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**REGION I
OFFICE OF REGIONAL COUNSEL**

Charles Berring
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Boston, MA 02114

Dear Charles:

Enclosed is a copy of the National Electrical Manufacturer's Association comments on the Greater New Bedford Health Study. Please send me a letter from your office requesting that our laboratory data be sent to your technical contractor.

Sincerely,

Ralph J. Timperi
Deputy Director

RJT:am

Encl.

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Review of the Report
"Proposal For a Greater New Bedford, MA
PCB Health Study"

Massachusetts Health Research Institute, Inc.
and
Massachusetts Department of Public Health

December 21, 1984

Review of the Report
"Proposal For a Greater New Bedford, MA
PCB Health Study"

Massachusetts Health Research Institute, Inc.
and
Massachusetts Department of Public Health

Submitted to the National Electrical Manufacturers Association
by:

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December 21, 1984

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I. Overview

This report presents a critical review of a proposal by the Massachusetts Department of Public Health (MDPH) which was submitted to the Centers for Disease Control (CDC) and the Environmental Protection Agency (EPA). The proposal is for a study of health effects associated with exposure to polychlorinated biphenyl (PCB) among residents of greater New Bedford, Massachusetts. Two phases are proposed. In Phase I a blood sample will be obtained from 1,400 residents of the New Bedford area to determine the prevalence of PCB contamination in the population, the route of exposure (occupational versus environmental) and the correlation between blood pressure and the level of PCB in blood. A series of skin tests are also proposed. In Phase II, two groups of subjects will be selected --150 with an elevated blood PCB level (greater than 30 ppb) and a matched group with low blood PCB levels (less than 10 ppb). A number of issues will be addressed in this phase including liver enzyme induction, alteration of lipid metabolism, depressed immune function and neurotoxicity. The proposal can be characterized as ambitious, complex and of dubious merit. The major contention of the proposal, that it will answer the community's concern about PCB exposure and subsequent health effects, cannot be met by the methods which are presented.

II. Background

The investigators do not make a convincing case for this study. PCBs are ubiquitous in our environment and there have been several studies and surveys which have not found adverse health effects in humans. The source of PCBs, its biochemistry, its distribution in the environment and potential health effects, as documented by previous investigations, is not

discussed in adequate detail in the proposal. This is of particular importance since the construct of the study depends on previous detailed information acquired from prior studies. In addition, some of the existing data are not dealt with in an logical fashion. For example, the acute effects of PCBs on skin are manifested as chloracne or allergic dermatitis. These observations would suggest that chronic PCB exposure might have a predilection for cutaneous tissue. In turn, this might suggest that more intensive evaluation of study subjects by dermatologists be available in this proposed survey. Alternatively, it would also reasonable to obtain skin biopsies on selected individuals as detected by the Phase I studies. While the proposed Phase I screening physical or questionnaire may pick up the skin problems, it is believed that it might be more judicious to emphasize evaluation of dermatologic changes in the Phase I.

There is reference to a possible occurrence of melanoma and rectal carcinoma in occupationally exposed individuals. While the investigators acknowledge that this is controversial, it would be appropriate to detail the exact statistical evidence in the referenced studies. This is of some importance because the investigators apparently have decided to evaluate the presence or absence of colonic bleeding based on this evidence. Finally, in the background section, there is need for a discussion of the possible immunologic aberations that PCB may induce in humans. The investigators have a rather extensive in vivo and in vitro plan for assessing immune function in individuals in New Bedford. Since this aspect of the investigation appears to be a relatively major part of their study, it is somewhat curious that there is no discussion in the background information about possible immune alterations in humans

(see proposal, pp.1-5).

It is stated in the proposal (pages 7 and 8), that literature on PCBs reveals a discrete number of postulated biochemical and physiological effects. Presumably, these biologic effects of PCB relate to the liver, lipids, immune status, neurotoxicity and blood pressure. It is not clear how it was determined that these were the most important parameters in this study. For example, there is discussions of the abnormalities in liver function tests found in animals and humans exposed to PCBs. Page 8, paragraph 4 begins with the statement that, "related to the above liver changes is a finding of hepatic porphyria in animals exposed to TCDD or PCBs". Apparently the investigators are suggesting that abnormalities in liver function may be associated with hepatic porphyria in humans. These kind of conclusions need to be detailed in a more convincing fashion.

On page 9, first paragraph, the statement is made that lipid abnormalities are due probably to the toxic effects of PCBs on the liver. This appears to be a totally unsubstantiated statement, either by reference to previous literature or by some discussion of how these abnormalities in liver function tests might be related to the altered lipid profiles. There is a paragraph (page 9) which discusses the altered immune function found in PCB exposed individuals. Two references in particular are cited which give data on the number and function of T & B lymphocytes in the peripheral blood of exposed individuals. The authors then make the statement that these data, although preliminary, suggest that there are significant alterations in immunologic competence in these patients, particularly with respect to T-helper cell function. If, in fact, T-helper cell function has been altered by PCBs and documented in prior

investigation, some detailed explanation of this observation should be provided. This in turn would help to understand why there is a focus on evaluating immune function in PCB exposed individuals. For example, depressed immunoglobulin levels, which have apparently been documented in PCB exposed individuals, may be due to abnormal T-helper cell function, excessive T-suppressor cell function, or primary B cell abnormalities. If this is the issue, then one could construct a detailed individual analysis to attempt to detect the specific immune abnormality. Finally, in this paragraph they mention that the latest techniques in T and B lymphocyte fractionation will be used. Here again, it is unclear exactly what methodology they are discussing. If they are referring to ficol-hypaque fractionation, this is hardly the latest technique, since it has been in use for almost two decades and is used routinely by many different laboratories. Presumably the reference is to the use of fluorescence activated cell sorter. Since one of the major immunologic techniques in the evaluation of PCB exposed individuals is T and B lymphocyte membrane phenotyping, it would be appropriate at this point to discuss in some detail the utilization of membrane phenotyping in normal individuals. This would provide a basis for the potential investigations as outlined for Phase II patients. The investigators also fail to discuss any possible pitfalls in the utilization of either skin testing for Phase I or doing membrane phenotyping to evaluate T and B lymphocyte populations in Phase II. For example, there is no discussion of the percentage of individuals who may have an adverse reaction to skin testing, or the problems with utilizing T-helper to T-suppressor ratios in the detection of "immunosuppression". This latter ratio, while in widespread use today, clearly is a very insen-

sitive indicator of the overall status of immune function. This particular parameter needs to be combined with other in vitro tests in order to allow an overall assessment of human immune function. The T-helper to T-suppressor ratio may, for example, be reversed dramatically in normal individuals with viral infections. This is a transient effect and quite clearly, if used by itself, would be misleading with regard to host immune function. In any case, some discussion of the possible negative aspects of utilizing these particular in vitro or in vivo tests is necessary and is not apparent in this protocol.

The investigators raise the issue of the possible relationship between blood PCB levels and diastolic blood pressure based on a single case report. This has clearly become a major issue in the proposal as blood pressure evaluation is prominent in both Phase I and Phase II. Exactly why this plays such a prominent part in the proposal is somewhat perplexing. The investigators admit that this relationship has not been documented in other PCB health studies. Here again, it would be informative to have a more detailed discussion of why the investigators chose to evaluate this potential biologic sequelae of PCB exposure.

III. PCB Exposure

Between the early 1940's and 1977, two companies in New Bedford, Aerovox Incorporated and Cornell-Dubiler Electronics Corporation, apparently discharged PCB-tainted waste water into the Acushnet River. The contention is made that PCBs in the river entered the aquatic food chain contaminating lobster and fish which were consumed by residents of New Bedford. Exposure may also have occurred from the placement of defective capacitors in a municipal landfill and contaminated water discharged

via sewers into the municipal water treatment plant. Therefore, exposure may have occurred through ingestion of seafood, through skin and respiratory absorption for employees at the two capacitor manufacturing companies and through air emission from the municipal waste water treatment facility and the municipal landfill.

Unfortunately, no data are presented to document the presence and extent of PCB exposure in fish or lobster, in the workplace, or in the air from emissions from the waste water treatment facility and municipal landfill. A reference (no. 3) is cited from the Massachusetts Coastal Zone Management which may contain data on measurements of PCB contamination in the treated water discharged into the Acushnet River. Considerably more data on the presence of PCBs would be useful to validate exposure through the purported systems. It is surprising that the studies in Michigan are not given more attention in the proposal since they include relevant material particularly with respect to the occupational versus environmental contribution to blood PCB levels.

Results of two pilot studies are presented in the proposal which show a median PCB blood level of 13 ppb in one group of subjects and 15 ppb in another group. About one-third of the subjects had levels greater than or equal to 30 ppb. These data are apparently presented to illustrate the extent of the exposure. Although based on a small number of volunteer subjects, the investigators use the proportion with values greater than or equal to 30 ppb to support the need for a study. However, the utility of these data are of dubious value in this regard for a number of reasons. First, they were obtained from a small, highly select group of volunteers. Second, using 30 ppb as a cutoff, implying that about one-third of the

study sample may be at risk for disease, is arbitrary since no data exist to relate blood PCB levels to health effects. The only rationale presented for using this cutoff is as stated in the proposal, "The Toxicology Laboratory of the CDC uses 30 ppb blood PCB as the level below which will be found 99% of 'unexposed' blood samples." In fact, one of the project investigators, Dr. Baker, published a paper in 1980 in which he showed no clinical disease associated with PCB exposure where the exposed group of workers had mean blood levels of 75.1 ppb. It is somewhat surprising that this paper was not cited as a relevant reference in the project proposal since it appears similar to methods in the proposed study.

Since consumption of contaminated fish and lobster essentially stopped in 1979, blood levels in dynamic equilibrium with fat stores would be expected to continue to fall. If the previous studies are any indication, the percentage exceeding 30 ppb could be as low as 13%. This low level would have important implications for the conduct of the Phase II study.

IV. Rationale and Study Objectives

The foundation for undertaking the proposed study is weak and consists of the following:

1. Two companies used PCBs and workers may have been exposed.
2. PCBs discharged in waste water entered the Acushnet River and may have contaminated the seafood. Residents consuming seafood were exposed to the
PCBs.
3. Air emissions of PCB may have occurred from the waste water treatment facility and the municipal landfill.

4. About one-third of a small group of volunteers had a blood PCB level greater than or equal to a somewhat arbitrary value of 30 ppb.
5. No occurrence of illness related to PCB was noted by local physicians, however, there was considerable public concern about possible health effects.

This latter point is important from two aspects. First, public concern is often a sufficient reason for a state health department to conduct a major health study. Second, the same public concern can have a profound effect on the results of a study, particularly when people know they may have been exposed (worked for the company, lived near the landfill, ate a lot of seafood) and many of the endpoints are based on the self-reporting of subjective conditions. The latter is an inherent problem in all such studies and every effort must be made to adhere to basic tenets of sound epidemiologic research in the design, conduct, analysis and interpretation of the study and the results.

Four basic study objectives are presented on page 7 of the proposal:

1. To define the prevalence of elevated blood PCB levels in the New Bedford population.
2. To establish the determinants of increased PCB exposure and to develop a basis for risk factor identification.
3. To determine whether there is a relationship between PCB levels and specific illnesses.
4. To study, in depth, certain postulated biological sequelae of PCB intoxication (i.e. liver enzyme induction; altered lipid metabolism; altered immune status; neurotoxicity and blood pressure).

The rationale presented for these objectives is vague and superficial--"... will add to the knowledge about baseline PCB levels...", "...help delineate exposure routes...", "...help in allocating resources for further study of the matter and in decision making about seafood quarantine as well as harbor clean-up..." Exactly how these decisions will be made based on the results from objectives one and two is not explained by the investigators. What is the meaning of "to develop a basis for risk factor identification?" How will this be done? Perhaps the investigators' concept of a risk factor differs from more common usage of the term. In fact, it is very unlikely that objectives 2 and 3 can even be achieved with the proposed study.

The investigators suggest that the specific and focused studies in objective 4 are preferable to the usual "shotgun approach". Given the many clinical and laboratory tests that are proposed, it would be difficult to consider this anything but a shotgun approach where the likelihood of finding at least one association is high in view of the number of factors being considered. How will the statistical problem of multiple hypotheses testing be handled? No discussion is presented on this important issue.

The investigators state, "The New Bedford population is an ideal study group because of the moderate PCB levels in a non-occupational group" (p. 11). This statement is puzzling since, given the lack of evidence incriminating PCB except at very high levels, why would a study of a moderate exposure group be ideal? Would not a more highly exposed group be preferable? The investigators further state, "Although it is unlikely that overt illness such as in the Yusho incident will be present with such

moderately elevated PCB levels, there is evidence from animal and human studies to warrant concern about chronic health effects, including carcinogenicity." (p.12). This sentence seems internally contradictory. Furthermore, there is no strong case to be made for carcinogenicity based on available evidence.

V. Study Proposal

A. General

The basic study plan is presented in three distinct parts: Pretest, Phase I and Phase II. The Pretest will be an opportunity to try out study procedures and questionnaires; in Phase I a random sample of New Bedford residents will be selected, blood will be drawn for PCB determination, blood pressure will be determined and skin tests administered; in Phase II 150 people with high blood PCB levels and 150 with low PCB levels will be selected for the battery of clinical, laboratory and neurobehavioral tests.

B. Pretest

Two pretests are proposed. The first will include pretesting the random sampling techniques, the telephone contact procedures and direct solicitations and the questionnaire. The second pretest will include a study of the various tests which will be utilized in Phase II.

The use of pretests as proposed is sound since these provide an opportunity to thoroughly test all aspects of the main studies. However, it is difficult to offer a detailed evaluation of the pretests since little information is provided in the proposal. For

example, how many people will be tested? How will they be selected? Will they also be part of the population invited to participate in Phase I? What validation procedures will be used to determine the acceptability of certain procedures, questionnaires, etc.? What is meant by, ..." attention will be paid to non-respondents and dropouts, and this will be included in the analysis."? What kind of attention, what does "this" refer to and how will it be included in the analysis?

The investigators are confident that an 85-90% response rate can be expected. This is based upon previous small nonrandom surveys. The high response may be achievable, but even under more ideal circumstances, it would be considered overly optimistic. To achieve such success, careful planning and elaborate mechanisms for "persuading" nonrespondents and dropouts to return to the study, consistent with human subjects procedures, must be devised. It should be anticipated that the emotional, politically charged arena in which this study will be conducted may engender many nonrespondents. Many may be fearful for their jobs (area has high unemployment), many may be disgusted with all the attention in the media that this issue is getting, and many may be just afraid to participate because of the blood drawing or the perceived invasion of privacy the study will involve. Unless the above concerns are ameliorated, it is very likely that biased recruiting will result which will have drastic implications for the validity of Phase I and Phase II.

