Uploaded to VFC Website

~ October 2012 ~

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

Veterans-For-Change is a 501(c)(3) Non-Profit Corporation
Tax ID #27-3820181

If Veteran's don't help Veteran's, who will?

We appreciate all donations to continue to provide information and services to Veterans and their families.

https://www.paypal.com/cgi-bin/webscr?cmd=_s-xclick&hosted_button_id=WGT2M5UTB9A78

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members.

Item ID Number	01687
Author	
Corporate Author	University of California at Los Angeles, School of Public
Report/Article Title	Protocol: Epidemiology Study, University of California
Journal/Book Title	
Year	1982
Month/Day	January
Color	☐
Number of Images	578
Description Notes	Includes Alvin L. Young's notes on the protocol, the Veterans' questionnaire, and literature reviews.

PROTOCOL
EPIDEMIOLOGY STUDY
Univ. of California
January 1982
Book I of II

(Book II of II)

Dr. Young's Notes

VETERANS ADMINISTRATION

REFERENCE SLIP

TO (Name or title—Mail routing symbol)	INITIALS—DATE
1.	
2.	
3.	
4.	
5.	

REASON FOR REFERENCE

☐ AS REQUESTED ☐ FOR YOUR FILES ☐ NOTE AND RETURN
☐ COMMENTS ☐ INFORMATION ☐ PER CONVERSATION
☐ CONCURRENCE ☐ NECESSARY ACTION ☐ SIGNATURE

REMARKS

Summary of Design - Pg 20
↓ TRACING OF Cohort
Mortality Analysis
↓
Questionnaire
↓ Medical Records (PAST)
Physical Exam

Summary of Experience Under Procedure Pg 24

FROM	DATE
	TEL. EXT.

VA FORM 1976 3230 EXISTING STOCKS OF VA FORM 3230, OCT 1956, WILL BE USED ☆U. S. GPO: 1979—290-573/701

Cover Ltr - Do NOT release

Australian Exposure Estimate Studies (pg 16)

I. Introduction → Releaseable

II. Background —
Presents sources that provide information on "expected" outcomes

III Proposed Protocol —
A. Confounding Factors
B. METHODS } DO NOT RELEASE
C. EXPOSURE LIKELIHOOD INDEX "
D. Cohorts
E. Source of Questionnaire Material
Pg. 43 (Australian/Air Force)

RANCH HAND Questionnaire - 186 Questions
Heavy on Psychological (2-3Hr)

Questionnaire - Male - 1b - 149b
172 Questions
Consent Form
Questionnaire Female 166 — 206
83 Questions
Computer Coding

Physical Examination - Pg 49-50
Discussion
Specific Recommendation — MISSING
1C 3C
Laboratory tests (Air Force furnished to Australia → Australians to UCLA)
1D — Presumeably the Laboratory Tests
Pyschological Assessment - 1E

Questionnaire - 86% - 34 RH 28 Control

92.8% compliance

Neuropsychological Assessment - 1F - 10F

Confounding Factors - - - Pg 61 -

Consent for Exams from Other Medical Facilities - MISSING

AF Physical Examination released during RFP

		Releasable	NR
Appendix A	Glossary	✓	
B	Research Methods	✓	
C	Environmental Fate	✓	
D	Animal Toxicology	✓	
E	Reproductive Effects	✓	
F	Human Effects		✓
G	Population Risks	✓	
Manual for Interviewers			✓
RAMIS II	Users Manual		✓
DOD LTR (Missing)			✓

Bill Wolfe - Houston
Susan Headly
Kelsey -
713 - 791 - 1575

1. VA Control all Copys of Protocol
- each Copy Numbered & assigned
OTA → Give Name
→ Will Limit unabridged Copies
ADUS Science Panel
Will Limit unabridged Copies
NAS -
AFEB
Advisory Committee
~~Restrict~~ Abridged Copies

Abstracted from pages 44 to 50

The procedures should be standardized, information should be collected on standard forms, and the study office should monitor the work. Both the participants and the staff members collecting data, performing examinations, and making laboratory tests must be blinded as to the exposure status of the participant.

b. Suggested questionnaire:

A suggested questionnaire has been prepared drawing from similar questionnaires but with changes to make the questions more appropriate for the target population. The UCLA Survey Research Center has reviewed and formatted the material. This Center has extensive experience and expertise in the development and administration of interview schedules. By making the questionnaire somewhat like others, some comparisons may be made of results from different studies. This may strengthen the study and increase confidence that the findings are real.

The draft questionnaire has been designed to elicit information on which to compare the two cohorts as well as details about the participant's activities and perceived health, past and present. These questions are included to permit comparison between cohorts of factors affecting health, and to allow assessment of possible predisposing factors that may enhance the adverse effects of exposure. To provide the opportunity for validating reported conditions, and to uncover unreported conditions, medical release forms

should be obtained for each source of medical care, including the current physician.

Information is requested on military service and perceived exposure to Agent Orange. This will serve as a check on data in the military records.

The draft questionnaire gathers information on the reproductive history of the veteran. In order to augment this information, a shorter questionnaire is designed for the spouse. It solicits a complete reproductive history along with information on all potential confounding factors. The best procedure (although more difficult, costly, and perhaps less acceptable) would be to interview all former, as well as current, spouses.

3.

Veterans Questionnaire - Abstracted from pages 1b to 160b

Questions are asked as usual to establish the participant's identity, places of residence, and the health of relatives. Other inquiries include the education, and occupation of the participant as well as of his parents, exposure of the veteran to various hazards, injuries sustained and illnesses suffered. Inquiries are included about habits, medications and attitudes as well as about military service and exposure to noxious substances during service. A detailed history is taken of past and present problems referable to the skin, the senses, head, heart and circulation, respiration, endocrine organs, gastrointestinal tract, kidneys, reproductive organs, tumors, allergies, bones and joints as well as less localized difficulties. Details are also sought of reproductive functions and the condition of offspring.

4.

Spouse Questionnaire: Abstracted from pages 161b to 203b.

The spouse, like the veteran, is asked questions to establish identity, places of residence, family, occupation, habits and possible hazards encountered. Fewer questions deal with health than for the participant but details are sought regarding pregnancies, their complications and their outcome. More attention is also given to the status of the children and their health.

c. Physical Examination

The physical examination was designed to screen for possible abnormalities in all organ systems. In consultation with Dr. Dennis Cope of the UCLA School of Medicine, we have modified an earlier form for recording the results. It was designed to require the physician specifically to check normal findings as well as abnormal findings to maximize the proper completion of the physical examination.

The general physical examination can be completed by a general physician. The neurological examination, however, should be conducted by a trained neurologist. All physicians from the examination centers should be given a five-day training program in the administration of this particular examination to standardize the procedures and conduct of the examination to the maximal extent possible.

