the causal chain was in the opposite direction, i.e., hypertensives tend to have lower blood plasma volumes and subsequently can have increased hematocrits. In that circumstance, the hemoglobin and hematocrit would be the explanation for the increased blood lead. Grandjean accepted that interpretation.

Schwartz confirmed Kannel's observation and noted that there was a negative association between smoking and blood pressure in the NHANES II and that was present controlling for both body mass index and body fat. Smith questioned the nature of the univariate association between smoking and blood pressure prior to adjusting. Schwartz could not recall the association in the NHANES data. Kannel noted that it was negative in Framingham, i.e., that the negative univariate association was changed to a positive one after addition of the control variables. Schwartz also reported that in NHANES the hemoglobin did not seem to be responsible for the blood lead-blood pressure association, as stratifying by hemoglobin levels did not change the regression coefficient of blood pressure on blood lead. Grandjean indicated that the association with smoking was complex in his study and blood pressure was higher among those who smoke between 1 and 14 g of tobacco/day, whereas it was lower in those who smoke 15 to 24 g.

Kromhout inquired about the association between change in blood lead and change in blood pressure. Grandjean did not have those data in a form available for presentation. Pocock requested information regarding regression coefficients rather than significance levels. Grandjean responded that the coefficients which approached statistical significance were positive and those that were not statistically significant were both positive and negative but very close to zero.

Pocock questioned the evidence regarding alcohol consumption having an acute metabolic effect. Grandjean responded that this is based on an experimental study performed in Yugoslavia wherein a few "shots of ethanol" resulted in an increased blood lead level after a few hours. Thus, even if participants had had a 13-hr fast, there could be a residual metabolic effect of alcohol. Pocock questioned the statement that there is no lead in cigarettes and pointed out that he found relationships that persisted even after adjustment for alcohol consumption. Grandjean reported that studies of liver enzymes suggested underreporting of alcohol consumption, particularly in women in whom the correlation of smoking with blood lead persists after adjusting for alcohol intake, i.e., that there probably was underreporting of alcohol intake. Pocock continued questioning regarding the change in lead content of cigarettes in recent years. Grandjean reported that there was definitely a very high lead content 30 or 40 years ago; at the time, lead arsenate was used for spraying tobacco fields, a practice not followed any longer. Recent analyses have indicated there is much less lead in tobacco at present. Lilis commented on the exquisite control for age in Grandjean's study, which might be too narrow to be able to comprehensively assess any relationship between blood lead and hypertension. She requested more detail regarding the distribution of blood lead levels and systolic and diastolic blood pressure in Grandjean's study to permit comparison with other cohorts.

Following the presentation by L. Neri (University of Ottawa, Canada), there was some discussion about the fact that the values for some blood lead measurements were so low that no parameter value was obtained. The authors tried several different methods to correct for these in the overall regression analysis.

Beevers described studies performed in the city of Birmingham, an industrial city with workers occupationally exposed to lead. In 1976, Beevers published a report on these workers in which only a weak association between blood lead and blood pressure was found. In a new study, additional analyses and clinical measures have been obtained on approximately 700 lead workers. No excess prevalence of hypertension was found in the lead workers. Workers with mean blood lead values of 33.6 μg/dL show a weak ($r = 0.09$), but statistically significant ($p < 0.01$), association between blood lead and blood pressure; this trend

remained significant after analysis of covariance which took into account age, body mass index, and duration of lead exposure. No convincing relationship was found between blood lead and alcohol intake, but cigarette smokers did have higher blood lead levels than nonsmokers. There was no correlation between systolic or diastolic blood pressure and zinc protoporphyrin levels. In the comment period after this presentation, Boscolo indicated that it was very important to recognize that these workers were carefully monitored by their employer and that this was not always the case in factory settings. Hodgson reminded Beevers that in his original publication it appeared there might be a different (even negative) correlation between blood lead at high levels and blood pressure. Regression coefficients determined by dividing the blood lead range into four segments appeared to be different. Beevers had not done this in the present study but thought it would be helpful in additional analysis. Rosen asked if there appeared to be a relationship between blood pressure and length of exposure but Beevers said that they had not found this to be the case.