The concern over selection (recruitment) bias is not just of academic interest. Control or minimization of this bias is a basic epidemiologic tenet. Whenever selection bias occurs there is substantial

difficulty in interpreting study findings. If recruitment is more likely in those who know they were exposed and are concerned about their "poor" health, the study will "discover" a positive relationship between exposure and health. Others who are heavily exposed may wish not to be studied because of fear for their job or loyalty to the company. If there is a real association between exposure and health and if self selection is operative, then the study's finding will be biased to the null hypothesis (i.e., no association). As described above, the potential for various forms of selection bias appear large. The assumption of a 85-90% response is a superficial treatment of this issue. What if the response rate to the first survey before alternates is only 30%? The investigators provide no hint that they understand this important issue and have provided no contingency plans for handling it.

How will a retesting of a small number of participants "validate both content and methods of obtaining data."? This will measure reliability or repeatability, not validity.

Perhaps the most troublesome aspect of the proposed pretest is the fact that the investigators expect to accomplish all the necessary testing in a two week period. Either they are extremely adept at conducting such studies and have an unusually highly compliant group of people, or they have grossly underestimated the amount of work required for an adequate pretest of such a difficult and involved study protocol. Surely some revisions will have to be made in their procedures and these in turn will require appropriate pretesting. It is unrealistic to expect to conduct an adequate pretest of this nature

in two weeks.

To help stimulate interest in the study and increase participation, it is proposed to make extensive use of the media and public meetings sponsored by the New Bedford Forum (an organization of concerned citizens). On the one hand, these can certainly increase public awareness and participation but, on the other hand, there is a risk of interjecting an element of bias into the study. Since many of the questions are subjective, the potential for biased responses is great. It is important in studies of this nature to maintain blindness and strive for unbiased, objective responses which can be validated whenever possible. Although the investigators state (p.11) that the neurobehavioral tests will be done in a blinded manner since neither the subject nor the investigator will know the blood PCB level, the fact is that some individuals will have some notion of their exposure by virtue of the fact that they worked at one of the companies or lived near the landfill or consumed a lot of seafood.

Other proposed strategies to increase participation rates include the use of language translators and flexible schedules for appointments. These are eminently reasonable and desirable considerations.

Two questionnaires are presented in the proposal - one labelled "Pre-Test Questionnaire" and one labelled "Greater New Bedford Health Survey Questionnaire - Phase I". It is unclear why these two questionnaires are presented and exactly how they will be used. It would seem logical to have a single Phase I questionnaire which would be pretested. Why is the designated Phase I questionnaire so different from the Pre-Test Questionnaire? Specific comments related to

the Pre-Test Questionnaire include:

1. What is meant by "normal" amount of sleep?
2. Will all subjects interpret "temporary physical ailments" in the same way?
3. Asking "Do you have any worries or other personal problems" is subject to a wide range of interpretations and therefore essentially of little value.
4. "How many drinks?" of what? hard liquor, wine, beer? More specificity is needed.
5. Validity of data on toxic chemical (Q. 14 and 15) is questionable. Perhaps a list would be preferable.
6. Medical history should be validated through physician and/or hospital records.
7. People often do not remember the name of their medications (Q. 23). Perhaps asking them to bring in their pill bottle would be helpful.
8. Alcohol section is quite extensive. How will these data be analyzed? Are so many questions needed?
9. Q. 40 asks about "average" amount of sleep. Is this the same as "normal"? How will people interpret this?
10. Q.41 is very subjective and probably of limited value.
11. An analytical plan for Symptom questions (41-57) should be presented. These are very subjective questions and responses could be influenced by subjects' knowledge of exposure.
12. How will the "Post-Test Questionnaire" and "Examiner Post-Test Questionnaire" be used? Will data be excluded for subjects who report that they didn't try at all?

C. Phase I

In general, the investigators do not make a good case for the need for conducting Phase I. Similar studies have been done in Michigan and Alabama which have descriptively examined many of the hypotheses described in the application. Since neither of them have found health risks it is not clear what service it would do the community to measure blood PCB levels cross-sectionally. Longitudinal studies might be useful but none are described. Phase I is also full of many substudies that do not appear to be integrated into the overall study design and cannot be used for their specified purpose - to evaluate confounding. Therefore, substantial rethinking and redirection of Phase I is necessary.

1. Study Population

The study population, defined as males and females between the ages of 18 and 65 who have resided in the study area for at least five years, will be selected from among the approximately 140,000 people from of the New Bedford area. Although there is no sampling frame (census) for children under 18, some thought should be given to sampling teenagers or young children in order to longitudinally evaluate blood levels. It is not clear why the investigators feel that obtaining consent to include children is more difficult. If the investigators consider the inclusion of children relevant to the study objectives, then recruitment procedures could be developed and pre-tested.

The substantial number of Portuguese (49%) in the community requires that tests and procedures be translated and administered

by Portuguese speaking interviewers. This is proposed by the investigators. More importantly, however, is the problem of using the neurobehavioral tests without first standardizing them to this population.

2. Sampling Technique

The ability to construct a population-based sampling frame based on the yearly census is very positive. However, the completeness and accuracy of this census must be verified if it has not already been done in another study. This is especially important considering that more than 50% of the population are ethnic minorities which have been traditionally under-represented in such surveys.

The initial solicitation will be by telephone. Names of individuals selected in the sampling frame will be checked in the telephone directory and if found, the person will be called. If the name is not found, individuals with similar names will be called. If verified, he/she will be invited into the study. If there is no answer, three additional attempts will be made at later times. Why only three? Will the subsequent attempts be on different days and at different times of the day? The three additional attempts to nonresponding calls are not generally adequate. Usually up to nine attempts are required staggered during the week, evenings and weekends before a telephone number can be discarded.

Similar problems exist with the procedure for dealing with

people without telephones. It is appropriate to visit such homes as proposed by the investigators but only one call-back is insufficient to resolve a nonresponder.

Why are people with mental impairments being interviewed? How valid are these data and how will they be used?

3. Phase I Visit

a. Blood Pressure

The three blood pressures will be taken in three entirely different emotional and stress situations. It is not clear that standard protocols for blood pressure measurements are being adhered to and therefore their interpretation and comparison will probably not be meaningful.

b. Questionnaire

The questionnaire (Appendix 4) needs more thought and attention. Why not limit residential history to identify residences in the New Bedford area only? What is the value of the residence information from other areas? The exposure history, which is an important set of data, is inadequate. The question refers to any contact and no distinction is made between very brief contact and very substantial contact (e.g. someone who may have done some painting once on a job and someone who has spent many years in this trade). Similar comments can be made of the following question related to insect sprays. How will the investigators distinguish between someone who used an insect spray more than three times a year once or twice in his life and someone who used it on many

occasions in his life. What about when the occasional exposure occurred? What if it happened many years in the past? This information will not be obtained from the existing question. Under medical history, who decides what a "serious" medical or surgical problem is? Surely different people will perceive these in different ways. Will everyone interpret and report "nervous or skin condition" in the same way? Will these be validated through medical or hospital records? What about underreporting? How will these be ascertained? In Question 5, it is necessary to get the name of the diagnosing physician so that the reported condition can be verified. The smoking history does not include information on the number of cigars or pipefuls of tobacco smoked. Questions 8 and 9 are very subjective and of limited value. Reporting can be influenced by knowledge of exposure. How will these be verified? The dietary history is incomplete. For example, there is no question on eating the skin of fish. In the Michigan study, it was shown that in contaminated fish, the skin and subcutaneous fat represent the highest level of PCB.

c. Skin Test

There are some concerns about the follow-up evaluation of the skin tests. The first concern rests with the visit of these individuals at home by a public health nurse. It would seem more reasonable to have these individuals repeat a visit to an outpatient area where the skin test can be read by trained personnel. If in fact, the study population will be

visited at home, the investigators state that either a public health nurse or other qualified medical personnel will evaluate the skin testing. Who are the "other qualified medical personnel"?

The skin testing portion of the protocol is inconsistent with the summary which calls for testing delayed hypersensitivity in Phase II.

4. Analysis of Blood PCB Level

The Phase I laboratory protocol is presented in considerable detail. It constitutes the best written and thought-out portion of the application. The quality control considerations appear to be good and a priori decisions about acceptable variability are already defined. The decision to run the assays at MDPH is curious. Why not send them to CDC instead of using CDC standards? It may be that this study is a demonstration project for CDC's desire to increase environmental monitoring capacity in state departments of health. However, even if the laboratory results represent the highest quality analytic procedures, this is not in itself a reason to justify a study that cannot meet its stated objective.

There is no justification for the specific isomer analysis (maximum 25 sample), hydrocarbon screen (5% sample) or heavy metal screen (10% sample). There is some language about confounders but these three "add-ons" have the appearance of several independent studies. Confounding involves the direct relationship between an exposure and both a factor and the disease outcome. Lead, which

also could be occupationally associated with PCB exposure, and also associated with similar gastrointestinal and neurologic manifestations as PCBs, would be a confounder. Evaluation of confounding rests on both analytic and biologic bases. It would seem impossible to analytically control for confounding of lead in the analysis if only 10% of the subjects have blood leads.

5. Statistical Analysis

The lack of consideration of the potential for nonrespondents and dropouts and their important impact on selection bias have already been discussed.

The statistical plan as described is woefully inadequate. The sample size of 1,400 is adequate to detect a doubling from 1% to 2% of the proportion of PCB levels exceeding 30 ppb with a power of 80% and an alpha of 5%. This is probably a reasonably justifiable method to determine sample size. However, it does not take into consideration the stratified random design. Since the population will be stratified by ethnicity, age and sex, a substantial savings on sample size for the stated purpose could be obtained. The sample size of 1,400 is apparently based on simple random sampling and does not take into consideration the increased efficiency of the stratified random design.

Justifying the sample size on the ability to detect a correlation of 0.11 is somewhat naive. This would convert to an R^2 of 1% which means that only 1% of the total variability in blood pressure is "explained" by the PCB blood level. An association of this magnitude has no biologic importance even if it is statisti-

cally significant.

The analysis of variance and covariance using SAS or SPSS is not straightforward. An experienced and well-trained statistician is required in order to determine which model is appropriate. The decision whether the experimental design is random, fixed or nested, and the effects of unequal sample size require judgments which can have important implications on resultant analyses.

Although standardly used in these situations ANOVA and ANCOVA may be too constrained to evaluate important interrelationships within the data. ANCOVA in particular, which also employs a regression model, may be prone to loss of this information. For example, age, occupation and ethnicity may be collinear as well as related to the outcome variable, blood PCB level.

Multicollinearity is a delicate matter that requires experience and knowledge of sophisticated methods such as ridge regression to deal with it. Synergism or interaction of the independent variables may be very important to identify factors associated with low or high PCB blood levels and to understand their joint and individual effects. Exploring these relationships is not straightforward with ANOVA or ANCOVA.

Although replacing a continuous measure with discrete levels would partially denigrate the data, consideration should be given to contingency table analysis and log linear models. Models can be constructed systematically and, through partial association tables, existence of confounders, effect modifiers and multicollinearity can be examined. These results would be very important to

the proper interpretation and modeling (contrasts) using ANOVA and ANCOVA methods. The loss of degrees of freedom using log linear models as a statistical screening tool is more than compensated by the resultant understanding of data structures that can be refined using other techniques such as ANOVA, ANCOVA and regression. Without the knowledge of data structure (e.g. confounders) the analytic methods produce biased results.

D. Phase II

It is apparent that the intention is to conduct Phase II regardless of what the findings from Phase I. There should be a priori decision criteria that lead to the initiation of Phase II. What if the prevalence of PCB levels in excess of 30 ppb is very small? What if there is no correlation with blood pressure? What if there is no relationship with delayed hypersensitivity? The reasons for conducting Phase I are marginal at best and Phase II should be initiated only if the findings from Phase I justify a second, more elaborate and expensive Phase. As described, the Phase II study cannot adequately evaluate the health effects of high and low exposure. It should not be represented as having this capacity. This phase has too little power and is fraught with selection bias. In addition, Phase II is in some ways a rehash of Phase I with the restrictions of much smaller sample size. Certainly, under any circumstances, Phase II as described is not warranted.

1. Sample Selection

No justification is given for the sample size of 150 "unexposed" and 150 "exposed". Most likely the joint sample of

300 was based, at least partly, on financial considerations. There is no recognition of the lack of power that an exposure-based case-control study of 300 people will have. In a matched analysis only the discordant pairs contribute to the relative risk estimate. The prevalence of individuals with major chronic diseases such as cancer and diabetes ranges from 0.5% to 2.5%. This would translate (if similar for the chronic conditions under study for PCB exposure) to no more than 8 discordant disease pairs. From the accompanying table it is clear that one would have little hope (power) of detecting even a relatively large risk (3.0) with this sample (power less than 0.3). To detect modest risks (2.0) with a reasonable power (0.8) would require several thousand more matched pairs and would only be useful for the more prevalent conditions. If the prevalence of conditions is closer to 0.5%, the sample size required to detect modest risks would be prohibitively large. Splitting the high PCB exposure groups for Phase II further decreases the power. The importance of power (chance of detecting a difference) cannot be overstated.

There is no indication how the additional sample of high exposed individuals would be drawn and no indication of how the low exposed individuals would be selected from the many eligible in Phase I. Recruitment and selection bias could be very important because of the small sample size and, in light of the above concerns, very possible. Reemphasizing an important point, if fastidious control is not maintained and if individuals with high exposure and "disease" are more easily recruited the resulting association will be artifactual.

TABLE - ODDS RATIOS (R), NUMBER OF DISCORDANT PAIRS (M) AND POWER (P)
OF A MATCHED CASE CONTROL STUDY

ODDS RATIOS R	NUMBER OF DISCORDANT PAIRS M	POWER P
1.25	5	0.04
1.25	10	0.05
1.25	15	0.06
1.25	25	0.08
1.25	50	0.12
1.50	5	0.06
1.50	10	0.09
1.50	15	0.11
1.50	25	0.16
1.50	50	0.29
2.00	5	0.10
2.00	10	0.17
2.00	15	0.24
2.00	25	0.38
2.00	50	0.66
2.50	5	0.13
2.50	10	0.25
2.50	15	0.37
2.50	25	0.58
2.50	50	0.88
3.00	5	0.16
3.00	10	0.33
3.00	15	0.49
3.00	25	0.73
3.00	50	0.97

2. Phase II Tests

a. Neurobehavioral Tests

i) Overview

A set of neurobehavioral tests will be introduced in Phase II of the study. Dr. E.L. Baker will be responsible for the neurologic and neurobehavioral evaluations with the support of a neurobehavioral technician. He appears to be the sole professional involved in the supervision of the neurobehavioral studies. His background in psychology appears to be limited to undergraduate work so that he may not be fully qualified to devise or supervise the administration and analysis of psychological test protocols. The proposal does not identify any specific, qualified individual who might serve as a consultant nor does it establish the qualifications of the neurobehavioral technologist. The American Board of Clinical Neuropsychology could assist in the identification of qualified individuals since there are a number in the East and in the Boston area who have now passed the board certifying examination. The Boston area is well known for its extensive resources in neuropsychology and behavioral neurology so that the necessary expertise could readily be obtained.

ii) Rationale for the Selection of This Neurobehavioral Test Battery

The rationale for the selection of these tests is

based primarily on the fact that they were used in the previous studies of neurotoxicity conducted by the author. In turn, the tests were devised in response to the modal complaint pattern of individuals who participate in such studies, namely, disturbances in attention, memory and mood. Thus, the proposal does not cite the growing and relatively vast literature on the neuroanatomical basis of behavior change in CNS disease. This literature reflects a convergence of many areas including neuropsychology, behavioral neurology, neuro-linguistics, cognitive psychology, psychophysiology, neuropathology, speech pathology, and psychopathology and provides a strong theoretical and empirical base for devising neurobehavioral batteries for this type of research.