The last portion of the form requires the examining physician to summarize his findings for each organ system and to express his level of certainty of them. This would allow group comparisons on both certain and suspected abnormalities. The examining physician should be responsible for explaining any abnormal findings to the veteran and for urging or providing appropriate diagnostic or therapeutic follow-up.

UCLA- January 22, 1982

UNIVERSITY OF CALIFORNIA, LOS ANGELES

BERKELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO

SANTA BARBARA · SANTA CRUZ

SCHOOL OF PUBLIC HEALTH
LOS ANGELES, CALIFORNIA 90024

January 22, 1982

Mr. J.R. Ryan
Contracting Officer
Office of Procurement and Supply
Veterans Administration
Washington, DC 20420

Dear Mr. Ryan:

Enclosed please find the protocol which we have developed for the Epidemiologic study of ground troops exposed to Agent Orange. The protocol has been extensivey revised from that previously submitted, incorporating the reviewer's comments as possible.

As you will see in the protocol itself, we do not believe that this protocol should be implemented in a full-scale study without a complete pilot test. You will also note that we have dropped the preliminary studies of existing records from this draft. We do, however, recommend that the VA complete a frequency distribution of the complaints in the Agent Orange register and the proportionate mortality analysis of death records as soon as possible.

As we have previously discussed, we feel that release of information on the presumed exposure status of individuals who might participate in this study or of information on expected or anticipated outcomes could lead to bias which might seriously jeopardize the validity of the study. It is our understanding that the VA has taken the responsibility for this problem.

The questionnaire and the physical exam, which are included in the protocol, have been based in part on those of the Australian Veteran study. This was done because we feel that eventually the results of the two studies will be compared for consistency and the closer the similarity in data collection procedures, the better this comparison will be. In addition, it may be possible in the future to perform some limited pooling of data from the two studies, if the data are collected in a comparable manner. We have formally requested and received permission of the Australian group to utilize this material. We suggest that before the pilot study is conducted, whoever will conduct the pilot contact Mrs. Glen Rose, head of the Survey and Data Collection team for the Australian Studies group. She could provide findings from their pilot test which would assist in revising the data collection instruments.

We have included a discussion of the steps necessary to construct an exposure likelihood index, and have outlined the most efficient approach. We recommend that the Agent Orange Working Group send guidelines on the information needed to Mr. Christian who is best equipped to do the actual work, and that the Agent Orange Working Group oversee the development of the index. We feel that it is essential that the epidemiologist from the selected Coordinating Center work closely with Mr. Christian so that the Coordinating Center will have a full understanding of the limitations of the gathered data. Because of our further discussions and this newly recommended approach to construction of the exposure likelihood index, we feel it appropriate to withdraw our own pending proposal.

At this time we believe that we have filled all the terms of the contract except for the final revisions after this review process. Therefore, we do not plan further efforts until the review process has been completed. However, it would be most helpful to us if you could forward the review comments from separate review committees as soon as they are received. We should like to note that there was overlap of several members between each of the review groups which can be seen from the xeroxed comments included in the different committee reports. We feel that independent review by separate committees would be more meaningful. At this time, we believe that both we and the VA would be best served by a completely independent peer review by the National Academy of Science.

Sincerely,

Gary H. Spivey

Gary H. Spivey, MD, MPH
Principal Investigator

Matthew C. Starr

Matthew C. Starr, PhD
Assistant Director
Office of Contracts and Grants

GHS/MCS:kc
enclosure

Mortality/Next-of-kin Determination - 29

Young

UNIVERSITY OF CALIFORNIA, LOS ANGELES

...LEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO — SANTA BARBARA · SANTA CRUZ

Withdrawal from Study - 12
Confidentiality --- 11,12
Human Oversight Committee --- 2,17,19
Exposure Likelihood Index - 5,24-25 (Selection)
Locating Participants --- 28

Incentive Fraction --- pg 4,29
Exposure Criteria --- 5,6
Non-Vietnam Cohort --- 6, 7, 26
Exclusion of Officers & Multitour personnel --- 3, 7, 27
Medical Records Validation 7
Questionnaire - 8
Physical Examination - 9
Laboratory Examination - 9
Pilot Test --- 13,17

SCHOOL OF PUBLIC HEALTH
LOS ANGELES, CALIFORNIA 90024

April 28, 1982

Mr. J.R. Ryan
Contracting Officer
Office of Procurement and Supply
Veterans Administration
Washington, DC 20420

Dear Mr. Ryan:

Enclosed is our revision of the Agent Orange Epidemiologic Protocol. We feel that the most productive method for handling the revisions is to incorporate the reviews and our response to those reviews as an addendum to the original protocol. In that fashion, the coordinating center will have the original protocol, the reviewers comments and our responses, When preparing the detailed place for the pilot study. Therefore, the enclosed materials include:

1) a detailed response to each of the three reviews (AOWG, OTA, VFW);

2) a veterans questionnaire, in two parts and a spouse questionnaire, revised in collaboration with the Survey Research Center of the Institute for Social Science Research, UCLA;

3) a neurologic examination form, revised in collaboration with a Professor of Clinical Neurology; and,

4) a physical examination form, revised in collaboration with a Professor of Clinical Internal Medicine.

We have considered the questions raised in your letter of April 9, 1982 and have addressed each of them in the response to the reviews. We do not favor the inclusion of a third cohort of non-Vietnam veterans and explain our reasons in the response. The limits of the study can be derived from the list of possible outcomes included in the response and from the information in the sample size section of the original protocol. Mortality information should certainly be collected on all deceased members of the cohorts. This matter is expanded upon in the response. In a cohort study such as this, the entire membership of the cohort is

established at the beginning of the study and there is no replacement of members who die, refuse etc. Death is, in fact, an outcome in this study.

Thank you for the opportunity to work on the development of this protocol.

Sincerely,

Gary H. Spivey, MD, MPH
Associate Professor
Division of Epidemiology

Philip Costic
Senior Contracts and Grants Officer
Office of Contracts and Grants Administration

GHS/PC:kc

VFW REVIEW

1) Basically, the VFW finds the general framework of the revised protocol quite an improvement compared to the original design and feel that once the modifications and changes that are recommended by the OTA and VA panels have been acted upon, the design should be acceptable.

We wish to thank the VFW for their careful and considered review of our protocol and for their support. We believe that the support of the VFW throughout the conduct of this study will be of the utmost importance to the coordinating center.

2) The length of time for the epidemiological study as pointed out at the February 16th OTA review, indicated that a minimum of five and a half years would be required to complete the entire study. We feel that, at this time, a specific timetable cannot be feasibly arranged. We feel that as the study progresses a deadline can be established depending on the accumulated findings and the number of participants at the various intervals of the study.