The following discussion took place after D. Sharp's (University of California at Berkeley) presentation. Sharp questioned the inclusion of cigarette smoking in regression analyses if it is not related to blood pressure. Smoking can act as a vehicle for lead exposure. Similarly, even though there is some evidence that alcohol intake is related to increased blood pressure, there is even better evidence that alcohol can act as a vehicle for lead exposure. This may bias the blood lead-blood pressure relationship toward zero by overcontrolling for lead exposure. Pocock responded that this has been an area of controversy and had it been excluded, he might have been accused of missing an important factor. Weiss indicated that, for a variable to be a confounder, it has to be associated both with the exposure and causally with the outcome variable. Pocock felt that the definition of a confounder and criteria of an appropriate covariate for inclusion in the model were two different things. He noted that among most of the studies presented there was a weak association between both smoking and alcohol and blood pressure. Since the blood lead-blood pressure association is weak and because the association of the covariates and the outcome variables vary among different data sets and are themselves weak, this might be one of the reasons why different results were being seen in different studies.

Kannel noted that causal inference is the issue. He cited the analogy of overweight in relation to coronary disease, which disappeared as a risk factor when one took into account variables such as blood pressure, glucose, cholesterol, and uric acid. This, however, merely indicated links in the causal chain; as weight increased, the intervening variables left no variation to be explained by weight. He pointed out the necessity to keep the processes in mind when drawing causal inferences.

Smith pointed out that the difficulty in interpretation relates to the research design. In the ideal model, one could determine the causal effects independent of each other. The difficulties with the experimental research relate to two factors; one, absence of hypotheses regarding the causal models and, second, in demographic survey research there is no unique model.

Carter reported experiments in rats that indicated that rats with very high blood lead levels were the ones that ingested more alcohol and cautioned against the interpretation of cross-sectional associations of blood lead and alcohol consumption in terms of the causal direction.

Schwartz declined to comment on whether people with higher blood lead values drink more or not. He commented that studies in humans show variability in the association of alcohol consumption with blood pressure. Similarly, there was variation among the studies between the relationship of blood lead and blood pressure. If alcohol is a source of lead, then the observational studies will be unable to distinguish the independent causal contribution of lead and alcohol to blood pressure. Pocock said that he did not see this as a major problem because alcohol remains a relatively minor source of lead. He noted that there are numerous individuals who are either nondrinkers or fairly light drinkers who still have measurable lead levels and that it was possible to treat these two as separable statistically and etiologically.

Grandjean indicated that in his population a reported intake of two "shots" of alcohol per day was associated with an increase of blood lead by about 1 μg/dL, which was not insignificant. In the presence of a weak association, adjustment for alcohol may eliminate a blood lead-blood pressure association. He suggested, in prospective studies, that the cohorts be restricted to individuals who ingest just a certain amount of alcohol per day and can then be followed over time, i.e., for example, being measured when hired and then later as exposed lead workers. Ware pointed out that the animal experimental work indicated no influence of alcohol on absorption of lead and that, in his opinion, the question was how much lead there is in the alcoholic beverage. He suggested that this varies among studies performed in different countries and that he did not believe that this was a significant question in this country.

M. Velasquez (George Washington University, Washington, DC) questioned whether anyone had studied the blood lead levels among a population of essential hypertensives and whether these were different from the normal population. Further, he questioned Kannel about the association of body mass index to blood pressure in the hypertensive range. Kannel responded that the regression between blood pressure and weight appeared fairly linear, that the regression between weight gain and change in blood pressure also appears to be quite linear and extends into

the hypertensive range. Kannel disagreed with Velasquez's interpretation of a flattening of the blood pressure, body mass index relationship for blood pressures above 150 systolic or 90 diastolic mm Hg.

Smith cited the use of standardized regression coefficients in the social science literature and questioned whether or not conversion of the NHANES data to that form might be a way of comparing association across studies and also within studies when controlling for other variables. There was no response to this suggestion. Gonick advanced an additional possible mechanism regarding alcohol. The diuresis associated with alcohol consumption could lead to hemoconcentration, increase the hemoglobin and therefore secondarily increase the measured total blood lead. He suggested that analyses should control for hemoglobin levels.