There is empirical evidence in support of regional localization theories that incorporate brain-behavior relationships at various levels of the central nervous system. Three major levels have been identified for activation, attention and arousal (I); affective modulation and expression (II); and higher cortical functions such as information processing (both verbal and nonverbal) learning and memory, and planning and executive abilities (III); any battery purporting to be sensitive to alterations in behavior emanating from pathophysiological changes at these three major levels of func-

tion should include validated measurements of functions at each level. Furthermore, the particular functions assessed should be identified on the basis of their relationship to structures that are relatively more vulnerable to neurotoxic influences.

These include the third layer of the frontal cortex, the hippocampus and parahippocampal grey, the dorsal medial nucleus of the thalamus and the mammillary bodies. While the literature implicating these structures is based largely on evaluation of individuals with Korsakoff's syndrome, it seems reasonable to utilize such studies as a point of departure in devising batteries of this kind. The test descriptions and suggested alternatives given below will attempt to provide such a frame of reference. It seems clear that the selection of tests for the purposes of this study was not based on an examination of the neuropsychological literature. In addition, selected methodologic issues are addressed.

iii) Neurobehavioral Test Selection

Appendix 13 describes a test battery that includes measures of visual attention and concentration (CPT), a hand-eye coordination task, the Digit Span subtest of the Wechsler Adult Intelligence Scale, the Sternberg Memory-Scanning Test, the Paired Associate Learning Test of the Wechsler Memory Scale, the Vocabulary Subtest of

the Armed Forces Qualifying Test (AFQT) and the Profile of Mood States (POMS). Test administration will be conducted by means of computerized stimulus presentations through a video display unit.

Visuomotor Performance

1. Dynamic Continuous Performance Test (CPT)

The application of this test utilizes only the single target letter monitoring procedures. It might be useful to add the contingency procedure which alerts the subject to the upcoming appearance of the target letter. Individuals with activation and arousal deficits sometimes do better under this condition whereas those with cortical lesions do worse. This is perhaps the most relevant test in the battery insofar as it addresses the attentional disturbances reported by patients with known neurotoxicity.

2. Hand-Eye Coordination Task

The task has face validity as a measure of coordination but has not been investigated in the neuropsychological literature. It has face validity for the purpose of measuring dexterity and coordination but should be normed, and more importantly, its reliability should be established. Reliability data are not reported for any of these procedures although such data are available for the more standardized procedures taken from the Wechsler Series.

Memory

1. Digit Span (Wechsler Adult Intelligence Scale)

This well known measure of immediate auditory retention is widely regarded as a measure of attention and concentration rather than memory. For example, individuals with severe disorders such as Korsakoff's syndrome may do exceedingly well on this task by overcompensating for their memory losses in this type of format. More important for the study of memory is the ability of the individual to store and retrieve the information over significant periods of time. Digit span procedures do not provide an assessment of recent or long-term memory functioning. They do, however, provide information about the individual's ability to attend for brief intervals of time. Reliability of such measures is characteristically low since performances vary as a function of momentary state changes of a kind seen, for example, in the functional psychiatric disorders. A low score, therefore, may reflect a reversible outcome of no significance for organic brain dysfunction. A better procedure has been shown in the literature to differentiate organic from nonorganic samples more effectively. This is a 9 digit (supraspan) sequence which is achieved by the

third trial in most normals. If a digit span procedure must be used, the 9 digit sequence is clearly more desirable and more sensitive to organic brain dysfunction than the traditional WAIS approach.

2. Sternberg Memory-Scanning Test

Again, this would appear to be more a measure of attention than memory though it does place a greater demand on the processing efficiency of the subject. Accordingly, it may conceivably be as sensitive as the 9 digit sequence in differentiating organic from nonorganic samples. However, the test has not been validated for drawing such inferences.

3. Associate Learning Test

This is the well known noun-noun pair learning procedure from the Wechsler Memory Scale. Of the 10 pairs, 6 have a very high association value and, therefore, have already been learned from previous experience and are relearned during the test. This is referred to as a crystallized function that is related to the semantic memory of the individual based on extensive previous experience. Such crystallized functions are relatively impervious to the effects of CNS involvement, especially when slowly progressive neuropathological processes underlie the memory complaints. Four of the noun-noun pairs are unrelated and, therefore, provide an

opportunity for new learning to occur. This involves acquisition of new episodically presented information and is relevant to the purposes of neurobehavioral assessment in the study. However, the four word pairs are insufficient to provide a stable or reliable measure of this type of function. Longer word-pair lists or lists of unrelated single words may provide a better basis on which to measure memory functioning. There is an extensive neuropsychological literature on the anatomical basis of immediate (or short-term) and delayed (or long-term) memory. There is also a literature on remote memories which tend to remain relatively intact even in severe memory disorders.

At this juncture, it is appropriate to identify three major deficiencies in this test battery. One relates to the absence of relatively nonverbal test formats; the second, where memory assessment is concerned, to the absence of a delayed recall procedure designed to test for recent (long-term) memory changes; and three, the absence of tests of planning and "executive" functions. It is well known that the earliest manifestations of generalized cerebral dysfunction on an organic basis appear on tests that introduce unfamiliar or novel stimuli. Such tests are more often nonverbal in nature and

sample what Cattell calls "fluid" abilities. These are to be contrasted with "crystallized" abilities since they involve greater demands on higher adaptive functioning owing to the fact that the individual has not had extensive, if any, experience in processing and organizing such unfamiliar information. Such tests are also more sensitive to early age-related changes and to dysfunction in the right or nondominant cerebral hemisphere. They may have some nonspecific implications for brain dysfunction in the context of neurotoxicity and, because of their greater sensitivity to underlying neuropathological changes, should be included in assays of this type. The second concern relates to delayed recall measurements which are essential for assessing storage and retrieval of memories from storage. Immediate or short-term memory may be entirely intact in a person with major memory problems. The memory deficit does not become evident until at least minutes have transpired. Characteristically, delayed or recent memory is measured over intervals of a half hour to an hour and beyond. Again, the protocol provides no indication of an awareness of this literature or its implications for devising a protocol in this context. These functions may be affected selectively with involvement of the temporal lobes. The third class of functions (planning and executive) are measured by tests of

serially-organized behavior and abstract reasoning. Again, the battery lacks such tests, and accordingly, does not assess these critical prefrontal functions.

Verbal Concept Formation

1. Vocabulary

This test is provided as an index of "stable CNS function". Vocabulary measures typically reveal the relative integrity of functional speech and comunciability and constitute another class of "crystallized" abilities. Performance on such a test is resistant to change even under conditions of extensive CNS involvement. For example, primary degenerative disorders may be advanced yet the individual may maintain a high level of function on this test even while other conceptual performances such as abstract nonverbal reasoning, have become grossly deficient. This battery lacks measures of the latter and appears merely to utilize vocabulary as a control measure for determining gross deterioration of intellectual functions from the baseline established by the AFQT for individuals who took the test while in the service. Vocabulary is not a measure of verbal concept formation, but rather of verbal concepts already established from extensive previous learning.

Batteries for this type of research should

include measures of (new) concept formation and inductive reasoning. Vocabulary measures do not provide a basis for inferring change in such functions. Tests in wide use for this purpose include the Block Design (nonverbal abstract reasoning) subtest of the Wechsler Adult Intelligence Scale, the Wisconsin Card Sorting Test, and the Halstead Category Test. Such tests are also sensitive to changes in the prefrontal regions which may not affect information processing and memory abilities but may produce selective effects on the ability to respond to changed environmental circumstances and to abstract the essential features of the information being processed for adjusting to environmental change.

A related aspect of prefrontal functioning involves what are known as planning or executive functions. Concept formation tests of a kind identified above can measure such functions to some extent but there are other tests that emphasize serially organized, goal-directed behavior that may be somewhat more revealing of impairments resulting from frontal disease. These include the Porteus Maze Test and an assortment of associative fluency procedures. The PMT is a problem-solving task which requires preliminary analysis of the maze and its

execution without entering blind alleys in an impulsive or judgmentally deficient way.

Associative influence procedures are more in the category of creative expression (at least in the sense of quantity of divergent productions). An example of such a test is the Controlled Word Association Test which requires the individual to generate words beginning with particular letters. There are norms for age and education and the test has been studied and shown to be sensitive to lesions of the left prefrontal region even in the absence of a Broca's aphasia. A corresponding procedure for right frontal dysfunction involves the generation of random forms that constitute more than squiggles but less than encodable objects that can be named. Again, the proposal reflects no awareness of the literature relating to such tests that are likely to be sensitive to lesions in regions that are known to be affected by neurotoxins.

Another class of functions that is not sampled adequately in this battery are verbal and visuospatial processing abilities. Processing abilities probably can be inferred from learning and memory test performances in this population, thus permitting significant efficiencies in terms of cost and testing time. Gross impairments of verbal pro-

cessing abilities would not be expected in the target population if vocabulary level is relatively intact. Prose passage recall procedures require initial processing before testing for recall after short and/or long intervals. Nonverbal or visuospatial processing abilities could be measured by means of the Block Design subtest of the WAIS or by means of a figure reproduction such as that provided by the Rey-Osterrieth Complex Figure Tests. Here the subject reproduces an elaborate figure from which a score that measures visuoconstructional and visuospatial functioning can be derived. The person is then asked to reproduce the figure from memory after a 30 minute interval to obtain a measure of recent nonverbal or figural recall. Corresponding tests in relatively wide use for verbal learning (and initial processing) are the Rey Auditory Verbal Learning Test and the Buschke Selective Reminding Test. The RAVLT calls for the learning over 5 trials of a list of 15 unrelated words. This is followed by a single trial learning of a second interference list with subsequent measure of recall of the first list both immediately and after a one hour delay. A recognition procedure is then introduced to determine the discrepancy between the individual's ability to actively recall and to recognize

the words. The Buschke Selective Reminding Procedure is similar except that only those words that were not recalled on the previous trial are given on the next trial. The test then measures the ability to hold the words that are not reinforced on that trial, a more direct measure of how much information is getting into memory storage. Each of these procedures requires adequate initial processing. The recognition procedure at the end of delayed recall testing, if it yields the usually relatively strong score, indicates that the information was adequately processed; otherwise, it would not have entered long term storage.

Since processing deficits are not likely to be severe in this population, it would perhaps make more sense to introduce a brief screening procedure such as reading of compound sentences and discrimination of fragmented concentric circle patterns, tests of which can readily be found in the neuropsychological literature. This would permit more time for the more important assessments of frontal and temporal functions (recent memory and executive).

In the above discussions of memory and executive functions, the focus has been on a family of procedures with known sensitivity to prefrontal and

mesial temporal lobe dysfunction. These areas are known to be relatively more vulnerable to toxic influence. Accordingly, a first priority would be placed on the use of such tests in a battery of this type. A major criticism, therefore, is that the key impairments expected both on theoretical and empirical grounds are not sampled by this battery.

Mood

Profile of Mood States (POMS)

Mood may be the primary affective change reported by individuals with neurotoxic disorders, though additional personality changes about which the individuals may not be as acutely aware could be present. These may reflect somatoform, interpersonal, ideational, and "mental loss" changes that are not sampled by a mood profile. Also, it is not clear that this form of self-report controls for individual variation in response set or a tendency toward dissimulation. More extensive personality tests provide measures of such functions, such as the MPPI.

iv) Computer Configuration

Computers provide a vast potential resource for administration of tests in studies of this kind. However, the conversion of a test into a computerized format may alter the psychometric properties of the test significantly to affect reliability and/or validity. Accordingly, reliability and validity studies should be done to determine the

accuracy of measurement and the likelihood that the test is measuring the same function or functions when administered by computer. Also, the basis on which interpretations are made may require some additional norming beyond any available norms for the test. In the case of the proposed battery (computer considerations aside), such psychometric properties have not been presented. The exceptions are the Wechsler subtests used in this study. Even these are much less reliable, for example, than the total score or IQ's derived from those instruments. The American Psychological Association is currently developing standards for the transformation of tests into computerized formats. This initiative is based on current misuses of well standardized and validated tests where such methodological issues arise despite the presence of a sizeable supporting literature for the test. Where such a literature does not exist, as in many of the behavioral tests in this protocol, that problem becomes compounded further.

v) Other Considerations

There is some concern with respect to the efficacy of the questionnaires and the matching procedures to control for the many covariates or confounders that may influence behavior in addition to the neurotoxic agent under investigation, Age, sex and ethnicity have been mentioned. Others include individual differences in cerebral dominance; pathophysiological changes due to other etiologies such

as stroke, tumor, previous head injury; developmental learning disabilities; time since exposure; rate and progression (or momentum) of the underlying changes; severity of exposure; and any genetically determined individual vulnerabilities or invulnerabilities to particular toxins (essentially unknown).

b. Clinical and Immunologic Studies

i) General Comments

The investigators seized upon potential biologic sequelae of PCB exposure, including such parameters as blood pressure and immunologic function, without conducting the necessary background review. With respect to the immunologic evaluation, there are many confusing or misleading statements about the implications of the various in vitro immunologic assays to be used. Also, the investigators should have provided more detail on the methodologies to be used in the evaluation of the various immune parameters.

ii) Specific Comments

There is a major concern about the potential interaction between the project physician and his or her consultation with medical specialists if unusual findings are documented. There is no clear explanation of exactly who these medical specialists will be, nor how the project physician will be able to contact them. This is of importance because individuals will clearly be quite

anxious and if, in fact, there is no well established pathway between a project physician and a medical specialist, additional anxiety will ensue.