We understand the VFW point that a time table is difficult to specify at this point. However, we feel that an expected time table should be part of the protocol so that the cost of the proposed study can be estimated and concerned individuals will know when it is reasonable to anticipate results from the study. We have suggested points at which the study should be terminated, if indicated. The data cannot be analyzed in stages during data collection to make a decision as to when the study should or should not be stopped. Rather, the nature of the study design requires that all prespecified data collection be completed before interpretation of results is possible.

3) A recommendation by one of the OTA panel members was that an oversight committee be established to guide the pilot study and the operational phases of the epidemiological study. We agree that an oversight committee needs to be established, however, the VFW strongly feels that any continuing monitoring or involvement of this herbicide issue and the epidemiological study should include the VFW's continued participation. It is a well known fact that the VFW has been one of the forerunners of this issue, therefore it would not be in the best interest of those we serve to neglect or fail to continue participating as the study progresses.

The oversight committee should be privy to all details of the study design and conduct including 1) information which may be withheld from the coordinating center for purposes of blinding and 2) information which could be extremely damaging to the conduct of the study if made public. Therefore, we feel that a condition for service on this committee should be agreement to maintain the confidentiality of study data until the results of the study are officially made public. We feel that a representative from the VFW could make an important contribution to the oversight committee.

4) In our recommendations on the original design, we suggested that an independent medical school conduct the physical examinations, surveys, and complete any questionnaires that would be devised. However, in light of the new information that was brought to our attention at the February 16th OTA review, we feel that the organization known as the National Center for Health Statistics (NCHS) Health and Nutrition Examination Survey (HANES), seems to meet our criteria of proper credentials and independence and should be considered as should any other similarly qualified contractor.

We agree.

5) The Veterans of Foreign Wars has long been involved in seeking a fair and expeditious solution of this issue and would certainly be most happy to assist in publicizing the conduct of the future study and encourage Vietnam veterans' participation.

We certainly believe that the cooperation and assistance of the VFW in publicizing the study should be sought and encouraged. The assistance of other veterans groups may also be similarly sought. Such cooperation may very well make the difference between success or failure of the study.

6) We find it hard to believe that the designer of this study feels that it is unnecessary to include officers as well as multitour enlisted men. It is inconceivable that officers were immune from the same conditions or maladies suffered by the enlisted man. We therefore feel there is no basis for such an exclusion. The designers should be reminded that the purpose of this study is to determine exactly where the individual veteran served, the type of herbicides to which he was exposed, and the amount of that exposure. The final question that needs to be answered (regardless of rank or numbers of tours of duty in Vietnam), is: the relationship between the exposure to these herbicides and the disorders being claimed by individual Vietnam veterans.

We would like to clarify our position in regard to officers and multiple enlisted men. We did not intend to imply that inclusion of officers or multitour enlisted men is unnecessary. Our feeling is that such a group cannot be included in a valid fashion unless a comparable group of exposed and unexposed officers and multitour enlisted men can be identified. We are in complete agreement with the OTA reviewers that a final decision on this question should be reserved until the cohort selection procedures have been completed. At that time it will be clear whether or not an appropriate comparison group can be identified. Unfortunately if an appropriate comparison group is not identified, any findings in the officers and multitour enlisted men could not be easily interpreted.

7) The VFW is aware that the examination which will be utilized in the epidemiological study was modeled after the Australian government's own study. However, as has been suggested by us and others, changes need to be made on the physical examination and must be implemented in a manner that is suitable and recognizable to the examining physician as that of a standard "Americanized" examination physical. In stating that the exam needs to be "Americanized", one only needs to compare the definitions, classifications, and scales used in the proposed physical examination.

We are not sure what is being referred to in the physical exam form as being not standard American practice. This physical exam form has been reviewed by several American trained physicians who have not identified any area needing Americanization.

8) Some panel members feel that an incentive factor should be included in this study to encourage participation in the examination and interview process. It is apparent that based on past cooperation by the Vietnam veterans and their willingness to participate in the Veterans Administrations Agent Orange examinations (which to date have totaled approximately 53,000 examination), that a distinction needs to be made between incentives and compensation factors. We do agree that a compensation factor needs to be considered, especially in light of lost wages, travel expenses and other incidentals that would be incurred through a veteran's participation. Consideration should be given to a compensation formula similar to that being used by the Air Force's Kelsey-Seybold contract to study personnel who participated in Operation Ranchhand. With regards to the different cohort groups, special attention should be given to maximizing participation by the non-country Vietnam Era veteran. Thus, proper compensation for their time must be a consideration, but certainly in the interest of equity, so should it be for all veterans participating.

The question of compensation and incentive pay is extremely difficult. We believe the question of compensation must be examined in the pilot test considering issues of ethics, practicality, costs and experience of other current studies. We certainly feel that any out-of-pocket expenses for travel, lodging and meals during the time of the scheduled examination procedures should be fully compensated. It might be appropriate to compensate the individuals for lost wages during this time period, but this could increase the cost of the study significantly. Alternatively, since this study is congressionally mandated, it might be possible to have the Congress legislate a practice of granting the appropriate amount of time-off with pay by the employers. A final point is that whatever compensation is provided must be done in a uniform and equitable fashion for all participants.

AGENT ORANGE WORKING GROUP REVIEW

Selection

The panel unanimously agrees that the Department of Defense (DOD) should select the cohorts in accordance with Dr. Bricker's cohort selection paper (Tab A). This will provide, we believe, for elimination of as much misclassification as is possible from the existing or potentially reconstructable records. We believe it is absolutely essential that the identification and assignment of these individuals to the different cohorts not be available to the participants or to the investigators until initial analysis of the data is completed. The Science Panel will oversee this cohort selection process. The study investigators must be aware of the method used to select the cohorts but must not be aware of the individuals placed in each group.

We recommend pilot testing the cohort selection procedure outlined in the proposal developed by Dr. Bricker along with our proposed procedure. We derived our own proposed mechanism for cohort selection taking into account the proposal submitted by Dr. Bricker. The major difference between the two proposals is that Dr. Bricker recommends assigning individual likelihood of exposure levels on a group basis whereas our proposal calls for an individual calculation of exposure likelihood. We believe that with the high rate of personnel turnover in military units in South Vietnam, the classification of individuals according to the exposure likelihood of their unit without examination of the actual time period of that individual's presence in the unit could lead to serious misclassification. This question should be examined in the pilot study. If serious misclassification is not encountered then we would certainly support the less costly procedure proposed by Dr. Bricker.