Tyroler introduced the final session of the symposium and stated that it was planned to provide a synthesis and overview of the material presented at the symposium. The objectives of the symposium were to have the principal investigators review their published research and to have open discussions among them and the audience, and to present all identified ongoing relevant research that had not yet been published. An assembled panel of discussants were to synthesize the observational epidemiologic, clinical, and animal experimental materials. Questions that were to be considered included the following: What do we think the assembled information means? Is there an association between blood pressure and blood lead levels in epidemiologic studies? If there is, what is its strength and does it vary among subpopulations? Combined with the clinical and experimental observations, do we believe that there is an association which persists after controlling for potential confounders? Do we believe that it is causal? Insofar as those questions can not be answered definitively, additional research needs are to be identified.

The summary that follows highlights the discussions in the order of their presentation. Considerable editing has been introduced; however, every effort was made to preserve the sense of the comments made and to convey the information presented without either an exhaustive or a literal recording of all comments.

Although not listed as a discussant in the program, Pocock was called on to present a quantitative overview he had prepared of the effect measures derived from the different epidemiologic studies presented. The key elements of Pocock's overview analysis and his interpretation of them were incorporated into his manuscript, which has been included in these proceedings. In his summarization remarks presented during the overview discussion, Pocock suggested that the point estimate of the regression coefficient of blood pressure associated with blood lead and the confidence interval around that estimate for each study indicated overlap among the various general population epidemiologic studies, with evidence of compatibility of estimates. It was his opinion that a zero increase in systolic blood pressure with a doubling of blood lead was not compatible with the overall data, nor was an increase of 3 mm Hg in systolic blood pressure compatible. His impression was that a doubling of blood lead seemed associated with an increase of about 1 mm Hg in systolic blood pressure. Further, he felt that the understanding of and the control of confounding factors were quite different among studies and incomplete in some. He cited the example of alcohol and suggested that other confounding factors remained to be discovered and, obviously, adjustments for unidentified factors can not have taken place in the observational studies reported to date. Although the overview was consistent with an association between blood lead and blood pressure, it was his impression that it was small in magnitude, weak in strength, and that the overall evidence did not permit an inference regarding a causal relationship between blood lead and blood pressure values. Following Pocock's remarks, the session heard from the planned panel discussants.

Smith stated that he would play the role of devil's advocate and, despite his being impressed by the amount and quality of work reported, that his comments generally would be of a critical nature. In particular, he pointed out that the quantitative overview, which suggested a general trend of positive coefficients of the relationship of blood pressure to blood lead levels, was fraught with difficulties. The models used among the studies were for the most part different. The number and type of covariants included were not the same among the models used and the mathematical treatment of the variables included across models often varied; for example, the square of age was used in some studies and not in others. He suggested that although the use of these covariants might not make much difference in terms of the estimator, it could make a major difference in terms of confidence intervals.

Smith called attention to the point of the implications of a policy decision to eliminate lead from gasoline focusing on new health outcomes based on alternative products. He emphasized the importance of this in the case of the relatively small effect associated with lead which the overview analysis had indicated.

Smith pointed out some fundamental differences between the research designs used in experimental biologic research and the multivariate type measurements and analyses performed in the epidemiologic studies. He focused particularly on the need for more detailed analysis of the relationship of blood lead to blood pressure across the multiple NHANES study sites and inquired about the consistency of a positive association when this was done. He also raised the point of differences in the blood lead-blood pressure relationship among demographic subgroups, with the possibility of a negative association for women.

Goyer presented an overview of a general nature regarding what he regarded as the two major objectives of experimental work: one was to confirm human observations and another to define mechanisms and

provide understanding for intervention and prevention programs. He stated that he believed that the experimental studies of Vander indicated that exposure of experimental animals to lead can produce changes in blood pressure and that the epidemiologic work shows the same; however, beyond that, it was his impression that the animal work becomes confusing. This may derive from the fact that the animal work has focused on different situations from that which produces elevations in blood pressure with lead exposure in the human situation. He reminded the audience that the main focus of the conference was on the relatively minor increases in blood pressure in the general population in relation to general blood lead levels and there were few experimental models that have addressed this. The majority of animal experiments in the older literature are probably not relevant to the understanding of this phenomenon as they are probably due to different mechanisms. The first experiments that begin to relate to epidemiologic observations are those of Vander and Victery, Perry and Erlanger.