On page 32 it is mentioned that tricep skin fold thickness will be measured by the public health nurse. There should be some explanation of exactly why tricep skinfold thickness will be measured. Patients will be given three hemocult cards with return envelopes to screen for gastrointestinal carcinoma. The investigators should be aware that no precise criteria for identification of occult gastrointestinal carcinoma have yet been developed. In fact, there is an ongoing national study which is attempting to answer this question. Will colonoscopy be performed on all positive hemocults? Will subjects be asked to adhere to a meat free diet prior to obtaining the stool sample? How many gastrointestinal carcinomas can be expected among 300 people age 18-65? The whole procedure is certainly of questionable value.

The in vitro testing will concentrate on evaluation of peripheral blood lymphocyte subsets in these heavily exposed subjects. This is somewhat confusing in that it suggests that only subjects with higher PCB levels will be studied. The investigators also state that they describe the methods in Appendix 14. Appendix 14 is simply a list of project investigators, consultants and area of interest. There is no description of immunologic

techniques in that particular appendix. Presumably they are referring to Appendix 12 on page 89, which has a brief description of Surface Marker Studies and Immunoglobulin Assays. The Surface Marker Studies do not discuss in any way how the surface marker analysis of peripheral blood lymphocytes will be done; all that is discussed in this particular section is how to transport the blood drawn from the study individuals and what time to leave them in the labs, dependent upon the particular part of the week the blood is drawn. The immunoglobulin assays do not have any description; all that is mentioned is how much blood should be drawn, where it should be sent and how it can be stored. On page 90 there is a flow diagram of how the 30 cc. of heparinized peripheral blood will be handled once drawn from the individual. While this is relatively clear, and shows the particular membrane phenotype characteristics that will be looked for using a fluorescence cell sorter and analyzer or a manual immunofluorescence technique, there is no detailed description of the methodology that is to be utilized for either technique. In addition, there is an extra preparative technique of the isolated peripheral blood lymphocytes which involves the neuraminidase treatment of red blood cells in order to ultimately yield a so-called "null" population. There is no detailed description of the methodology other than what is noted

in the flow diagram. While the immunologic investigator involved in this study is clearly a well established and competent investigator, it is still very appropriate to have the techniques outlined for the manual immunofluorescence technique and the additional purification techniques involving neuraminidase treatment and adherence in order to result in "null" cell populations described somewhere in the protocol.

The investigators mention the use of monoclonal antibodies of the OK or Leu series. While they do mention what OKT-4 and OKT-8 monoclonal antibodies detect, they should also define for the reader the specificity of monoclonal antibodies OKT-3, OKT-6 and OKT-10, which are mentioned in the text. No description is mentioned of the particular monoclonal antibodies which will be used from the Leu series. The investigators mention that the OKT-4/OKT-8 ratio is of "great value as an index of immunocompetence". This statement is definitely a gross overestimation of the value of an OKT-4/OKT-8 ratio. There is no question that it has been of great use in the diagnosis of patients with acquired immunodeficiency syndrome. However, in and of itself, it has not been of great utility in the pathophysiology or understanding of any particular disease.

It would be more interesting for the investigators to correlate the OKT-4/OKT-8 ratio with various immune para-

meters such as skin testing and serum protein levels. In addition, it would seem very reasonable to include some additional in vitro immunologic assays in order to obtain a more complete evaluation of individual host immunocompetence. While this admittedly is somewhat limited because of the large study population, it would not be difficult to include T-lymphocyte proliferation assays, natural killer cytotoxicity assays and monocyte cytotoxicity assays.

The investigators state that additional monoclonal antibodies will be used to evaluate B cell function. This is really a misstatement because the determination of membrane B cell phenotype by monoclonal antibodies merely permits detection of various antigens or receptors on a B cell membrane. This does not imply, necessarily, normal or abnormal B cell function. This raises the issue of whether the investigators have clearly thought out their approach to the immunologic evaluation of the study population.

The investigators state that they will estimate activated T cells by doing double fluorescence labelling with OKT-3 and Ia antibodies. First, there is no description of how they will do the double fluorescence labelling in the methods section. Second, there is no description of the source of antibodies used to detect membrane-bound Ia molecules. Third, it is unclear why the investigators

would have chosen OKT-3 and Ia as estimates of activated T cells. While these may be justified, it would have been interesting to have seen some speculation about the use of other activation antigens such as the transferrin receptor detected by OKT-9 or the Interluken 2 receptor detected by the monoclonal antibody TAC.

The investigators state that if a significant null cell population is found, the population will be concentrated and characterized with a panel of monoclonal antibodies. It is unclear what is meant by significant null cell population and exactly how this population will be concentrated. What method will they utilize? In addition, they state that these null cell populations will be characterized with monoclonal antigens (they probably mean monoclonal antibodies) that primarily detect T and B associated antigens. It might be useful to also include antibodies that detect monocyte, myeloid, or natural killer antigens.

Finally in the third paragraph on page 35, the investigators state that the above studies will provide "qualitative and quantitative information regarding T, B and null cell populations in these patients". While this may be of some value, the investigators do not state the advantage of the detection of either activated T cells or null cell populations in understanding immune abnormalities in the study group. This, again, underscores

the relative lack of detailed information about the utility of utilizing the particular types of immunologic assays the investigators propose to use.

There is some concern about the pathway between drawing blood in the study participants and transportation to a laboratory. This has been particularly emphasized by the fact that preparation and transportation of blood are really the only detailed methodology presented in this proposal (see page 89). While there is no real concern about the ability of the immunology investigator's laboratory to perform any of these assays, there should be some detailed description of how long it would routinely take blood to be transported from the blood drawing site to the immunology laboratory. In addition, it is not clear where the serum immunoglobulin assays will be performed. Since this is a standard technique, routinely available in most hospitals, presumably this could be performed at a participating or nearby hospital site. There is no detailed methodology describing the methods for serum immunoglobulin quantitative or immunoelectrophoretic techniques.

There appears to be a very heavy emphasis on detection of B cell function. This should be distinguished clearly from analysis of B lymphocyte membrane phenotyping by monoclonal antibody techniques. It is suggested that the investigators may wish to determine

specific B cell quantitative capacity by incorporating in vitro immunologic assays in selected individuals in order to specifically determine this aspect of B cell function.

3. Statistical Analysis

Too few details about the analytic plan are provided, however, the previous reservations apply here. In addition, nonparametric tests such as Rank Sum paired test would be much more appropriate than the paired t-test to explore relationships with continuous dependent variables. Again, there is no indication of the investigators' sensitivity to the multiple comparison problem. With all the tests being conducted and correlations of "independent" variables, many "statistically significant" results will occur by chance alone.

VI. Personnel

There are several resumes in the application that represent well trained, experienced people. Unfortunately, their specific role in the study is unclear, as is the role that others, not as well trained or experienced, will play in the development, execution and analysis of the study and the resultant data. It appears that despite the long list of consultants and advisors, relatively inexperienced investigators may be in charge.

VII. Conclusions

As is evident from the preceding material, the proposed study needs considerable revision prior to its initiation. Major deficiencies exist in design, conduct and analysis. If conducted as proposed, it will, in all likelihood fail to achieve its stated objectives. Not only will a

substantial amount of money be wasted, but many people will be inconvenienced, misinformed and, to some extent, placed at needless, albeit minimal, risk. Hopefully, the investigators will carefully rethink and revise their strategies for studying PCB effects on the New Bedford population.

CURRICULUM VITAE

JACK SHELDON MANDEL

Birthplace: Winnipeg, Canada
Birthdate: November 24, 1944
Marital Status: Married with two children

EDUCATION:

University of Minnesota - Graduate School
Major: Epidemiology
Minor: Supporting Program Ph.D., 1981

University of Minnesota - School of Public Health
Major: Epidemiology
Minor: Biometry M.P.H., 1973

University of Manitoba - Graduate School, 1966-7
Major: Psychology
Minor: Statistics

University of Manitoba
Major: Mathematics and Statistics
Minor: Psychology B.Sc., 1966

CURRENT POSITIONS:

Associate Professor, Division of Environmental Health
School of Public Health, University of Minnesota 1984-

Associate Professor, Division of Epidemiology
School of Public Health, University of Minnesota 1981-84

Assistant Director, Division of Epidemiology
School of Public Health, University of Minnesota 1979-83

Instructor, Graduate Summer Session in Epidemiology
University of Minnesota 1980-

Instructor, Midwest Occupational Health Institute
University of Minnesota 1983-

Director of Graduate Studies, Division of Epidemiology
University of Minnesota 1982-84

PREVIOUS POSITIONS:

Assistant Professor, Division of Epidemiology School of Public Health, University of Minnesota	1980-1
Instructor, Division of Epidemiology School of Public Health, University of Minnesota	1975-80
Assistant Professor, Department of Epidemiology and Community Medicine, University of Ottawa	1974-5
Lecturer, Department of Epidemiology and Community Medicine, University of Ottawa (Leave of absence 1972-5)	1969-74
Acting Senior Analyst, Mental Health Section Health and Welfare Division, Statistics Canada, Ottawa	1968-9
Statistician, Mental Health Section Health and Welfare Division, Statistics Canada, Ottawa	1967-8
Instructor in Computer Programming (MATOP) Statistics Canada, Ottawa	1968-70
Instructor in Psychology, Adult Education Evening Program, Collegiate Institute Board, Ottawa	1968-9
Teaching Assistant in Psychology University of Winnipeg	1966-7
Teaching Assistant in Statistics University of Winnipeg	1966-7

RESEARCH EXPERIENCE:

Project Director, "Epidemiologic Study of Prostatic Cancer" 1975-9
(Funded by National Cancer Institute)

Consultant, North Minneapolis Association for the Retarded, 1974-5
"Prevalence Survey of Developmental Disabilities"

Consultant, Department of Surgery, University of Minnesota, 1975-6
"Multi-Site Cancer Screening"
(Funded by National Cancer Institute)

Project Director, "EPA/NCI Special Skin Cancer Epidemiology 1977-8
Study" (Funded by National Cancer Institute)

Consultant, Minnesota Environmental Quality Council 1976-8
"Copper-Nickel Environmental Impact Study: Potential Health
Effects" (Funded by State of Minnesota)

Consultant, Fairview Hospital 1977-80
"High School Football Injuries"
(Funded by Health Research Program, State of Minnesota)

Co-Investigator, Los Alamos, New Mexico 1978-80
"Health Study of Plutonium Workers"
(Funded by University of California)

Co-Investigator, "Endocrine and Thermorhythmometry on 1975-8
Japanese and North American Female Volunteers with a View
of Temporal and Other Patterns that May Differ in Relation
to Mammary Carcinogenesis"
(Funded by National Cancer Institute)

Consultant, Department of Pathology, University of Minnesota 1976-9
"Epidemiologic Study of Cancer in Immunodeficiency Families"
(Funded by National Cancer Institute)

Consultant, Veterans Administration Hospital 1978-9
"Epidemiology of Alzheimer's Disease"

Co-Investigator, "Minnesota Kidney Cancer Study" 1979-81
(Funded by National Cancer Institute)

Co-Investigator, "Long Term Mortality Study of Minnesota 1979-81
Iron Ore Miners"
(Funded by National Cancer Institute)

Co-Prin. Invest.. Department of Surgery, University of Minnesota 1975-88
"The Use of a Screening Technique for Blood in the Stool
as Means of Detecting Early Cancer of the Bowel"
(Funded by National Cancer Institute)

RESEARCH EXPERIENCE: (Continued)

Co-Investigator, "Cancer Incidence in Northern Minnesota: Potential Effects of Asbestos" (Funded by Environmental Protection Agency)	1977-82
Project Director, "Health Status of American Men Study" (Funded by NICHD)	1976-83
Co-Investigator, "Potential Health Risks Associated with Organic Contaminants in Great Lakes - Feasibility Study" (Funded by Environmental Protection Agency)	1978-82
Co-Investigator, "Study of the Risk of Cancer in X-Ray Technologists" (Pilot Study) (Funded by National Cancer Institute)	1980-2
Consultant, U.S. Air Force Study of the Health Effects of Herbicide Orange	1980-2
Consultant, Minnesota Department of Health	
Gastrointestinal Cancer Incidence in Duluth	1975-82
Development of a Statewide Breast Cancer Screening Program	1976-8
Epidemiology of Snowmobile Fatalities	1976-7
Development of a Hypertension Education and Control Program	1978-9
Evaluation of Statewide Screening Program for Cervical Cancer	1978-80
Health Effects of Creosote in Drinking Water in St. Louis Park, Minnesota	1979-80
Etiologic Factors in Toxic Shock Syndrome in Three States	1980-2
Potential Health Effects of a High Voltage Powerline	1980-1
Principal Investigator, "Study of the Risk of Cancer in X-Ray Technologists" (Funded by National Cancer Institute)	1982-5
Co-Investigator, "Prevention of Cancer by Naturally-Occurring and Synthetic Compounds" (Funded by American Cancer Society)	1982-7
Principal Investigator, "Chemopreventive Trial of Beta Carotene in Skin Cancer" (Funded by National Cancer Institute)	1982-8
Co-Investigator, "Alcohol and Drug Use and Employee Injuries" (Funded by Office of Alcohol and Other Drug Abuse Programming)	1983-4
Consultant, "Epidemiologic Studies of Occupational Exposures" (FMC Corporation)	1983-

RESEARCH EXPERIENCE: (Continued)

Consultant, "Potential Health Effects of Exposure to Heavy Metals Among Welders" (Northern States Power)	1983-
Editorial Consultant, "T&D Health and Safety Report" (Robert S. Banks)	1983-
Consultant, "Epidemiologic Studies of Employees" (3M Corporation)	1984-
Principal Investigator, "Nutritional Prevention of Adenomatous Colonic Polyps" (Funded by National Cancer Institute)	1984-9
Co-Investigator, "Analysis of Effects of Brain Injuries" (Funded by Insurance Institute for Highway Safety)	1984-5

AWARDS AND HONORS:

Health Scientist Fellowship from the Department of National Health and Welfare, Ottawa, Canada 1972-5

Student Workshop, Society for Epidemiologic Research, Seattle 1977

Sigma Xi Society 1978-

MEMBERSHIP IN PROFESSIONAL ASSOCIATIONS:

American Public Health Association

Society for Epidemiologic Research

American Statistical Association

Biometric Society

International Chronobiology Society

Association of Teachers of Preventive Medicine

International Epidemiological Association

COMMITTEE MEMBERSHIPS:

Faculty Council, School of Medicine, University of Ottawa 1970-2

Epidemiology Committee, American Cancer Society 1974-80

Committee on the Use of Human Subjects in Research, University of Minnesota 1976-84

Chairman, Breast Cancer Detection Task Force, Minnesota Health Department 1976-8

Design and Analysis Committee 1976-83
National Study of Health Status of American Men

Steering Committee 1976-83
National Study of Health Status of American Men

Space Planning Committee 1977-9
School of Public Health, University of Minnesota

Research Committee 1977-80
School of Public Health, University of Minnesota

Executive Subcommittee on Policy 1977-80
Use of Human Subjects in Research
University of Minnesota

Grievance Committee 1977-80
School of Public Health, University of Minnesota

Planning Council 1978-81
School of Public Health, University of Minnesota

Executive Committee 1980-3
Society for Epidemiologic Research

COMMITTEE MEMBERSHIPS: (Continued)

Chairman, Nominating Committee Society for Epidemiologic Research	1980-1
Committee on Committees School of Public Health, University of Minnesota	1980-2
Educational Policy Committee School of Public Health, University of Minnesota	1980-3
Epidemiology Section, Program Planning Committee American Public Health Association	1980-1
Chairman, Curriculum Subcommittee School of Public Health, University of Minnesota	1981-2
Appointments, Promotions and Tenure Committee School of Public Health, University of Minnesota	1981-3
Research Committee School of Public Health, University of Minnesota	1982-3
Constitutional Review Committee School of Public Health, University of Minnesota	1982
Faculty Advisor, Council of Graduate Students University of Minnesota	1983-
Faculty Consultative Committee School of Public Health, University of Minnesota	1982-3
Advisory Board, Institute for Athletic Medicine Fairview Hospital	1983-
Senate University of Minnesota	1983-6
Twin Cities Campus Assembly University of Minnesota	1983-6
Administrative Council School of Public Health, University of Minnesota	1983-6
Research Advisory Committee Department of Family Practice and Community Health University of Minnesota	1983-
Chairman, Task Force on Examinations American College of Epidemiology	1983-4
Steering Committee, Cariology Training Program School of Dentistry, University of Minnesota	1984-6

COMMITTEE MEMBERSHIPS: (Continued)

Advisory Committee, Immunodeficiency and Cancer Registry
Department of Pathology, University of Minnesota 1984-

Advisory Committee, Department of Conferences
University of Minnesota 1984-6

International Affairs Committee
American College of Epidemiology 1984-7

PUBLICATIONS:

Mandel, J.S. Notes on Methodology: Expectation of First Admission. Statistics Canada, April, 1969.