We disagree with one procedure suggested in Dr. Bricker's proposal - the proposed validation of exposure status by use of the Agent Orange registry. Dr. Bricker suggests that if the exposure likelihood assignment is correct, a high proportion of name matches from the presumed highly exposed battalions to individuals in the Agent Orange registry should be found. This procedure is based on the assumption that high exposure did in fact cause health problems that would lead an individual to report to the Veterans Administration for inclusion in the registry and/or that the individual had sufficient knowledge of the fact of his exposure to lead him to report to the registry. Either of these assumptions could be incorrect. Therefore, any lack of "validation" by this method would have no meaning. In addition, the individuals who have filed claims through the Veterans Administration are not a scientifically selected group, but are a self-reporting group. We feel strongly that abandoning the selected cohorts or the currently proposed protocol on the basis of "non-validation" from use of the Veterans Administration Agent Orange Registry records would be a serious error.

We endorse the suggestion of the Agent Orange Working Group that the investigators from the selected coordinating center should be blinded (until the analysis phase) as to the actual presumed exposure status of individuals selected for this study. We believe that the coordinating center investigators, however, must be involved in developing the mechanism of selection of the study cohorts and in particular must be involved in the determination of comparability of the proposed high and low likelihood of exposure cohorts and any non-Vietnam cohort. This can be accomplished, while maintaining blinding, by involving the coordinating center in the development of the criteria to judge comparability, and by providing them with the relevant information to judge comparability but with any unit identifying information suppressed.

We must point out that while it may be very desirable to blind the coordinating center as to the exposure status of the study participants during the data collection phase, the coordinating center must have some kind of cohort identifier prior to the beginning of analysis. It would be impossible to do meaningful analysis without being able to separate the study participants into their respective cohorts. The analysis could, however, still be done blind by providing the coordinating center with the individual assignments to their respective cohorts but identifying the cohorts only as "A" or "B". To assure that information will not be lost, the inclusion of one or more deeply encoded cohort identifiers (group A, group B) might be imbedded in the identification number. The code on such identifiers would not be broken until the analysis phase.

Criteria For Each Group

We recommend that groups be composed of high probability of exposed Vietnam veterans, high probability of nonexposed Vietnam veterans, and a non-Southeast Asia veterans group. Some felt that it would be desirable to include a Vietnam veterans group exposed midway between the first and second groups in order to make an assessment of dose response. The consensus is that though this may be desirable, the inclusion of the fourth group is not essential nor critical to the study.

We continue to have reservations about the ultimate utility of a non-Vietnam service cohort. However, if such a cohort is to be included, we strongly recommend that consideration be given during the pilot study to the use of those units which were scheduled to be sent to South Vietnam but which, at the last minute, were not sent. We feel that these groups would be more likely to provide a comparable cohort to those serving in South Vietnam than would the use of all troops from the southern part of the United States (as suggested in Dr. Bricker's proposal).

We feel that the comparison of a non-Southeast Asia veterans group with combat veterans would be very difficult to interpret because of the different selection biases related to area of service. In addition combat veterans represent survivors whereas the non-South Vietnam veterans do not. Also, the use of this extra cohort with all of its problems in interpretation will add considerably to the cost of the study.

Proposed Exclusions from the Cohort Group

We believe it is unreasonable to exclude officers and multi-tour Vietnam veterans. These may be separately identified so that appropriate analysis can take place but they should not be excluded from the study.

We recommended in the protocol that the officers and multitour enlisted men be separately identified. Meaningful analysis of this group, however, can be done only if there are appropriate comparison groups. Whether or not both high and low likelihood of exposure groups can be identified will be clear by the completion of the cohort selection procedure and at that point this question can be reconsidered.

Questionnaire to Personal Health Providers of the Individual Veterans

Some of the selected veterans may have had multiple health care providers since returning from Vietnam. The panel doubts that many private physicians will fill out detailed questionnaires on their patients and thus wonder about the usefulness of this part of the study. The needed information may have to be obtained in other ways.

We understand the Working Group's concern about whether private physicians will respond to questionnaires on medical record validation. We can point to the experience that we have had in the Health Status of American Men project which has undertaken validation of medical records on approximately 20,000 men. The physician non-response rate in this study has been less than 10%. Thus, we have no reason to believe that this would be a serious problem for the Agent Orange study. In addition, we know of no other mechanism by which medical record validation could be achieved. We expect that the number of veterans who will have sufficient Veterans Administration records for validation purposes will be small. Furthermore, such a group would be unlikely to be representative of the total cohort.

Individual Veteran Questionnaire

The questionnaire as it now exists is unacceptable. It is overly long and uses highly technical terminology which many people including many physicians will not understand. We recommend that careful thought be given to the information that is needed to be gathered, who will administer and where the questionnaire will be administered (telephone, home visits, etc.), and that the questionnaire be redesigned to meet those criteria. The questionnaire should be limited to information that is critical to the study and that will be used in the analysis of the results.

The questionnaire in the proposed form is, admittedly, too long. We have now separated the questionnaire into a section which includes demographic information, Vietnam exposure information and the majority of the potential confounders. The second section of the questionnaire is the medical history section. Each of these questionnaire segments should take about an hour to complete and since they can be done in separate sessions, should be perfectly acceptable to the veterans. Separating the medical history section from the questions on Vietnam experience should further help to reduce potential bias from tying the two together. We specified in the protocol and will reiterate here that the questionnaire must be administered by a trained interviewer at the appropriate examination center. We feel strongly that the questionnaire should not be administered in the home or any other location prior to the veterans' attendance at the examination center. The primary reason for our concern is that the use of such a two stage procedure would greatly increase the probability of dropouts between the administration of the questionnaire and the conduct of the physical examination. The questionnaire has been carefully reviewed and we believe that all information included in the questionniare is potentially necessary and should be pilot tested. We have also revised the questionnaire to avoid the use of unnecessarily technical language.

Other Instruments

The psychological and neuropsychological instruments, all of which were not available for review, should be evaluated and should include only information that will be used in the analysis of the results and presented in a way that would not be offensive to the participants.

We certainly concur that neuropsychological and psychological test batteries should not be offensive to the subjects. These are standard test batteries which have been widely used and accepted by a wide range of subjects.

Physical Examination

Data collected from the physical examination should be limited to those items that will be used in the analysis of the study. This does not mean that the physcial examination should not be comprehensive as determined by the examining physician for the particular individual, although items to be used for analysis of results must be collected according to a standard protocol.

The examination procedures were chosen to include items that can be used in the study. These procedures are almost entirely standard procedures that would be conducted during a physical examination in any event. The length of the form reflects the fact that we have required a specific checkoff of conditions which would generally only be noted if they were found on physical examination. Such a checkoff list is necessary to insure standardization and can be rapidly completed. The examination protocol has been reviwed by a professor of medicine at UCLA and, in his opinion, conforms to standard American medical practice.