Goyer noted that Vander's model showed relatively small increases in blood pressure at relatively low levels of lead exposure and that these effects could not be produced at higher blood lead levels in a manner that seemed analogous to that observed in the general population. He noted that the blood lead levels achieved appeared to be similar despite markedly higher exposure levels and raised the question of the inability of the rat to modify its blood lead in response to high levels of lead exposure and that the blood lead levels may not validly reflect tissue levels, a question which came up in other contexts and raised the question of measuring lead in human tissues other than that of blood, despite its obvious difficulties.

Goyer identified as one of the major research needs the development of animal models that resulted in predictable changes in blood lead and blood pressure on fixed exposure. Essential to doing this would be a better definition of diet, the genetics of the animal and the environment. Ideally, studies should provide more longitudinal information. Much more information is required about calcium and lead interactions, the mechanisms of which require further explanation.

Johns then reviewed the evidence presented for mechanisms by which lead could increase blood pressure. Those mentioned included:

a) Alteration in intracellular calcium in all forms of hypertension is assumed, but the level of intracellular free calcium ion is of importance and these concentrations have not been measured, just assumed.

b) Noncalcium mechanisms: With prolonged muscle contraction, the intracellular calcium concentration returns to normal; C kinase, a calcium-dependent enzyme affected by lead, can promote smooth muscle contractions which are not calcium-dependent.

c) A prime target for lead is the endothelial cell of the blood vessel wall; these cells contribute to the conversion of angiotensin I to angiotensin II (AII) and since the level of AII in some of the Vander reports is observed to be low, it may be a result of direct action of lead on the endothelial cell. These cells also produce endothelium-derived relaxing factor (EDRF), which is responsible for basal tone in blood vessels, and if the endothelial cells are destroyed by lead, this could cause a contraction in the smooth muscle. An increase in blood calcium level would tend to increase the relaxation of the blood vessel due to noncontrolled leak of ionized calcium into the endothelial cells.

d) Lead could alter calcium entry or calcium cycling across the membrane or the release of calcium from sarcoplasmic reticulum, any of which can affect contractile systems. It appears from the *in vitro* studies of Webb that the increased reactivity of isolated vessels to agonists may be due to increased sarcoplasmic reticulum calcium content.

The plasma membrane of vascular smooth muscle has a number of cation channels and pumps. It is not unusual for a compound to promote calcium entry at low concentrations and block calcium entry at high concentrations. Therefore, it did not surprise him that lead at different levels appears to have opposite effects on blood pressure. Possibly at low lead levels, the endothelium is destroyed while at high lead levels, it can also act as a calcium channel blocker. The potassium channel may also be affected, leading in some cases to membrane depolarization and calcium entry via voltage sensitive channels. Levels of lead required to inhibit sodium-potassium ATPase seem to be quite high, perhaps of pharmacologic significance only. Lead could also affect sodium-calcium exchange which may not directly affect contractility but alter the filling or emptying of the sarcoplasmic reticulum after contraction.

Johns wrapped up his remarks by indicating that since all ion channels could be affected in smooth muscle membranes, and if there is endothelial cell involvement as well—there will be a need to find out which of these pathways are affected by lead through continued basic research. If a 2 to 3 mm Hg rise in human blood pressure attributable to lead exposure is considered important, then it would be interesting to follow up these research needs.

Dustan continued with a discussion of the animal experimental model which, in the instance of lead exposure, she thought could be an excellent model of mild hypertension in man. Most of the experimental models we have of hypertension had been associated with rather severe hypertension and with consequences of severe hypertension in terms of arterial damage, whereas what we need is something more of replication of what we see in man, where much of hypertension is mild. Further, this model offers the opportunity to see the relationship of mild blood pressure to atherosclerosis in the animal model.

Dustan commented on the confusing observations in clinical studies of the apparent lack of relationship between hypertension and kidney damage with lead. Despite the methodologic limitations and defects in the

data available, she was impressed with the striking finding that people who have died of lead nephropathy or have died of renal failure have not had secondary hypertension. For future research, she called for detailed analysis of the black examinees in the NHANES sample, noting the somewhat higher blood lead levels and well-known excess of hypertension in blacks. In these analyses, studies of serum creatinine might provide insight into whether or not hypertension in the black is kidney-related in either of two ways: one, the kidney as a victim of elevated pressure, and the other, the kidney as the culprit.