Johnson, G., Cooper, J. and Mandel, J.S. Expectation of admission to a Canadian psychiatric institution: Conditional expectancy measure, Can. Psychiat. Ass. J., 14, 295-298, 1969.

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Neri, L., Hewitt, D. and Mandel, J.S. Relation between mortality and water hardness in Canada. Lancet, 1, 931-934, 1972.

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Neri, L.C., Mandel, J.S., Hewitt, D. and Jurkowski, D. Chronic obstructive pulmonary disease in two cities of contrasting air quality. Can. Med. Ass. J., 113, 1043-1046, 1975.

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Hoxtell, G., Mandel, J.S., Murray, S., Schuman, L.M. and Goltz, R.W. Incidence of skin carcinoma following renal transplantation. Arch. Derm., 113, 436-438, 1977.

Schuman, L.M., Mandel, J.S., Blackard, C., Bauer, H., Scarlett, J. and McHugh, R. Epidemiologic study of prostatic cancer: Preliminary Report. Cancer Treat. Rep., 61, 181-186, 1977.

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PUBLICATIONS: (Continued)-

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Questionnaires complement tensopsy and hemopsy in chronoepidemiologic
inquiries into risk of diseases associated with high blood pressure.
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Gilbertsen, V., Church, T., Grewe, F., Mandel, J., McHugh, R., Schuman, L.
and Williams, S., The design of a study to assess occult-blood screening
for colon cancer. *J. Chron. Dis.*, 33, 107-114, 1980.

Mandel, J.S. and Schuman, L.M. The Epidemiology of Cancer of the Prostate.
In: Cancer Epidemiology, Lillienfeld, A.M., ed. Elsevier Publications,
New York, 1980.

Radke, A.Q., Halberg, E., Hillman, D., Halberg, F., Haus, E., Mandel, J.
and Schuman, L. Correlations between breast cancer risk and circannual
rhythm characteristics as well as seasonal components of circannual rhythms.
Chronobiologia 7, 134-136, 1980.

McHugh, R., Church, T., Mandel, J., and White, C. The parameterization
of predictive value for multi-site screening. *Biometrics*, 36, 523-529, 1980.

Schuman, L.M. and Mandel, J.S. Prostatic cancer in blacks. *J. Prev. Med.*
9, 630-649, 1980.

Mandel, J.S., Halberg, F., Radke, A., Seal, U.S. and Schuman, L. Circannual
variation in serum TSH and prolactin in prostatic cancer patients. *Chrono-
biologia*, 7, 129, 1980.

Perry, G., Spector, B., Schuman, L., Mandel, J.S., Anderson, V., McHugh, R.,
Hanson, M., Fahlstrom, S., Krivit, W. and Kersey, J. The Wiskott-Aldrich
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Schuman, L., Mandel, J., Radke, A., Seal, U., and Halberg F. Some selected
features of the epidemiology of prostatic cancer: Minneapolis-St. Paul
case-control study. In: Magnus, K. (ed.) Trends in Cancer Incidence.
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Halberg, F., Cornelissen, G., Sothorn, R.B., Wallach, L.A., Halberg, E.,
Ahlgren, A., Kuzel, M., Radke, A., Barbosa, J., Goetz, F., Buckley, J.,
Mandel, J. et al. International Geographic Studies of Oncological
Interest on Chronobiological Variables In: Neoplasms-Comparative
Pathology of Growth in Animals, Plants and Man. H. Kaiser, Ed., Williams
and Wilkens, Baltimore. 1981

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- Sigurdson, E., Levy, B., Mandel, J.S., Mchugh, R., Michienzi, L., Jagger, H., and Pearson, J. Cancer morbidity investigations: Lessons from the Duluth study of possible effects of asbestos in drinking water. Environ. Res. 25, 50-61, 1981.
- McLaughlin, J.K., Mandel, J.S., Blot, W.J., and Schuman, L.M. A case-control study of kidney cancer. Am. J. Epid. 114, 443, 1982, (abstract).
- Osterholm, M.T., Davis, J.P., Gibson, R.W., Mandel, J.S., Wintermeyer, L.A., Helms, C.M., Forfang, J.C., Rondeau, J., Vergeront, J.M. Tri-state toxic shock syndrome study: Epidemiologic findings. J. Inf. Dis. 145, 431-440, 1982.
- Lawler, A., Mandel, J.S., Schuman, L.M. and Lubin, J.H. Mortality study of Minnesota iron miners: Preliminary results. Proceedings of Fourth Annual Rocky Mountain Center for Occupational and Environmental Health Conference, Ann Arbor Science, 1982.
- Osterholm, M., Gibson, R., Mandel, J. and Davis, J. Tri-state toxic shock syndrome study: Methodologic analysis. Ann. Int. Med. 96, 899-902, 1982.
- Levitt, S. and Mandel, J. Breast irradiation and future risk of carcinogenesis. Front. Radiat. Ther. Onc. 17, 131-142, 1982.
- McLaughlin, J.K., Blot, W.J., Mandel, J.S., Schuman, L.M., Mehl, E. and Fraumeni, J. Cancer of the renal pelvis: Cigarette smoking and other risk factors. J.N.C.I. 71, 287-291, 1983.
- McLaughlin, J., Mandel, J.S., Blot, W., Schuman, L.M., Mehl, E. and Fraumeni, J.F. A population based case-control study of renal cell carcinoma. J.N.C.I. 72, 275-284, 1984.
- Olsen, G., Mandel, J. and Bender, A. Evaluating pet facilitated therapy in long-term care facilities. In: The Pet Connection. ed. Anderson, R.K., Censhare Pub., 1984.
- McLaughlin, J., Blot, W., Mehl, E. and Mandel, J. Problems in the use of dead controls in case-control studies. I General Results. Am. J. Epid. (in press).
- Levitt, S. and Mandel, J.S. Benefit versus risk in radiation and conservation surgery for breast cancer. Am. J. Med. 77, 93-100, 1984.
- Visscher, W., Mandel, J., Batalden, P., Russ, J. and Giebink, G. A case-control study exploring possible risk factors for childhood otitis media. In: Lim, D. (ed.) Recent Advances in Otitis Media With Effusion. B.C. Decker, Inc. Philadelphia, 1984.

PUBLICATIONS: (Continued)

Massey, F.J., Bernstein, G.S., O'Fallon, W.M., Schuman, L.M., Coulson, A.H.,
Crozier, R., Mandel, J.S. et al. Vasectomy and health. Results from a
large cohort study. JAMA 252: 1023-1029, 1984.

MANUSCRIPTS SUBMITTED FOR PUBLICATION OR IN PREPARATION:

Mandel, J., Gibson, R., Schuman, L. and Snowdon, D. Dietary factors in the etiology of prostatic cancer.

Mandel, J. Epidemiologic study of the etiology of prostatic cancer.

Mandel J. and Sopko, G. Beta carotene and retinol binding protein levels in prostatic cancer cases and controls.

McLaughlin, J., Blot, W., Mehl, E. and Mandel, J. Problems in the use of dead controls in case-control studies. II The effects of excluding certain causes of death.

Lawler, A., Mandel, J., Schuman, L. and Lubin, J. A retrospective cohort mortality study of iron-ore (hematite) miners in Minnesota.

PAPERS PRESENTED AT PROFESSIONAL MEETINGS:

Neri, L. and Mandel, J.S. The relationship between water hardness and cardiovascular mortality. The Canadian experience. Paper presented to the Society for Epidemiologic Research, Minneapolis, Minnesota, 1970.

Neri, L. and Mandel, J.S. Epidemiological survey of respiratory disease in Ottawa. Paper presented to the Canadian Thoracic Society. Toronto, Ontario, 1970.

Neri, L., Mandel, J.S. and Davies, J. Household survey for chronic respiratory disease in Ottawa. Paper presented to the Canadian Thoracic Society, Toronto, Ontario, 1971.

Neri, L., Mandel, J.S., Hewitt, D. and Jurkowski, D. Chronic obstructive pulmonary disease in two Ontario communities. Paper presented to International Epidemiologic Association, Brighton, England, 1971.

Neri, L. Hewitt, D., Schreiber, G. and Mandel, J.S. Is there a water factor: A case for magnesium. Paper presented to Seventh International Water Quality Symposium, Washington, D.C., 1974.

Mandel, J.S. Epidemiologic study of etiologic factors in prostatic cancer. Paper presented to Society for Epidemiologic Research, Seattle, Washington, 1977.

Windler, C., Mandel, J. and McHugh, R. Test predictivity in multi-site cancer screening. Paper presented to the American Public Health Association, Washington, D.C., 1977.

Sigurdson, E., Mandel, J.S., McHugh, R.B., Michienzi, L., Levy, B. and Jagger, H. Investigating possible effects of amphibole fibers in city water: Surveillance of cancer incidence in Duluth. Paper presented to the American Public Health Association, Los Angeles, California, 1978.

Sigurdson, E., Levy, B., Mandel, J.S., et al. Cancer morbidity investigations: Lessons from the Duluth study of possible effects of asbestos in drinking water. Paper presented to the Second Workshop on Health Surveillance Around Point Sources of Pollution. Albuquerque, New Mexico, January 22-24, 1979.

PAPERS PRESENTED AT PROFESSIONAL MEETINGS: (Continued)

Schuman, L.M. and Mandel, J.S. Prostatic cancer in blacks. Proceedings of a Workshop on Esophageal and Prostatic Cancer: The Basis for Black-White Difference in Incidence. Washington, D.C., October 23, 1979.

Mandel, J., Halberg, F., Radke, A., Seal, U. and Schuman, L. Circannual variation in serum TSH and prolactin of prostatic cancer patients. Proc. 3rd Conf. Indian Soc. Chronobiol., Varanasi, India, Dec. 27-29, 1979.

Radke, A.Q., Halberg, F., Haus, E., Kawasaki, T., Mandel, J., Halberg, E., Schuman, L., Lakatua, D., Ueno, M., Uezono, K., Matsuoka, M. and Omae, T. Questionnaires complement tensopsy and hemospy in chronoepidemiologic inquiry into risk of diseases associated with high blood pressure. Proc. 3rd Conf. Indian Soc. Chronobiol., Varansi, India, Dec. 27-29, 1979.

Mandel, J., Control selection in case-control studies. Paper presented to Society for Epidemiologic Research, Snowbird, Utah, 1981.

Mandel, J. Assessing health status, identifying health risks and evaluating the efficacy of health programs for industry. Paper presented at conference on The Expanding Role of Occupational Medicine, Charleston, South Carolina, October 1-3, 1981.

Levitt, S.H. and Mandel, J. Breast irradiation and future risks of carcinogenesis. Paper presented to Seventeenth Annual Cancer Symposium, San Francisco, February 27-28, 1982.

Mandel, J. Prevention of cancer by naturally occurring and synthetic compounds. Paper presented to American Cancer Society, 42nd Annual Meeting, Minneapolis, Minnesota, October 8-9, 1982.

Lawler, A., Mandel, J., Schuman, L., and Lubin, J. A methodologic issue in occupational mortality studies: Selection of an appropriate comparison group. Paper presented to Society for Epidemiologic Research. Winnipeg, Manitoba, June 14-17, 1983.

Olsen, G., Mandel, J., and Bender, A. Epidemiologic strategies and methods to evaluate pet facilitated therapy in long term care facilities. Paper presented at Human-Animal Bond Conference. Minneapolis, Minnesota, June 13-14, 1983.

Schuman, L.M. and Mandel, J.M. Methodological issues in screening: The University of Minnesota study and screening for colo-rectal cancer. Paper presented at Society for Epidemiologic Research. Winnipeg, Manitoba, June 14-17, 1983.

REPORTS:

Mandel, J. Breast Cancer: A Review of the Literature and a Proposal for a Breast Cancer Detection Program. Submitted to the Minnesota Department of Health, 1977.

Schuman, L., Mandel, J., Murray, S., Lawler, A. and Weiss, H. Copper-Nickel Mining, Smelting and Refining as an Environmental Hazard to Human Health. A Review of the Epidemiologic Literature and Study Recommendations on Copper and Nickel. Submitted to the Minnesota Regional Copper-Nickel Study Environmental Impact Task Force, 1976.

Schuman, L., Mandel, J. and Wannamaker, J. Copper-Nickel Mining, Smelting and Refining as an Environmental Hazard to Human Health. A Review of the Epidemiologic Literature and Study Recommendations on Asbestos. Submitted to the Minnesota Regional Copper-Nickel Study Environmental Impact Task Force, 1977.