Laboratory

The final decision for the inclusion of laboratory tests for this study should be made after consultation with laboratory scientists to ensure that the best tests for that particular purpose are being used. There are other tests such as chest x-ray, spirometry, nerve conduction tests, etc., that probably have limited usefulness because of the inability to standardize and to intrepret between multiple examining centers.
It is critical that the standardization of laboratory procedures proceed with quality control and quality assurance for collection, transportation, handling, and analysis and that this process be begun immediately in the participating laboratories.

We certainly agree that some tests such as spirometry and nerve conduction would be difficult to standardize between multiple examination centers. However, the varability between centers could be evaluated within exposure groups. The utility of these tests, and particularly the ability to standardize their application, could be examined in the pilot study.

Other Areas of Concern

For all participants, the panel believes that information should be collected only on those items that are critical to the study, can be standardized, and are such to appropriately interpret between multiple examining centers and laboratories. If the practising physician feels that additional information is necessary for a particular patient to evaluate the health status, it obviously should be done but should not be part of the overall data collection and analysis for the purposes of this study.

Certainly if the examining physician feels that additional information is necessary to evaluate a particular participant, he or she should be free to do so. However, at a minimum, the standard protocol must be followed to insure standard collection of data.

It is not clear from the proposed protocol the duration of the overall study or time estimates for each individual participant. These should be determined. A possibility that should be considered in regard to future duration is that after completion of the initial examination and analysis, the cohorts names be matched against the National Center for Health Statistics (NCHS) Annual Mortality Index. This would provide nearly all of the necessary followup information and would be more efficient than a mail survey or a hands-on followup of each individual.

The duration of the overall study was specified in the timetable section of the protocol. The duration of the examination time for each individual participant is more difficult to estimate at this point. It certainly could be expected to take at least two days. More accurate estimates can be developed at the completion of the pilot study.

We support the suggestion that future follow-up be accomplished, if possible, through the use of the National Center for Health Statistics Death Registry. However, it must be kept in mind that not all states participate in the death registry and the impact of registry incompleteness on follow-up must be ascertained in a pilot study. In addition, we suggest that future consideration be given to the possibility of actual re-contact of subjects for evaluation of non-fatal illnesses which may be of potentially serious concern to the veterans.

After the initial analysis has been completed and depending upon the results, additional well focused, smaller studies, such as specific case control studies, may be necessary to further define the extent of possible uncovered problems.

After the initial analysis has been completed, the method of cohort selection should be made public. While still ensuring individual confidentiality, each participating veteran should be informed of his or her status in the cohort selection process.

We certainly would support the suggestion that specific case-control studies or other such relevant studies be conducted after completion of base-line analyses from this study. Also, at that time the method of cohort selection and/or the full protocol can be made public and participants informed of their presumed exposure status as determined by the study.

It should be explicitly stated in the final design that when an abnormality for an individual is found, how that abnormality will be followed, who will follow and treat it, and what system will be set in place to ensure that each individual will receive the necessary medical care.

The panel suggested that we specify a mechanism for insuring appropriate follow-up for individuals found to have abnormalities at physical exam. The basic mechanism for follow-up of these abnormalities is provided in the protocol draft. Any necessary adjustments to this procedure to guarantee its practicality and workability should be made on the basis of experience from the pilot study. (See also comments in next section.)

The panel assumes that the final protocol will address the usual concerns of patient confidentiality, freedom to withdraw from the study, and methods of providing the individual veteran specific medical information of which he or she or his or her physician should be aware for the proper care of the individual veteran.

Confidentiality. This involves knowledge of an individual's participation in the study, connection of the individual with results of the study, and reporting of results to others. The first should be managed by maintaining limited name and address card files, with encoding for fact of participation, available only to study staff working directly with records. No inquiries about participation, not authorized by the participant in writing, should be answered other than with a form letter stating that all such inquiries concerning participation must be made to the possible participant.

Segregation of identifiers and data, can be handled with removable identifiers and reencoded identification numbers for data from different sources. However, straight or encoded initials for error checking should also be incorporated. No data forms should have identifiers left on them. Cover pages with identifiers should be filed separately. Computer records should be maintained without identifiers and the connection between data and identifiers, if needed for information checks or notification of participants, should be made by specially trained staff.

Data collected in the study on any individual should not be made available to any third party without the express written consent of the participant. All analyses should be reported in statistical terms; any anecdotal reporting and/or reporting on individual or very infrequent findings, should be made with sufficient alteration to protect the individual's identity while preserving the information.

Freedom to Withdraw. The informed consent form should include a statement about freedom to refuse to participate in the study and freedom to withdraw from the study at any time without prejudice. It will be particularly important to reassure the veteran during recruitment that his status with the VA and his access to VA benefits is not affected by his refusal or withdrawal. The freedom to withdraw should probably be reiterated at each major contact, especially if the study contacts are at VA facilities.

Notification. Notification (methods of providing the individual veterans with specific medical information concerning their proper care) can be handled in three ways (see also the discussion in section III.B.13 of the protocol):

a) The physician responsible for the initial examination should be allowed, at the end of the exam, to discuss findings, especially any findings needing urgent follow-up, and to recommend such follow-up to the veteran. A similar mechanism should be set up for immediate notification concerning laboratory findings requiring urgent follow-up. There should be later follow-up from the study to assure that appropriate medical attention was obtained.

b) Reports of findings should be sent to the physician or medical care entity designated by the veteran at the time of the examination. The report should include findings, notation of abnormal findings and some recommendation for follow-up, if necessary. The veteran should be notified that such a report has been sent. If the veteran has not specified a health care source, and if there are not notable problems, he/she could be advised that such a report is available to be sent if requested later. If there is need for follow-up, the veteran should be urged to contact a health care source to which the report can then be sent.

c) A specially prepared report and interpretation of findings could be sent to the veteran. This could be based on the computerized reports sent out following screening examinations or health risk appraisals by companies such as Cardio-scan or General Health. In these, the findings are reported and reviewed in terms of range of normality or abnormality, and appropriate actions, if any, recommended in terms of health care, habits and future activities.

Pilot Study

We believe the Pilot Study should include 5 percent of the anticipated study population. We recognize it may not be possible that this be a random sample of the population but that it be clearly stated and understood what that 5 percent represents. The panel unanimously disagrees that the Pilot Study should take place in only one study site but recommends strongly that it be conducted in all examination centers and study sites that will be used in the overall study. The Pilot Study should be used to determine participation rates and to further refine the instruments to be used in this study. An analysis of the results of the pilot study can be used to make a determination of the possibility of success of the larger study. The results should in no way be interpreted as to effects but only whether it is possible to conduct a scientifically valid overall study.