Kannel presented a synthesis of the studies and a community perspective. He reviewed the rules of evidence in determining whether an observed association reflects a causal relationship. He noted consistency of results with a similarity of trends among population surveys, although in some instances the results were not statistically significant and other times when risk factors other than lead were not taken into account. He called for prospective studies on the predictive value of lead for subsequent hypertension and the need to study its effect on age trends in blood pressure over time. The strength of the blood lead-blood pressure relationship is rather weak and does not fulfill the usual criterion for causality. The weak association does not lead to a clear dose-response relationship and the shape of the dose-response curve is not known with certainty. There seems to be some loss of effect at higher or toxic doses of lead. If the relationship does hold at ambient levels of lead, this is of great public health importance owing to the large attributable risk and the modifiable nature of lead as a potential risk factor for hypertension. Although the effect seems to be independent, more data are needed concerning the associated cadmium and calcium intake and exploration for possible interactions should be carried out. The final criterion, biologic plausibility, is partially met. Although a number of possible mechanisms have been postulated, it is not clear from the evidence reviewed which are operative. In summary, Kannel suggested that the available information suggested a possible, but by no means certain, causal relationship; however, the public health implications are large in view of the current ubiquitous exposure, the effects of low-lead exposure on blood pressure, and the possibility of modification.

Kannel felt that in terms of population research, there was a need for ongoing prospective studies to include blood lead in their next round of exams and then study prospectively the relationship to the trends in blood pressure over time. There will also be the opportunity to take advantage of areas with declining lead exposure and measure blood pressure before, during, and after change. Two particular deficiencies in the data available as identified by Kannel were those regarding information on the association in women, where the effect seems to be less pronounced than for men, and the need for more information on the contribution of blood lead differences to the well-known black/white differences in blood pressure.

In opening the general discussion, there were comments from Goyer, Smith, and Vander regarding the interpretation of epidemiologic findings compared with those derived from experimental work. Smith emphasized the point that the independent effect of one factor was not what was relevant to the human circumstance, but rather the potential for interaction of lead with other factors. This was agreed to by the experimentalists who had demonstrated positive interactive effects with cadmium and negative interactive effects with calcium. Schwartz elaborated on the point and suggested that this might explain why in Perry's experiments elevation in blood pressure was seen at lower doses of lead in contrast to Vander's experiments; one possibility is Perry may have had less calcium in the diet of his rats than was present in the experiments performed by Vander. Pocock indicated that he had blood cadmium measures on 7000 of the men in his studies and that cadmium did not seem related to blood pressure; however, he added he had not yet tested for interaction effects. Further, he pointed out that cigarette smoking is a major source of cadmium and that if cadmium were affecting blood pressure, one would expect a positive blood pressure smoking relationship which was not observed in his study. de Kort added that he too observed the absence of an association between cadmium and blood pressure in a small study of lead workers in the Netherlands.

Kannel emphasized the desirability of performing animal experiments which have relevance to hypertension in humans, and this led to discussion of the desirability of study of exposures early in life. Vander advanced the idea of beginning animal experiments of this type based on lead exposure *in utero*. Wedeen returned to the question of the absence of hypertension in association with lead exposure in the presence of renal disease. He suspected that this follows from the epidemiologic ascertainment of the general population with normal pressure and blood-lead levels, and exclusion of diseased persons. He advanced the hypothesis that the massive overrepresentation of black males in dialysis units could be related to lead exposure in childhood combined with lower calcium intakes and the association with alcohol.

Webb returned to the association of calcium with hypertension and pointed out that the evidence suggested that the problem was not so much one of concentration but regulation of the way calcium moves (flux) or activates contractile responses. He suggested that studies should be directed to regulation in terms of calcium interactions with lead.

In response to a question that returned to the issue of the association of blood lead and blood pressure in blacks, Schwartz indicated that in some of his analyses, blood lead explains some of the black excess in high blood pressure, but not all of it. Schwartz returned to