Schuman, L., Mandel, J., Hanson, M. and Nelms, J. Copper-Nickel Mining, Smelting and Refining as an Environmental Hazard to Human Health. A Review of the Epidemiologic Literature and Study Recommendations on Sulfur Dioxide and Particulates. Submitted to the Minnesota Regional Copper-Nickel Study Environmental Impact Task Force, 1977.

Schuman, L., Straub, C., Mandel, J., Norsted, S., and Sprafka, M. Assessment of Potential Health Risks Associated with Organic Contaminants in the Great Lakes Basin. Submitted to the Environmental Protection Agency (Contract No. EPA R806282010), June 1, 1982.

Lawler, A., Mandel, J., and Schuman, L. Retrospective Cohort Mortality Study of Minnesota Iron-Ore (Hematite) Miners. Submitted to the National Cancer Institute (Contract No. NCI-CP-FS-91014), February 1, 1983.

Alan Paul Bender
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Golden Valley, Minnesota 55426
(612) 623-5216 (office)
(612) 542-8011 (home)

EDUCATION:

1963-1967	University of Minnesota Minneapolis, Minnesota	B.A., 1967	Mathematics
1967-1968	University of Minnesota Minneapolis, Minnesota	M.S., 1968	Mathematics (Numerical Analysis)
1972-1973	University of Minnesota Minneapolis, Minnesota		Biometry and pre- veterinary work
1973-1977	University of Minnesota St. Paul, Minnesota	B.S.V.S., 1975 D.V.M., 1977	Veterinary Medicine (small animal)
1977-1980	Ohio State University Columbus, Ohio	Ph.D., 1980	Epidemiology

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PROFESSIONAL EXPERIENCE:

1966-1967	Research Assistant Computer Center	University of Minnesota Minneapolis, Minnesota
	Responsibilities: Fortran programmer and computer operator	
1967-1968	Graduate Teaching Assistant Department of Mathematics	University of Minnesota Minneapolis, Minnesota
	Responsibilities: Teaching and assisting in courses of calculus, differential equations, and numerical analysis	
1969-1972	Lieutenant (j.g.), U.S. Navy	U.S. Navy Postgraduate School Monterey, California
	Responsibilities: Teaching beginning to advanced courses in engineering mathematics. Course coordina- tor for calculus sequence. Collateral duties included Officer of the Day and Cryptography Officer.	
1973-1974	Teaching Assistant Biostatistics and Epidemiology School of Veterinary Medicine	University of Minnesota St. Paul, Minnesota
	Responsibilities: Participation in the development and teaching of a course in biostatistics and epidemiology. Authored the workbook for the statistical portion of the course.	

1977-1980 Graduate Teaching Associate
Veterinary Preventive Medicine
School of Veterinary Medicine
Ohio State University
Columbus, Ohio

Responsibilities: Teaching veterinary professional students in the areas of quantitative epidemiology, disease simulation, and zoonoses.

1977-1980 Part-time Staff Veterinarian
Hudson Animal Clinic
Columbus, Ohio

Responsibilities: Supervised canine and feline out-patient clinic. Provided clinical and preventive medical and surgical services.

1981-present Section Chief
Chronic Disease Epidemiology
Minnesota Department
of Health
Minneapolis, Minnesota

Responsibilities: Directed chronic disease epidemiology for State of Minnesota. Supervised epidemiologists, EIS officers, preventive medicine residents, systems analysts, programmers, staff working on cancer, diabetes, maternal and child health, environmental epidemiology, and program evaluation. Provided quantitative epidemiologic services and data base management consultation for Division. Trained professional staff in analytic epidemiology. Collaborated with members of academic, medical and industrial communities in development and execution of chronic disease epidemiologic investigations.

1982-present Associate Member, Graduate Faculty
Field of Epidemiology
Graduate School
Division of Epidemiology
University of Minnesota
Minneapolis, Minnesota

Responsibilities: Taught graduate courses in epidemiology of chronic disease and analytic epidemiology. Advised master and doctoral students. Member of Executive Committee

1984-present Member, Immunodeficiency-Cancer
Registry Scientific Advisory Council
Division of Immunology
School of Medicine
University of Minnesota
Minneapolis, Minnesota

RESEARCH:

1974-1977 Consultant, Metabolic Profile
Study of Dairy Cattle
School of Veterinary Medicine
St. Paul, Minnesota

- | | | |
|-----------|--|--|
| 1975-1976 | Senior Research Analyst, Clinical Epidemiologic Study of Canine Globoid Cell Leukodystrophy | School of Veterinary Medicine
St. Paul, Minnesota |
| 1978-1980 | Principal Investigator, Epidemiologic Study of Canine Multiple Primary Neoplasia | Columbus, Ohio and
Davis, California |
| 1979-1980 | Principal Investigator, Immunologic Aspects of Canine Multiple Primary Neoplasia | State of Ohio Canine
Research Fund |
| 1981-1982 | Chairman and Consultant, Design for a Statistical/Epidemiologic Study of Bovine Performance Associated with the CPA/UPA High Voltage Direct Current Power Line in West Central Minnesota | Environmental Quality Board
Scientific Advisory Panel |
| 1981-1983 | Principal Investigator, Protocol Development for Feasibility Study of a Statewide Cancer Surveillance System | Minnesota Division,
American Cancer Society |
| 1981-1984 | Senior Epidemiologist, Population-Based Epidemiologic Studies of Diabetes Mellitus in Minnesota | Centers for Disease Control
Diabetes Control Project |
| 1982-1983 | Senior Epidemiologist, Evaluation of Childhood Screening Programs in Minnesota | Childhood Screening
Legislative Task Force |
| 1983-1985 | Principal Investigator, Feasibility Study of a Pathology-Based Statewide Cancer Surveillance System | The Bush Foundation |
| 1983-1986 | Co-Investigator, Epidemiology of ALL/NHL in Children less than 16 years of age | National Institute of Health |
| 1984-1985 | Co-Principal Investigator, Feasibility of Full Scale Epidemiologic Studies of Contaminated Drinking Water in St. Louis Park, New Brighton, Minnesota. | Minnesota State Legislature |

HONORS:

Undergraduate, Johnson's Wax Fund College Scholarship, 1963
 Graduate School Graduate Training Scholarship, 1968
 Navy Teaching Commendation, 1969
 Public Health Service Fellowship, 1972
 Phi Zeta, Veterinary Honor Society, 1978
 Phi Kappa Phi, Honorary Society, 1980
 Treasurer, Minnesota Cancer Council, 1983

MEMBERSHIPS:

Society for Epidemiologic Research, 1980
Minnesota Cancer Council, 1981
American Diabetes Association Council on Epidemiology and Statistics, 1982
Associate, American College of Epidemiology, 1982

LICENSED:

Minnesota
Ohio

OUTSIDE INTERESTS:

Photography
Stamp Collecting
Running
Micro Computers

PUBLICATIONS:

1. Fletcher TF, Jessen CR, Bender AP: Quantitative Evaluation of Spinal Cord Lesions in Canine Globoid Leukodystrophy. *Journal of Neuropathology Experimental Neurology* 36:84-99, 1977.
2. Bender AP, Bender GP, Dorn CR, Schneider R: Associations Between Canine Benign and Malignant Neoplasms. *Prev Vet Med* 1:77-87, 1982.
3. Wannamaker JL, Bender AP, Muckala K: Population-Based Studies of Diabetes Mellitus in Minnesota: Rationale and Methods. *Minn Med* 65:429-431, 1982.
4. Bender AP: Development of a Feasibility Study for a Statewide Cancer Surveillance System in Minnesota. *Minn Med* 65:571-573, 1982.
5. Bender AP, Dorn CR, Schneider R: A Quantitative Index for Diagnostic Surveillance of Neoplasms in Dogs. *Am J Vet Research* 44: 395-398, 1983.
6. Bender AP, Sprafka JM, Jagger HG, Wannamaker JL, Muckala KH: Incidence, Prevalence, Mortality and Population-Based Profile of Diabetes Mellitus in Wadena, Minnesota, 1981. *Minn Med* 66:251-256, 1983.
7. Bender AP, Sprafka JM, Jagger HG, Wannamaker JL, Muckala KH: Evaluation of the Effect of Record Source on the Profile of Patients with Diabetes Mellitus in Wadena, Minnesota. *Minn Med* 66:383-394, 1983.

8. Bender AP, Dorn CR, Schneider R: A Quantitative Epidemiologic Study of Multiple Primary Neoplasia of the Canine Reproductive Systems. *Prev Vet Med* 2:715-731, 1984.
9. Bender AP, Olsen GW: A survey of the American College of Surgeons Hospital Based Tumor Registries: Effect of Hospital Size, Region of Country and Number of cases on operating Costs. *J Am Med Rec Assoc* 55:20-23, 1984.
10. Bender AP, French LR, Woolley RE, Sprafka JM, Moen ME, Dean AG: An Assessment of comprehensive child health screening programs in Minnesota. (In press.)
11. Bender AP, Olsen GW: A Quantitative Study of Centralized Cancer Registries in the United States. (Submitted for publication.)
12. Martin FB, Bender AP, Steuernagel G, Robinson RA, Reusbach R, Sorenson DK, Williamson N, Williams A: Epidemiologic Study of Bovine Performance Associated with the exposure to 400 KV DC power line. (Submitted for publication).
13. Bender AP, Sprafka JM, Jagger HG: Incidence, Prevalence, Mortality of Diabetes Mellitus in Wadena, Marshall, Grand Rapids, Minnesota. (In preparation.)
14. Bender AP, Sprafka JM, Jagger HG: Population-based natural history of Diabetes Mellitus in Wadena, Marshall, Grand Rapids, Minnesota: A Longitudinal View. (In preparation.)
15. Sprafka JM, Bender AP: Prevalence of Diabetes Mellitus Complications and Implications For Community Programs. (In preparation).
16. Sprafka JM, Bender AP: Effect of Record Source on Perceived Natural History of Diabetes Mellitus: The Three City Study. (In preparation).
17. Sprafka JM, Bender AP, Jagger HG, Muckala K, Martin CP, Edwards T: The Epidemiology of Diabetes Mellitus in Wadena, Marshall, Grand Rapids, Minnesota. (In preparation).
18. Bender AP, Sprafka JM: A Population-based case control study of diabetes mellitus complications. (In preparation).

LETTERS:

1. Bender AP, Angrick E, Dorn CR, Donohue JR: Microfilaremia in Dogs. *Vet Rec* 108:41, January, 1981.
2. Bender AP: Statewide Cancer Surveillance System for Minnesota. *Northwest Dentistry* 61:37, 1982.

3. Bender AP: Classification of Diabetes Mellitus. Minn Med 65:687, 1982.
4. Bender AP, Sprafka JM: Abnormal Blood Glucose and Coronary Heart Disease. Diabetes Care 7:302, 1984.

PAPERS PRESENTED:

1. Bender AP, Sprafka JM, Jagger HG, Wannamaker JL: A Population-Based Epidemiologic Study of Diabetes Mellitus in Wadena, Minnesota. Plenary Session, CDC 5th Annual Diabetes Control Meeting, Lexington, Kentucky, 1982.
2. Bender AP, Dorn CR, Policello GE, Robinson RA: Cautions About the Estimation of Summary Relative Risk from Veterinary Epidemiologic Studies. Third International Symposium on Veterinary Epidemiology and Economics, Arlington, Virginia, 1982.
3. Bender AP: Cancer Incidence Data Needs and Plans--Minnesota Program. Third Annual Meeting Cancer Control Consortium of Ohio, Columbus, Ohio, 1982.
4. Bender AP, Sprafka JM, Jagger HG: The Population-Based Epidemiology of Diabetes Complications in Wadena and Marshall, Minnesota. CDC Sixth Annual Diabetes Control Meeting, Cincinnati, Ohio, 1983.
5. Bender AP, Sprafka JM, Jagger HG: Population-Based Studies of Diabetes Mellitus in Wadena, Marshall and Grand Rapids, Minnesota. Scientific Meeting ADA Council on Epidemiology and Statistics. San Antonio, Texas, 1983.
6. Wilcox S, Sprafka JM, Whipple D, Bender AP: Minnesota Diabetes Control Program Overview. CDC Seventh Annual Diabetes Control Meeting, Chicago, Illinois, 1984.
7. Bender AP, Sprafka JM: A Population-Based Epidemiologic Study of Diabetes Complications in Wadena, Marshall and Grand Rapids, Minnesota. ADA Scientific Meeting, Las Vegas, Nevada, 1984.
8. Bender AP, Woolley RER: Cancer Cluster Investigations. Conference of State and Territorial Epidemiologists Annual Meeting, Minneapolis, 1984.

RESOURCES AND REPORTS:

1. Olsen GW, Bender AP: Annotated Review of the Cancer Registry Literature, 1961-1981. Minnesota Department of Health, Minneapolis, Minnesota, 1982.
2. Bender AP, Sigurdson EE: Minnesota Cancer Mortality, 1968-1973 and Cancer Morbidity in Minneapolis, St. Paul and Duluth, 1969-1971. Minnesota Department of Health, Minneapolis, Minnesota, 1982.

3. Martin FB, Steuernagel GR, Bender AP, Robinson RA, Revsbeck RM, Sorenson DK, Williamson, NB: Final Report, December, 1982. A Statistical/Epidemiologic Study of Bovine Performance Associated with the CPA/UPA High Voltage Direct Current Powerline in West Central Minnesota. To the Minnesota Environmental Quality Board, 1982.
4. Bender AP: Annotation, Interpretation, and Documentation of Goodman Procedure, Mantel-Haenszel, Logistic Regression, and Log Linear Model Programs Developed for the Chronic Disease Epidemiology Section, Minnesota Department of Health. Minneapolis, Minnesota, 1983.
5. Moen ME, Bender AP, Dean AG, French LR, Woolley RE, Sprafka JM: Comprehensive Child Health Screening. An evaluation of Minnesota's E.P.S./P.S.S. Programs. Minnesota Department of Health, Minneapolis, Minnesota, 1984.