If cohorts of 6,000 veterans are identified, the proposed sample size for the pilot study of 5% of the cohort will be larger than recommended in the protocol. If cost is not a factor in the decision we would agree with the panel. However, we feel that a sample size of 400 subjects would be adequate.

We believe that the 400 subjects (or 5% of the study cohorts) selected for the pilot study must be a <u>random</u> sample of the different cohorts. Otherwise, conclusions from the results of the pilot effort will be very difficult to interpret.

We understand the panel's concern about conducting a pilot study in only one examination center. We, however, do not agree that the pilot study should be conducted in all potential examination centers as the mechanics and cost of the pilot study would be very much increased. In addition, because of the small number of subjects that would be anticipated in any given examination center, we anticipate that the results might be more confusing than helpful. We would support the recommendation of the OTA review panel that two or perhaps three examination centers be included in the pilot test. This would allow for examination of problems of coordination between centers but would keep the pilot study within a more feasible range of effort.

Optimism about the protocol and the study was not universal among the OTA Advisory Panel members. Some panel members, while commending the UCLA team for their industry in writing a protocol of this complexity and their ambition in the scope of their proposal, expressed great reservations for the project. These feelings represent a lingering disagreement about whether such a study should be done at all, and to a lesser extent whether the current protocol is adequate to the task. The pessimism stems principally from two sources: the undeniable fact that the investigators are proposing to embark on a very general search for disorders of various organ systems, and the circumstance that exposure to the agent was at variable dosage levels and took place between 10 and 15 years ago. In view of such reservations it is important that the investigators clearly describe the limits of the study, and that the decision to continue be based on estimation of the kinds of health effects detectable by the study.

> The limits of the study in terms of detection of health effects are provided in general terms in the protocol section on sample size. Outcomes of any given frequency can be compared to the recommended sample size, utilizing the figures in that protocol section. We have attached to this addendum a table (Table I) which includes effects which have been noted in animal studies, effects which have been noted in human studies, and our guess, at this point, as to the most likely possible effects to be seen in humans based on the combination of animal and human evidence. This list includes items such as reproductive effects which we do not consider likely but which we feel must be included in this study.

2. Timetable

An overall study length of five and a half years, divided into two and a quarter years for development and pilot testing, two and a quarter years for implementation of the full protocol and one year for data analysis is proposed. The division into stages is appropriate and the initial stage is about right in length. However, the implementation and analytical stages appear overly optimistic, allowing little or no time for enrollment, scheduling and the general milling around which is the inevitable concomitant of any large, complex, multi-institutional study. An overall length of at least 7-1/2 to 8 years seems a more reasonable planning horizon for this investigation. Time estimates can be refined as planning progresses.

We agree with the comments.

3. Checkpoints

The investigators have identified a number of points at which progress should be evaluated and the study halted if certain criteria are not met. OTA endorses such step-wise decisionmaking and cautions only that the criteria for making decisions concerning continuation must be stated clearly in advance.

Obvious checkpoints involve several issues discussed in this review. For example, early in the detailed study design the following questions must be addressed:

1. Can troops be successfully assigned to high or low likelihood of exposure categories?

2. Are there sufficient numbers of troops in each cohort to carry out a meaningful study?

3. Are the endpoints to be examined sufficient to justify executing the study?

A negative answer to any of these questions should result in calling a halt to the study and a rethinking of possible approaches to learning about possible health effects from Agent Orange.

We agree

4. Oversight Committee

The proposal that an oversight committee of eminent scientists be empaneled to guide the pilot and full operational phases of the study is excellent and should be adopted without question. Representation from one or more of the veterans' organizations also should be considered. Such a committee will provide a buffer for an investigation of great public and personal sensitivity. The committee should be appointed as soon as possible, to be available during planning for the pilot study and to play a key role in the "checkpoint decisions" of whether to proceed through the stages outlined in the protocol.

> The Oversight Committee must have access to all pertinent information regarding the design and conduct of the study including the details of exposure estimation and endpoint determination. The members of the committe, therefore, must be sworn to absolute confidentiality concerning all aspect of the study. We agree that the committee should be appointed as soon as possible and, in fact, feel that it should be in place even before the selection of the coordinating center. A representative from a veterans organization may be very helpful on this committee.

5. Pilot Test

The investigators propose an overall pilot test of 2-¼ years involving 400 participants and a single examining center. The time allotted for and size of this investigative phase seem appropriate. However, the choice of a single examining center, though defended, may be unwise. Lack of standardization and comparability between centers will be one of the most difficult problems in the full study. To conduct a pilot study which provides no information in this area would be regrettable. At lease two pilot centers should be identified.

> We agree that two or three examining centers would be valuable. We do not recommend more than three. (See comments from AOWG review section.)

6. Limits of the Study

Before pilot testing can begin, the limits of the study must be clearly drawn. Statistical probability dictates that, for a study of any size, no matter how perfectly designed, effects occurring with low frequencies, as a result of an exposure, may, by chance, not be observed at all. The ability to detect effects at lower and lower frequency increases with the number of participants, but there are always limits.

These two limitations, that imposed by a limited number of participants and that of limited ability to infer causation, are both pertinent to the proposed study. The total population of Vietnam veterans is finite, and very rare events such as certain malignant tumors at these young ages may be undetectable because of sample size, even if they are strongly associated with Agent Orange exposure. On the other hand, some common effects may indeed be due to Agent Orange, with only a slightly increased frequency. In these cases, large numbers of exposed subjects may experience the effect, but it will also be seen in large numbers of non-exposed men. Even if a difference is demonstrated and with the large numbers of cases is highly significant, it cannot be assured that the excess is not due to some initial vulnerability of the exposed.

A different limitation of this type of study is that of determining causation. Even if a study is sufficiently large to be clearly significant statistically, it is at times impossible to conclude that an excess of effects seen in exposed subjects is caused by the exposure studied. The alternative explanation must be considered that the exposed subjects were a more vulnerable group initially and would have experienced the effect more commonly whether or not they had been

exposed. This problem cannot be solved by including large numbers of subjects, even if very large numbers are available for study. The problem can be alleviated if it is possible to study the subjects carefully and to determine that they were not initially different in any important way. If there is a strong association between exposure and effect, and if the two groups seem to have been generally similar before exposure, it is reasonable to conclude that a large effect is probably due to the exposure. But if the association is weak, so that the effect is only a little more common after exposure, it is generally impossible to be assured that some minor initial difference between exposed and not exposed is not the true cause. The requirements here are both adequate number of subjects and adequate strength of association.