the question raised by Smith regarding the issue of what replaced lead when it was to be removed from gasoline and he cited cost benefit analyses prepared for regulatory hearings. The possibility of some increase in emission of carcinogens, secondary to increases in the aromatic content and branching paraffins of gasoline, were estimated to result in markedly lower effects on health than those putatively associated with lead. J. Cole (ILZRO) asked the panel to discuss a comment that Schwartz made that a 1 mm Hg rise in blood pressure could be associated with a 1% increase in ischemic heart disease. Pocock stated that a 1% heart disease rate change was roughly that estimated to be associated with a 1 mm Hg change in blood pressure; however, he argued that it was necessary to recognize two links in the chain of the argument, the lead blood pressure link and the blood pressure ischemic heart disease link. He suggested that the blood pressure ischemic heart disease link relates to the long-term pattern of blood pressure and its association with the risk of ischemic heart disease in late middle age, whereas the lead blood pressure association may be of a much more short-term nature and whether or not it reflects a chronic association is unknown. Tyroler and Kannel each advanced the idea that the human experimental data, i.e., the clinical trials evidence, clearly showed that lowering blood pressure decreases direct pressure related phenomena such as renal, cerebral, and congestive heart failure sequelae; however, clear evidence of efficacy of blood pressure reduction in prevention of atherosclerotic complications, such as ischemic heart disease, was not available.

Mahaffey raised the question of the body burden of lead and asked what recommendations would be made to this end. Wedeen suggested that the measurement of bone stores of lead by *in vivo* X-ray fluorescence was an approach. Grandjean stated that his group has developed a method of analyzing lead in teeth using the lead level in circumpulpal dentine. There was some debate as to whether pulpal dentine or X-ray fluorescence was a more valid index of lead accumulated over a lifetime. Vander repeated a suggestion he had made regarding the possibility of estimating ultrafiltrable lead in plasma. Although theoretically ideal, he emphasized that it had been impossible in the past because of contamination, but that rigorous methodologic techniques, including absolutely ultraclean laboratory settings for determination, would make this feasible. He suggested also that isotopic equilibration of plasma with an isotope of lead, followed by ultrafiltration, might provide a technique applicable to large surveys. Grandjean pointed out that an additional reason for not using plasma lead other than the difficulty of its measurement is its marked variability with time and Bernard indicated that the half-life of plasma lead is only hours to perhaps a few days.

S. Snedeker (NIEHS) expanded upon the implications of dealing with interactive effects of minerals. She pointed out that this covers different levels of research: the effect of calcium and other minerals on lead bioavailability and the lead body burden. These might be substantially different than the interactive effects of lead and calcium on tissue levels, such as vascular tissue or the kidney. Snedeker also pointed out that there are some subgroups that have not been discussed at length, in particular, women at the menopause. The release of calcium and the effects of hormone treatment were worthy of investigation since some preliminary data indicated a slightly higher blood lead-blood pressure slope in the 40- to 55-year age range with subsequent leveling off. Schwartz indicated that his group has a paper in manuscript suggesting that blood lead levels increase immediately after menopause and that a statistical interaction term for age suggests that they then decline and that this is similar to the pattern of calcium release after menopause following calcium mobilization from bone.

A presentation and review of the design and plans for the National Health and Nutrition Examination Survey (NHANES) III were considered and served as a basis for discussion regarding studies that could be added to this survey to further elucidate the blood lead-blood pressure relationship.

S. Haynes (NCHS) described the plans for NHANES III. She indicated that with a sample size of 16,000 it would be larger than the previous two surveys. The plan is to start the survey in 1988 and to complete it by 1994; however, estimates from the field will be available by 1991 for blacks and whites and at the end of the 6 years for Mexican Americans and Puerto Ricans. Planning is moving forward to do a mortality follow-up of the population using the national death index. There also are plans to have a reexamination or reinterview of the NHANES III population, probably in 1996. Among the elements of the examination, she mentioned a special kidney exam which will be more extensive than others previously done in the NHANES surveys to follow up persons at risk of kidney disease with special reexaminations for glomerular filtration rate in clinical centers. Wedeen pointed out that information could be derived from detailed analysis of serum creatinine and Haynes indicated that a manuscript was in preparation based on analyses of the serum creatinine values of NHANES II and that additional studies of their relationships to blood lead would be feasible by secondary analysis of these extant data.

Haynes added that a home examination is to be added to the mobile unit survey. In this home survey, limited examinations will include blood pressures so that it will be possible to have home blood pressures measures as well as clinic measures for the entire population. This will permit better definitions of hypertension. In response to a question by Smith, Haynes pointed out that detailed plans for analysis have been developed in advance to identify the basic questions that need to be addressed following completion of this survey. Haynes also indicated that there is

a new philosophy at the National Center for Health Statistics in disseminating results. The first target is early publication in medical journals and following that, publication of the material in Center reports. In summary of the overall scope of the exam, excluding the environmental components, Haynes indicated that there will be an electrocardiogram, kidney exam, oral glucose tolerance test, hearing exam, visual and dental exams, a 24-hr diet recall, and a series of neurologic tests, measurement of height, weight, anthropometrics, body impedance, and bone densitometry to determine osteoporosis.