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CURRICULUM VITAE

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1. PERSONAL

NAME: Manfred J. Meier
 BIRTHDATE: July 17, 1929
 MARRIED: Yes, 2 Children
 HOME ADDRESS: 200 River Drive North
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2. EDUCATION

<u>University</u>	<u>Address</u>	<u>Degree</u>	<u>Years</u>	<u></u>
Wisconsin	Madison, Wisconsin	B.A.	1948-52	Psychology
Wisconsin	Madison, Wisconsin	M.S.	1952-53	Psychology
Wisconsin	Madison, Wisconsin	Ph.D.	1953-56	Psychology

3. ACADEMIC AND PROFESSIONAL HISTORY

<u>Dates</u>		
1952-53	Research Assistant	University of Wisconsin
1953	Teaching Assistant	University of Wisconsin
1953-56	Clinical Psychology Trainee	Veterans Administration
1956-57	Instructor, Dept. of Psychology	University of Wisconsin
1956-57	Clinical Psychologist	Veterans Administration
1957-62	Assistant Professor	University of Minnesota Medical School
1962-66	Associate Professor & Director Neuropsychology Laboratory	Department of Psychiatry and Neurology
1962--	Full Member, Graduate School Faculty	University of Minnesota
1966--	Professor & Director Neuropsychology Laboratory	Department of Neurosurgery University of Minnesota
1972--	Coordinator, Allied Health Professions	Office of the Vice President for Health Sciences

Joint Academic Appointments in Departments of Psychology, Psychiatry,
 Neurosurgery, and Program in Health Care Psychology--School of
 Public Health

4. HONORARY SOCIETIES AND AWARDS

Phi Beta Kappa

Phi Eta Sigma

Sigma Xi

5. SALIENT RESEARCH AND EDUCATIONAL GRANT AWARDS

Psychological Consequences of Focal Cerebral Lesions and Ablations
(with Lyle A. French, M.D., Ph.D., then Head, Department of Neurosurgery),
National Institute of Neurological Diseases and Blindness, HEW, 1962-65.

Neuropsychological Assessment in Cerebrovascular Disease (with A. B.
Baker, M.D., Ph.D., then Head, Department of Neurology), National
Institute of Neurological Diseases, Communication Disorders, and Stroke,
HEW, 1962-78.

Research Career Development Award, National Institute of Neurological
Diseases and Blindness, HEW, 1962-72.

Special Educational Improvement Grant, Division of Associated Allied Health
Professions, Bureau of Health Manpower Education, HEW, 1972-77.

Interdisciplinary Clinical Team Education, Division of Associated Health
Professions, Bureau of Health Manpower, HEW, 1978-81.

Education for Changing Allied Health Roles, Division of Associated Health
Professions, Bureau of Health Manpower, HEW, 1978-81.

Steering Committee for Comprehensive Epilepsy Program, National Institute
of Neurological Diseases, Communication Disorders, and Stroke, HEW,
1975--.

6. SCIENTIFIC, PROFESSIONAL, AND ADMINISTRATIVE ACTIVITIES

Medical Advisory Board, Minnesota Epilepsy League, 1962-70

Consultant, Program Projects Committee
National Institute of Child Health and Human Development, HEW

Consultant, St. Paul-Ramsey Hospital, Hennepin County Medical Center,
and Veteran's Administration Hospital

Consultant, Collaborative and Field Research
National Institute of Neurological Diseases and Stroke, HEW

Area Health Education Center: Operations and Planning for Allied Health

Area Health Education Center: Member, Program Advisory Committee, 1972--

Chairperson, Program Planning Committee, Region V Training Institute,
American Society of Allied Health Professions, August, 1973

Chairperson, Minnesota Allied Health Education Consortium, 1973-75

- Chairperson, Health Sciences Educational Policy Committee, 1972-75
Health Sciences Educational Policy Committee: Regular Allied Health Representative, 1972--
Task Group--Faculty/Student Retreat, 1977-78
Chairperson, Long-Range Planning/Funding Task Group, 1978-79
Chairperson, Health Sciences Consumer Health Education Committee, 1972-73
Chairperson, Health Sciences Council of Allied Health Program Directors, 1973--
Chairperson, Health Sciences Advisory Council for Allied Health Studies 1973-76
Health Sciences Committee for Minority Students: Allied Health Programs Representative
Member, Drug Abuse Education Advisory Committee to Central Administration, University of Minnesota
Health Sciences Coordinating Council for Continuing Education: Allied Health Sciences Representative
All-University Council on Aging: Allied Health and Health Care Psychology Representative
Chairperson, Funding Committee, 1976
Chairperson, Membership Committee, 1978
Member, Committee on Faculty-Student Affairs
Member, Publications Committee, 1979
All-University Council on Aging: Frontiers in Aging: Life Extension, April 27-28, 1978
Program Planning Committee
Organizer, Local Contributors
Member, Advisory Committee, Geriatric Research Education and Clinical Center, Veteran's Administration
Health Sciences Representative: Multidisciplinary Perspectives on Aging-- All-University Course (Psychology of Aging section)
Health Sciences Planning Committee and Task Force for Geriatric Health Care
Member, Health Sciences Task Force on Aging
Planning Committee for Health Sciences Gerontology
Preparation of Mission Statement: Task Group or Subcommittee
Presentation: Health Sciences Gerontology Retreat
Conference on Interdisciplinary Approaches to the Maintenance of Mental Health
Chairperson, Planning Committee, June, 1977
Editorial Consultant: Journal of Consulting and Clinical Psychology
Referee for various psychological and neurological journals
Member, Research Merit Review Board, Veterans Administration, Washington, D.C., 1979-82.
Member, Steering Committee, Health Manpower Study, 1979

Advisor, Dietetic Internship Program, 1979

Editorial Board: Journal of Clinical Neuropsychology

Editorial Board: Journal of Consulting and Clinical Psychology

Over 150 presentations to scientific and professional organizations--
state, national, and international

Planning Consultant, Bowman-Gray Medical School, Wake Forest University

Elected President, American Board of Clinical Neuropsychology, Inc.,
1982-84

Elected to Board of Trustees, American Board of Professional
Psychology, Inc., 1983-87

Diplomate, American Board of Professional Psychology (Clinical Neuro-
psychology)

Editorial Board, Developmental Neuropsychology, 1984-

President-Elect, Division of Clinical Neuropsychology, American
Psychological Association, 1984-85

7. SCIENTIFIC AND PROFESSIONAL ORGANIZATIONS

Academy of Aphasia

American Academy of Neurology

American Heart Association Fellow, Council of Cerebrovascular Disease

American Psychological Association

- a. Member, Divisions of Physiological and Comparative Psychology, Clinical Psychology, Adult Development and Aging, Health Psychology, and Clinical Neuropsychology
- b. Elected to represent Division of Clinical Neuropsychology on APA Council of Representatives 1981-84

American Society of Allied Health Professions, University of Minnesota
Representative

Gerontological Society (State and National)

International Neuropsychological Society

- a. Steering Committee, 1965-70
- b. Board of Governors, 1970--
- c. Chairperson, Program Committee, 1975
- d. Chairperson, Committee on Scientific and Professional Affairs, 1975--
- e. Re-elected, Board of Governors, 1975-77, 1978-81
- f. Program Committee, Sixth Annual Meeting, 1978
- g. Chairperson, Arrangements Committee, Sixth Annual Meeting, Minneapolis, 1978
- h. Chairperson, Task Force on Education, Accreditation, and Credentialing, 1978--
- i. President-Elect, 1979-80
- j. President, 1980-81

Midwestern Psychological Association

Minnesota Board of Psychology (Appointed, 1980-83)

Minnesota Psychological Association

- a. Chairperson, Program Committee, 1979
- b. Chairperson, Committee on Relations With Other Professions, 1974--

Minnesota Society of Neurological Sciences

- a. Secretary-Treasurer, 1965-68
- b. President-Elect, 1972-73
- c. President, 1973-74

8. PROFESSIONAL LICENSURE AND CERTIFICATION

Licensed Consulting Psychologist (Minnesota)
Member, Minnesota Board of Psychology, 1980-83
Diplomate, American Board of Clinical Neuropsychology

9. RESEARCH AND PROFESSIONAL INTERESTS

Clinical Psychology: Competency Domain/License
Clinical Neuropsychology: Competency Domain/License
Gerontological Psychology: Competency Domain/License
Program Evaluation
Consumer Health Education
Health Care Systems: Interdisciplinary Operations

10. PUBLICATIONS

- Meier, M.J. Interrelationships among MMPI variables, kinesthetic figural aftereffects and reminiscence in motor learning. Amer. Psychol., 1957, 12, 406. (a)
- Meier, M.J. and French, L.A. Quantitative assessment of handwriting and gait in Parkinson's Disease. Univ. Minn. Med. Bull., 31, 1960, 611-622.
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- Meier, M.J. and French, L.A. Psychological correlates of unilateral temporal lobectomy in psychomotor epileptics. Univ. Minn. Med. Bul., 1964, 35, 233-235.
- Meier, M.J. and French, L.A. Personality changes following unilateral temporal lobectomy. Amer. Psychol., 1963, 7, 450. (a)
- Meier, M.J. and French, L.A. Longitudinal assessment of intellectual function following unilateral temporal lobectomy. Amer. Psychol., 1964, 19, 500. (a)
- Meier, M.J. Reminiscence in inverted alphabet printing as a function of degree of EEG abnormality. Perc. Mot. Skills, 1964, 19, 219-225.
- Meier, M.J. and French, L.A. Caudality scale changes following unilateral temporal lobectomy. J. Clin. Psych., 1964, 20, 464-467.
- Meier, M.J. and Resch, J.A. Behavioral correlates of short-term change in neurological status following acute onset of cerebrovascular symptomatology. Amer. Psych., 1965, 20, 483. (a)

- Meier, M.J. and French, L.A. Some personality correlates of unilateral and bilateral EEG abnormalities in psychomotor epileptics. J. Clin. Psych., 1965, 21, 3-9.
- Meier, M.J. and Resch, J.A. Inferential concordance between clinical neurological, psychometric, and EEG estimates of cerebral dysfunction in cerebrovascular disease. J. Clin. Psych., 1965, 22, 239-242.
- Story, J., Meier, M.J., Chou, S.N., and French, L.A. Experiences with subthalamotomy in the treatment of Parkinson's Disease. Proc. 2nd Int. Symp. Stereoencephalotomy, Part I, Copenhagen, 1965. (a)
- Meier, M.J., Story, J., French, L.A., and Chou, S.N. Quantitative assessment of behavioral changes following subthalamotomy in the treatment of Parkinson's Disease. Excerpta Medica, 1965, 94, 247-248.
- Meier, M.J. and French, L.A. Lateralized deficits in complex visual discrimination and bilateral transfer of reminiscence following unilateral temporal lobectomy. Neuropsychologia, 1965, 3, 261-272.
- Meier, M.J. and French, L.A. Changes in MMPI scale scores and an index of psychopathology after unilateral temporal lobectomy for epilepsy. Epilepsia, 1965, 6, 263-273.
- Meier, M.J. and Resch, J.A. Behavioral correlates of short-term changes in neurological status following acute onset of cerebrovascular symptomatology. J. Clin. Psych., 1966, 22, 126-159.
- Story, J., Meier, M.J., Chou, S.N., and French, L.A. Thalamotomy in the treatment of Parkinsonism. Minn. Med., 1965, 48, 852-855.
- Story, J., Meier, M.J., Chou, S.N., and French, L.A. Thalamotomy in the treatment of Parkinsonism. Mod. Med., September 27, 1965. (a)
- Meier, M.J. and French, L.A. Longitudinal investigation of intellectual function after unilateral temporal lobectomy in psychomotor epileptics. J. Clin. Psych., 1966, 22, 22-27.
- Story, J., French, L.A., Chou, S.N., and Meier, M.J. Experiences with subthalamic lesions in patients with movement disorders. Confinia Neuro., 1965, 26.
- Meier, M.J., Story, J., French, L.A., and Chou, S.N. Quantitative assessment of behavioral changes following subthalamotomy in Parkinson's Disease. Confinia Neuro., 1966, 27, 154-161.
- Meier, M.J. and Resch, J.A. Prediction of neurological change with psychological tests. Univ. Minn. Med. Bull., 1966, 37, 250-255.
- Meier, M.J. and Resch, J.A. Readaptation to prismatic rotations of visual space in predicting short-term neurological change following acute onset of cerebrovascular symptomatology. Proc. XVIIIth Int. Cong. Psychol., Aug., 1966.
- Meier, M.J. and Story, J.L. Quantitative effects of stereotaxic lesion of Forel's Area H on two-hand coordination in man. Amer. Psychol., 1966, 21, 601. (a)
- Meier, M.J. and Resch, J.A. Behavioral prediction of short-term change in neurological status in cerebrovascular disease. Amer. Psychol., 1966, 21. (a)

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- Meier, M.J. and Story, J.L. Selective impairment of Porteus Maze Test performance after right subthalamotomy. Neuropsychologia, May, 1967, 5, 181-189.
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- Meier, M.J. and Martin, W.E. Intellectual changes associated with L-Dopa therapy. J. Amer. Med. Assn., 213: 465-566, 1970.
- Meier, M.J. and Martin, W.E. Measurement of behavioral changes in patients on L-Dopa (II). The Lancet: London, 1970, #7650, 1, 786.
- Meier, M.J., Baker, A.B., and Martin, W.E. Some behavioral changes in L-Dopa therapy, Geriatrics, June 1972, pp. 89-97.
- Meier, M.J. The perceptual maze test. In Mental Measurements Yearbook, (O. Buros, Ed.) 1972.
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- Meier, M.J. The Sklar aphasia scale, revised 1973. In Mental Measurements Yearbook (O. Buros, Ed.) Volume 2, The Gryphon Press: Highland Park, New Jersey, 1978, pp. 976.
- Meier, M.J. Education for competency assurance in human neuropsychology: Antecedents, models and directions. In Handbook of Clinical Neuropsychology (S.B. Filskov and T.J. Boll, Eds.) Wiley Intersciences Series, Wiley and Son: New York, 1981.
- Meier, M.J. Book Review: The Pioneering Role of Clarence Luther Herrick in American Neurosciences by William Frederick Windle. Archives of Neurology, Vol 37, June 1980.
- Meier, M.J. Educational Models for Neuropsychology Presidential Address-8th Annual Meeting. International Neuropsychological Society Bulletin. In Press.
- Meier, M.J. Educational and Credentialing Issues in Clinical Neuropsychology. In Foundations of Clinical Neuropsychology (C.S. Golden and P.J. Vicente, Eds.) Plenum. New York. In Press.
- Meier, M.J., Ettinger, M.G. and Arthur, L. Recovery of Neuropsychological Functioning after Cerebrovascular Infarction. In Cognition and Neuropsychology (R. Malatesha and L. Hartlage, Eds.) Sijthoff and Noordhoff. Alphen. The Netherlands, 1982.

CURRICULUM VITAE (Continued)
Manfred J. Meier, Ph.D.

10

Meier, M.J. and Thompson, W.G. Methodological Issues in Clinical Studies of Right Cerebral Hemisphere Dysfunction. In Cerebral Hemisphere Asymmetry: Method, Theory and Application (J.B. Hellige, ed.). Praeger: New York, 1983, pp. 46-94.