Probably the main strength of the study is that it will provide upper estimates of the magnitude of each endpoint for which analysis is carried out. Upper estimates will be available even for rare diseases and diseases weakly associated with exposure. But only for diseases sufficiently common to occur in large numbers and which are also strongly associated with Agent Orange will clear demonstration be possible that the disease is due to this exposure. There may be no such conditions identified.

> Utilizing the sample size determination section of the protocol, the probability of being able to detect a difference between high and low exposure groups of any given magnitude or a condition of any known frequency can be determined. It is certainly clear that the study would be highly unlikely to detect rare events such as soft tissue sarcomas in a study of this size. The determination of whether the detected effect is most likely due to the exposure or some other factor is a central part of the conduct of any epidemiologic study. The procedures for handling this problem are specified in detail in the study protocol sections dealing with selection of study groups and confounding. The initial selection of the high and low likelihood of exposure cohorts must be very carefully done to ensure comparability of these groups. We feel that it is mandatory that both the coordinating center personnel and the Oversight Committee be heavily involved in this process.

7. Structure of the Study

The investigators have suggested a number of procedural mechanisms to be considered as the details of the study are developed. These basically concern responsibility for conducting interviews and medical examinations and the sites of such activities. Though these logistical aspects need not necessarily be decided in the scope of the current contract, the Panel made some suggestions. The investigators raised the possibility of using VA medical facilities to carry out the examinations. The Panel did not reject the idea of using VA facilities, but a number of concerns were expressed. Some of these issues were raised in OTA's review of the first draft protocol, and are mentioned in the current protocol. There is long-standing concern about various factors which might affect participation rates, and it may be that some veterans would be deterred from participating if the examinations were to be carried out at VA hospitals. Before any decision is taken to use VA hospitals for the full-scale study, the effect on participation should be determined during the pilot study.

An encouraging note in this regard is that, currently, about 3,000 veterans monthly are examined as part of VA's Agent Orange Registry. This participation may be interpreted as showing that veterans will participate in a study in VA facilities.

An organizational structure for conducting studies already exists within the VA, namely the Cooperative Studies Program (CSP) which conducts collaborative clinical trials among VA hospitals. The organizational structure for each clinical trial within the CSP consists of a chairman's office and a designated biostatistics research support center (of which there are four around the country) who together coordinate the study and perform monitoring, quality control, and analysis. There is an external Operations Committee that meets periodically and reviews progress and adherence to the protocol. This background of experience in conducting collaborative research within the VA, with an organizational structure similar to that proposed by UCLA, could be valuable to the investigators in fleshing out the details of the protocol.

Aside from the possible effects on participation rates of using the VA medical facilities, the other major concern, and perhaps the more serious one, is the problem of standardization among personnel and procedures in the examination centers. This will be a thorny problem regardless of who conducts the examinations. The opinion was expressed and supported that it might be more difficult to achieve standardization in the VA system than in other health facilities.

A suggestion that garnered nearly unanimous support of the Panel was to consider contracting with the National Center for Health Statistics (NCHS) Health and Nutrition Examination Survey (HANES) for both the interview and the medical examinations. This program uses mobile examination facilities. The purpose of HANES is health assessment (as opposed to the treatment orientation of most general medical institutions) which is exactly what is needed in this type of study. The usual complement of HANES study personnel might have to be augmented by neurologists and other specialists for this effort, but that should pose no major problem. HANES personnel are accustomed to following strict protocols, and are equipped to gather

analyze biological samples. Collecting and storing biological samples might be considered as part of the study. If pertinent new tests become available, they can be run on the stored samples.

OTA urges the investigators and VA to consider HANES or another equally qualified such group. (For a brief description of HANES see Attachment A.) Regardless of the organization performing examinations, the appropriate referral would be made for any condition requiring medical attention, whether it be to a VA facility or to the participant's private physician.

> We fully support the recommendation that a contract with the National Center for Health Statistics Health and Nutrition Examination Survey (HANES) be considered. However, we caution that the HANES personnel must be willing to revise their procedures in accord with the protocol examination.

6. Cooperation and Coordination Among the Organizations to be Involved in the Study

Beginning with the pilot stage, the Agent Orange study will involve cooperative efforts on the parts of several organizations. Aside from the review groups such as OTA, the VA Herbicide Panel, the Agent Orange Working Group and perhaps the National Academy of Sciences, attention has to be directed at the organizations that will plan and execute the study.

First of all, the VA will have to decide upon a primary contractor to develop the detailed plan, and the contractor will presumably arrange subcontracts with other organizations to administer the questionnaire and medical examinations. If the suggestion in the protocol is followed, some agreements should be made with veterans organizations so that their good offices can be used to publicize the study and encourage participation in it. Furthermore, the relation between the Department of the Army, which will contribute to the exposure index, and the VA and the primary contractor will have to be detailed. The sooner the links can be made among all these organizations the better.

We agree completely with the reviewers on this point. The proper cooperation and coordination among the organizations will be essential to the conduct and completion of the study.

Exposure Likelihood Index

The contractors provide an orderly description of the steps necessary to prepare an exposure likelihood index. At the same time, the authors remain properly cautious about whether any index which can be constructed will have a useful degree of correlation with likelihood of exposure.

During the time the investigators were working on the present protocol, Dr. Jerome Bricker of the Department of Defense developed a different method for constructing an index (Dr. Bricker's scheme is included in the protocol as Appendix H). Dr. Bricker enjoys and benefits from a working relation with Mr. Richard Christian who, by general agreement, knows more than anyone else about the records necessary for the study of Agent Orange exposure in Vietnam. Dr. Bricker and Mr. Christian strongly hold the opinion that Dr. Bricker's suggested methods would be quicker and easier to use. Mr. Christian, who was at the OTA Advisory Panel meeting, said that his organization could provide an index based either on the UCLA or Dr. Bricker's proposal.

The UCLA protocol recommends that a member of the organization that will coordinate the study work closely with the Army in developing criteria for the exposure index. For example, the cut points that will establish whether a unit is considered to be in the high or low likelihood of exposure groups must be defined in a cooperative manner between the contractors and the Army. The protocol also recommends that the Agent Orange Working Group be involved in establishing the criteria that will establish which units are considered to be in different exposure groups. These are commendable ideas.

OTA did not decide which method of constructing an exposure index was better. Further discussion and collaboration between the contractors for the pilot study and

e Army and possibly the Agent Orange Working Group should lead to a decision about the preferred method. That is considered a detail best left to the designers of the study and the records experts.