G. Provenzano (U.S. EPA) summarized the EPA plans for measurement of environmental aspects within NHANES III. The exposure measurements will be based on estimation of exposure primarily in the home. These were ascertained by expanding the household interview to provide information on factors that affect indoor air quality, such as types of heating equipment, cooking equipment, size of indoor spaces, number of rooms, etc. The questionnaire information was to be supplemented by some indoor air monitoring, e.g., radon measurement. Tap water is to be analyzed for toxic and essential metals. In addition to environmental measurements, measurements of individuals are to be performed both to assess exposure and for effects estimation. Among the effects measurement, in addition to blood pressure, there will be a neurobehavioral test battery. The body measurements will include those determined from serum, whole blood, and urine and include a larger number of toxic metals and essential metals that were not measured in NHANES II. The final list of metals to be analyzed in addition to lead has not been determined, but will include cadmium, and most probably serum selenium, manganese, and aluminum, and urinary arsenic. Serum cotinine will be assessed to provide sensitive and objective evidence of exposure to tobacco smoke. Provenzano concluded with the posing of three types of questions relevant to the blood lead-blood pressure question. First, what laboratory analysis protocol should be used for measuring lead in blood in the NHANES III? Do we need increased sensitivity in view of the anticipated markedly lower blood lead levels in the early 1990s? Will we be able to detect low levels with appropriate precision and accuracy? Will it be possible to detect the shape of the dose response function at very low blood lead levels? Second, which covariates should be included in NHANES III? Despite the very long list available and analyzed in NHANES II, what other potential confounders were missing from NHANES II and should be added to the NHANES III? Finally, what are the recommendations for the techniques for blood pressure measurement in NHANES III.

Schwartz reinforced Provenzano's comments regarding the anticipated much lower levels of blood lead in NHANES III and emphasized the need for more accurate and precise measurements of blood lead levels. Schwartz questioned whether there were going to be home dust samples analyzed for routes of exposure to metals other than drinking water. Provenzano indicated that the difficulties in sampling for metals made it unlikely that this would be attempted.

Mahaffey emphasized the need to develop indices of integrated exposure to lead. Wedeen suggested that the estimation of bone density might provide techniques close to those used to measure bone lead. V. Bonar pointed out that there is considerable evidence that social variables are related both to blood pressure and blood lead and inquired regarding the measures of potential, social confounders in NHANES III. Lilis emphasized the importance of estimation of alcohol and smoking and added that these two plus water were major sources of lead exposure.

Cole pointed out the limitations in the observational epidemiologic data available in the past and urged a systematic planned approach to NHANES III to contribute to the question of whether or not any observed association was causal.

Tyroler noted that the morning's session began with an overview by Pocock and asked Schwartz if he would conclude the session with his perspective on the overview of the blood pressure-blood lead relationship. Schwartz indicated that he generally agreed with Pocock's summarization, that is, that there is a broad consistency in the results across studies, that the coefficient relating blood lead to blood pressure on the log scale indicated that doubling of blood lead was associated with a 1 to 2 mm change in mercury. Thus, based on the epidemiologic data, he concluded that there is an association, it is not large in respect of the millimeters mercury explained, and the studies are consistently positively around that range. He disagreed with Pocock regarding the causal interpretation and suggested that although causal inferences could not readily be drawn from the epidemiologic data *per se*, that they were consistent with the animal data and that for the animal data it was not difficult to draw a causal inference. Information was emerging within the animal studies regarding mechanisms such as exaggerated alpha adrenergic responses, and disturbance of calcium metabolism and that similar mechanisms have been postulated for mild hypertension in humans. Based on these observations, Schwartz concluded that there is probably, although not definitively established, a causal relationship. Schwartz emphasized that lead is a controllable element in the environment and that removal of exposure early in life could prevent the emergence of elevated blood pressure, an approach much safer than that of treating elevated blood pressure after it had emerged.