CURRICULUM VITAE

NAME: Neil Elliot Kay
MARITAL STATUS: Married, two children
BIRTHDATE: December 11, 1943

Social Security #108-46-1071

EDUCATION:

B.Sc.	University of Manitoba, Canada	1960 - 1964
M.D.	University of Manitoba Medical School	1964 - 1968
B.Sc.M.D.	University of Manitoba	1964 - 1968

TRAINING:

Intern	Department of Medicine, Winnipeg General Hospital, Winnipeg, Canada	1968 - 1969
Resident	Department of Internal Medicine, Upstate Medical Center, Syracuse, New York	1969 - 1971
Fellow	Department of Hematology, Upstate Medical Center, Syracuse, New York	1971 - 1973
Fellow	Department of Immunohematology, The Mount Sinai School of Medicine, New York, New York	7-1-73 - 6-30-74

ACADEMIC APPOINTMENTS:

Assistant Professor	Department of Medicine, State University Hospital, SUNY, Upstate Medical Center Syracuse, New York	7/1/74 - 6/30/75
Assistant Professor	Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN	7/1/75 - 6/30/76
Assistant Professor	Department of Medicine, University of Minnesota Medical School, Minneapolis Veterans Administration Medical Center, Minneapolis, MN	7/1/75 - 12/31/80 7/1/76 - 12/31/80
Medical Director	American Red Cross, St. Paul, MN	7/1/75 - 6/30/76
Research & Educational Fellow	Minneapolis Veterans Administration Medical Center, Minneapolis, MN	7/1/78 - 1981
Visiting Investigator	Scripps Research Institute, Dept. of Molecular Immunology, LaJolla, CA	March - Sept. 1980
Associate Professor	Department of Medicine, University of Minnesota Medical School, Minneapolis Veterans Administration Medical Center, Minneapolis, MN	1/1/81 - Present

retract
SECRET
5/5/01
#1

ORGANIZATIONS:

Canadian Medical Association
Fellow, Royal College Canada F.R.C.P. (C) Internal Medicine, 1974

Licensure: State of New York, State of Minnesota

Board Certification: Internal Medicine, 1972; Hematology, 1976; Oncology, 1982

MEMBER:

American Society of Hematology
Member Subcommittee on Immunohematology 1980-1983
American Federation for Clinical Research
American Association for Pathologists
Proceedings, Society Exp. Biol.
Reticuloendothelial Society
Central Society for Clinical Research

MEMBER:

American Society of Hematology

Member Subcommittee on Immunohematology 1980-1983

American Federation for Clinical Research

American Association of Pathologists

Proceedings, Society Exp. Biol.

Reticuloendothelial Society

Central Society for Clinical Research

BIBLIOGRAPHY

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2. Kay, N.E., Gottlieb, A.J.: Hypouricemia in Hodgkin's Disease. *Cancer* 32: (Dec.), 1973.
3. Kay, N.E., Stockman, J.A., Stuart, M.J., Gottlieb, A.J. and Oski, F.: L-Asparaginase-induced megaloblastic changes. *J. Amer. Med. Assoc.* 226:(Nov. 5) 1973.
4. Smith, J.R. and Kay, N.E.: Polycythemia. *Postgraduate Medicine*, November, 1973.
5. Kay, N.E., Douglas, S.D., Mond, J., Flier, J., Kochwa, S. and Rosenfield, R.: Hemolytic anemia associated with low molecular weight IgM. *Clin. Immunol. and Immunopathol.* 4:216-225, 1975.
6. Kay, N.E., Douglas, S.D. and Estren, S.: T cells in chronic lymphocytic leukemia. *Lancet* ii: 1326, 1974.
7. Smith, J.R., Kay, N.E., Oski, F.A. and Gottlieb, A.J.: Heinz body hemolytic anemia in cirrhosis. *Blood* 46:955, 1975.
8. Kay, N.E. and Douglas S.D.: Monocyte-erythrocyte interaction in vitro in immune hemolytic anemias. *Blood* 50:889-897, 1977.
9. Douglas, S.D. and Kay, N.E.: Fluctuations of lymphocyte surface markers in chronic lymphocytic leukemia. *New Eng. J. Med.* 295:504-505, 1976.
10. Kay, N.E. and Douglas, S.D.: The mononuclear phagocyte: Its development, structure, function and involvement in the immune response. *New York State J. Med.* 77:327-340, 1977.
11. Kay, N.E. and Anderson, K.: The incidence of direct antiglobulin test in the normal population. Retrospective study by a large regional blood center. *New York State Journal of Medicine.* Vol. 78, 8:1244-1246, 1978.
12. Murray, K.J., Kay, N.E. and Douglas, S.D.: Blood group antigens and antibodies in human brain tumor cysts. *Journal of Neurosurgery* 48: (Feb), 1978.
13. Kay, N.E., Murray, K.J. and Douglas, S.D.: Neutrophil chemotaxis and chemotactic potential of serum and tumor cyst fluid in patients with cerebral astrocytoma. *Surgical Neurology* 8:255-257, 1977.
14. Handwerger, B.S., Kay, N.E. and Douglas, S.D.: Lymphocyte-mediated antibody-dependent cytotoxicity: role in immune hemolysis. *Vox Sanguinis* 34:276-280, 1978.
15. Kay, N.E., Gordon, L.I. and Douglas, S.D.: Autoimmune hemolytic anemia in association with monoclonal IgM(k) with anti-i activity. *Am. J. Med.* 64:845-850, 1978.

16. Kay, N.E., Bumol, T.F. and Douglas, S.D.: Effect of phagocytosis and Fc receptor occupancy on complement dependent neutrophil chemotaxis. *J. Laboratory and Clinical Medicine* 91:850-856, 1978.
17. Ackerman, S.K., Bumol, T.F., Kay, N.E. and Douglas, S.D.: Cellular immunologic studies of a patient with monocytic leukemia. *American Journal of Medicine*, 64:1061-1068, 1978.
18. Kay, N.E., Ackerman, S.K. and Douglas, S.D.: Detachment of adherent human monocytes from glass surfaces induced by antibody-coated and uncoated erythrocytes. *Clinical Immuno. and Immunopath.* 13:269-276, 1979.
19. Harris, R.D., Kay, N.E., Seljeskog, E.L. and Douglas, S.D.: Prolactin suppression of leukocyte chemotaxis. *J. Neurosurgery*, 50:462-465, 1979.
20. Kay, N.E. and Douglas, S.D.: Monocyte metabolic activation in rheumatoid arthritis. *Proc. Soc. Exp. Biol. Med.* 161:303-306, 1979.
21. Gordon, L.I., Douglas, S.D., Kay, N.E., Yamada, O., Osserman, E.F. and Jacob, H.S.: Modulation of neutrophil function by lysozyme: A potential negative feedback system of inflammation. *J. Clin. Invest.* 64:226-232, 1979.
22. Gordon, L.I., Douglas, S.D., Kay, N.E., Osserman, E.F. and Jacob, H.S.: Modulation of neutrophil function by lysozyme, a macrophage secretory product. The 8th International Conference on Sarcoidosis and other Granulomatous Diseases. Cardiff, Wales, September, 1978 (In press).
23. Gordon, L.I., Douglas, S.D., Kay, N.E., Jacob, H.S. and Siltzback, L.E.: Inhibition of neutrophil migration by sarcoid sera, with partial reversal by the trisaccharide of N-acetyl glucosamine (NacGlc)₃, a lysozyme inhibitor. The 8th International Conference on Sarcoidosis and other Granulomatous Diseases, Cardiff, Wales, September, 1978 (In press).
24. Kay, N.E., Johnson, J., Stanek, R. and Douglas, S.D.: Abnormal T-cell subpopulations in chronic lymphocytic leukemia: Increased Fcγ cells and impaired in vitro receptor transitions. *Blood* 54:540-544, 1979.
25. Smith, J.R., Kay, N.E., Gottlieb, A.J. and Oski, E.A.: Abnormal erythrocyte metabolism in hepatic disease. Effects of NADP repletion. *Amer. J. Hematol.* 6:313-321, 1979.
26. Kay, N.E., Nelson, R. and Douglas, S.D.: Human neutrophil migratory function: Modulatory effect of opsonized particles. *Infect. and Immun.* 26:12-14, 1979.
27. Handwerger, B.S., Giroux, B., Kay, N.E., Goodspeed, B., Hadfield, S. and Schmidtke, J.R.: Human T lymphocyte-mediated antibody dependent cytotoxicity. Proceed 13th International Leucocyte Conference. Ed. J.G. Kaplan, Acad Press, p. 568-571, 1979.
28. Gordon, L.I. Hrushesky, W., Oken, M.M., Kay, N.E. and Rydell, R.E.: Chronic lymphocytic leukemia in association with a second lymphoproliferative disorder: Response to chemotherapy in two cases. *Med. and Ped. Onc.* 7:111-116, 1979.

29. Zuckerman, S.K., Kay, N.E. and Douglas, S.D.: Effect of adenosine deaminase inhibitors on Fc γ receptor expression in human T cell cultures. *Cell. Immunol.* 56:112-119, 1980.
30. Kay, N.E., Bumol, T.F., and Douglas, S.D.: Effects of 2-Deoxy-G-Glucose on human monocyte metabolism and function. *J. Retic. Soc.* 28:367-379, 1980.
31. Ascensao, J.L., Kay, N.E., Earenfight-Engler, T., Koren, H., and Zanjani, E.: Production of erythroid potentiating factor(s) by human monocyte cell line. *Blood* 57:170-173, 1981.
32. Kay, N.E.: Abnormal T-cell subpopulation functions in CLL: Excessive suppressor (T γ) and deficient (T ν) activity with respect to B-cell proliferation. *Blood* 57:418-420, 1981.
33. Ascensao, J.L., Kay, N.E., Banisadre, M., and Zanjani, E.D.: Cell-cell interaction in human granulopoiesis: Role of T lymphocytes. *Exp. Hematol.* 9:473-478, 1981.
34. Ziegler, H-W, Kay, N.D., and Zarling, J.M.: Deficiency of natural killer cell activity in patients with chronic lymphocytic leukemia. *Intl. J. Cancer* 27:321-327, 1981.
35. Allen, J.I., Kay, N.E., and McClain, C.J.: Severe zinc deficiency in humans: Association with a reversible T-lymphocyte dysfunction. *Ann. Int. Med.* 95: 154-157, 1981.
36. Oken, M.M. and Kay, N.E.: T cell subpopulations in multiple myeloma: Correlation with clinical disease status. *Brit. J. Haematol.* 49:629, 1981.
37. Kay, N.E. and Douglas, S.D.: Detection of shedding of human blood monocyte Fc receptor bearing in vitro culture. *Int. Arch. Allergy Immunol.* 66:131-135, 1981.
38. LeMarbre, P., Kay, N.E., Rinehart, J., Osserman, E., and Jacob, H.J.: Lysozyme enhances monocyte-mediated tumoricidal activity: a potential amplifying mechanism of tumor killing. *Blood* 58:994-999, 1981.
39. Perri, R.T., Oken, M.M., and Kay, N.E.: Enhanced T cell suppression is directed towards sensitive circulating B cells in multiple myeloma. *J. Lab. Clin. Med.* 99:512-519, 1982.
40. Perri, R.T. and Kay, N.E.: Monoclonal B-cells may be induced to grow in an in vitro B-cell colony assay system. *Blood* 59:247-249, 1982.
41. Kay, N.E., Howe, R.B., and Douglas, S.D.: Effect of therapy on T cell subpopulations in patients with chronic lymphocytic leukemia. *Leuk. Res.* 6:3, 1982.
42. Allen, J.I., Korchik, W., Kay, N.E., and McClain, C.J.: Zinc and T lymphocyte function in hemodialysis patients. *Am. J. Clin. Nutr.* 36:410-415, 1982.

43. Perri, R.T., Kay, N.E., McCarthy, J., Vessella, R.L., Furcht, L.T., and Jacob, H.S.: Fibronectin enhances in vitro monocyte-macrophage mediated tumoricidal activity. *Blood* 60:430-435, 1982.
44. Kay, N.E., Holloway, D.E., Hutton, S.W., Bone, N.D., and Duane, W.C.: Human T-cell function in experimental ascorbic acid deficiency and spontaneous scurvy. *Am. J. Clin. Nutr.* 36:127, 1982.
45. Kay, N.E., Johnson, J., and Douglas, S.D.: Effects of human T cell subpopulations on B cell proliferation as determined by [³H]-thymidine incorporation. *Diagnostic Immunol.* 1:11-16, 1983.
46. Perri, R.T., Royston, I., LeBien, T.W., and Kay, N.E.: Chronic lymphocytic leukemia progenitor cells carry the antigens T65, BA-1 and Ia. *Blood* 61:871-875, 1983.
47. Imai, K., Natali, P.G., Kay, N.E., Wilson, B.S., and Ferrone, J.: Tissue distribution and molecular profile of a differentiation antigen detected by a monoclonal antibody (345-1345) produced against human melanoma cells. *Cancer Immunology and Immunotherapy* 12:159-166, 1982.
48. Wilson, B.S., Kay, N.E., Imai, K., and Ferrone, J.: Heterogeneity of human melanoma associated antigens defined by monoclonal antibodies and conventional antisera. *Cancer Immunology and Immunotherapy* 13: 69-74, 1982.
49. Zarling, J.M., Kay, N.E., Grant, B.W., and Bach, F.H.: Clinical regression of nodes in a lymphocytic lymphoma patient following immunization with allogeneic transfusion. *Cancer Immunology and Immunotherapy* 15:233-239, 1983.
50. Kay, N.E. and Zarling, J.W.: Impaired natural killer activity in chronic lymphocytic leukemia is associated with a deficiency of azurophilic cytoplasmic granules in putative NK cells. *Blood* 63:305-309, 1984.
51. Kay, N.E., Oken, M.M., and Perri, R.P.: The influential T cell in B cell neoplasms. *J. Clin. Oncol.* 1:810, 1983.
52. Kay, N.E., Kaplan, M.E.: Defective expression of T cell antigens in chronic lymphocytic leukemia: Relationship to T cell dysfunction. *Brit. J. Haematol.* 57:105-111, 1984.
53. Peacock, T., Kay, N.E., Ascensao, J.A., and Kaplan, M.E.: Establishment and characterization of a subclone (U937-AG) from a permanent human monocyte cell line. *Leukemia Research* 8:435-439, 1984.
54. Kay, N.E. and Morley, J.E.: Endorphins stimulate normal peripheral blood lymphocyte NK activity. *Life Sci.* 35:53-59, 1984.

Invited Chapters

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Bairus Walker, Jr. Ph.D. M.P.H.
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December 6, 1985

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Charles Berring
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OFFICE OF REGIONAL COUNSEL

Dear Charles:

Enclosed is a copy of the National Electrical Manufacturer's Association comments on the Greater New Bedford Health Study. Please send me a letter from your office requesting that our laboratory data be sent to your technical contractor.

Sincerely,

A handwritten signature in cursive script that reads "Ralph".

Ralph J. Timperi
Deputy Director

RJT:am

Encl.