We would agree with this series of comments. However, please see the detailed comments concerning Dr. Bricker's proposal in the section in the Agent Orange Working Group review above.

a. Cohort Selection

The question of how an individual would finally be selected to a cohort based on likelihood of exposure received a great deal of attention from the Panel. There was concern that the problems of determining whether or not an individual was indeed with his company on a given day might be overwhelming. How much error would be introduced by the assumption that the entire roster of a company was present on a given day, leading to assignment of all company members to the same exposure status for that day? A test run on a few companies to determine how great a difference there would be between the group method and the individual method of exposure determination might be of value and should be considered. If the group method did not create a significant amount of misclassification (a level determined by the investigators before the test begins) the need to resort to the individual method might be obviated.

We certainly agree that a test of the amount of misclassification from the use of a group method of exposure estimation should be made.

b. Third Cohort

About one year ago, there was a general impression that a study of Agent Orange was impossible. At that time, discussion began about a study of the "Vietnam experience" as an alternative to the seemingly-impossible Agent Orange study. Such a study would necessarily involve study of some comparison population not exposed to the "Vietnam experience," a third cohort. Since then, the efforts of the Department of the Army and the Agent Orange Working Group, with prodding from veterans organizations, have produced records that provide some assurance that exposures to Agent Orange can be estimated. That assurance, in turn, means that an Agent Orange study can be mounted. The fact that an Agent Orange study can be mounted, however, does not mean that it will necessarily produce meaningful results or clarify important issues.

The contract placed with UCLA called for the development of a protocol for an Agent Orange study. OTA, in reviewing the protocol, has restricted itself to consideration of an Agent Orange study in contrast to a Vietnam experience study.

However, the issue of a "third cohort," a group of veterans who did not serve in Vietnam, was discussed at the OTA Advisory Panel meeting. Those who favored expansion of the study saw an opportunity to answer a number of questions by including the third study group. Those opposed to expansion cited the major problem of choice of endpoints to be included in such a study. Concentrating largely on health effects expected from toxic chemicals is seen as a necessary step in refining the questionnaire and medical examinations to study Agent Orange. If the study is expanded, other endpoints more directly related to war experiences will have to be considered.

We still believe that this additional cohort would not only be expensive but unlikely to be meaningful because of differences in selection and survivorship.

c. Officers and Multiple Tours

The exclusion of officers and individuals with multiple tours of duty, as is proposed in the protocol, would be unfortunate in that these individuals may include a large proportion of the most highly exposed soldiers. The suggestion was made that such individuals be segregated from the others, but that no decision be made about excluding them until every effort was made to include them in the study. The difficulty in including officers and multiple-tour veterans in the study arises from the fact that the probability of a multiple-tour veteran's being in the low likelihood of exposure group is very small. A comparison of multiple tour exposed subjects with single tour unexposed subjects was considered uninterpretable because of confounding factors. If that is the only comparison possible, the UCLA proposal to exclude officers and multiple-tour individuals should be supported.

We agree.

0. Locating and Recruiting Veterans for Participation in the Study

The protocol thoroughly outlines steps for locating veterans. Certainly the use of IRS files to locate veterans would make the process more efficient. Permission for such use of IRS data is granted for National Institute of Occupational Safety and Health studies, and it should be sought for this study.

In contrast to the details provided about tracing veterans, there were too few about problems of recruiting the located veterans into the study. Problems with differential response rates, that is, differences in the willingness to participate among the low and high likelihood of exposure groups are mentioned, but no specifics are provided about what is to be done to improve participation. There is also a lack of discussion of the treatment of cohort members who already have died. Some ata collection procedures must be developed for those individuals.

> It is difficult to anticipate the direction or magnitude of differential nonresponse rates. A case could be made for either the high or low likelihood of exposure cohort having a different response rate. However, in order for there to be such a differential, the individuals would either have to know their status according to the study criteria or there would have to be a high degree of correspondence between their perceived status and that documented by the study. If there is no such correspondence, the differential would be unlikely to exist. We feel that maintaining strict confidentiality of the presumed exposure status of the individuals, including blinding of the coordinating center and examination centers during the data collection process, and agressive recruiting for all study participants will help to minimize differential response rates. Furthermore, if the examination procedures can be run so as to be as pleasant as possible to each participant, response rates should again be maximized. However, if a differential response rate is, in fact, encountered then a subsample of nonrespondents should be diligently pursued in order to ascertain their characteristics.

The collection of data on cohort members who have died since their discharge from the service can be a difficult problem. The death certificate should be obtained. If possible, available medical records on these individuals should also be collected. This would require consent of next-of-kin. The next-of-kin would also probably be the source of information about the existence of such medical records. However, certain things can be obtained including the military records which should be abstracted as for any other study participant and any existing VA records. If possible, it might be desirable to conduct an interview of the next-of-kin to elicit information parallel to that obtained for the live participating veterans. Our own experience in a somewhat similar study found the next-of-kin of young men extremely reluctant to cooperate in any fashion with the study. In addition, the next-of-kin in this study may carry considerable bitterness if they feel that the Vietnam experience was in any way related to the veteran's death. In fact, the next-of-kin may have filed claims against the government.

We recommend that a trial of at least 25 deceased veterans be conducted during the course of the pilot study, in which an attempt is made to obtain as much information as possible. The success rate and value of the information obtained can be reassessed at that point.

Compensation for time lost from work, and perhaps, additional money might be offered for participation. The Air Force is paying its Ranch Hand participants $100 per day. In addition, the appropriate referral should be provided for any condition requiring medical attention which is detected in the study.

See the response to paragraph 8 of the VFW letter concerning the issues of compensation.

The procedures for notification of subjects concerning medical conditions and referral for medical care are outlined in the study protocol and should be refined during the pilot study. (See also the section on this subject in the AOWG review response.)

Safeguards are necessary so that the initial letter and telephone contacts are handled in a similar manner for all participants. Offering different inducements for participation or making suggestions about exposure status could affect response rates. The recruitment letter needs careful attention. The wording of the sample letter provided with the protocol must be reconsidered. The present form and tone might generate avoidable non-participation.

The suggestion was made that the initial telephone contact might be expanded in order to gather some information. That conversation will be the only source of data for veterans who do not choose to participate. A standard inquiry about demographic and other characteristics should be made at that time if at all possible. The Air Force has developed a minimum data set for this purpose.

> We agree completely that the initial contact and telephone contacts must be handled in a similar manner for all participants. We believe that blinding of the coordinating center and data collection centers as to the cohort membership of the study participants during the data collection phase would obviate this problem. Differential inducements for participation should certainly be avoided. The recruitment letter can be revised by the coordinating center for the pilot study and tested at that time. We would make an additional recommendation which was not made in the original protocol, that serious consideration be given to hiring at least a part-time public relations expert to assist the study in such things as the handling of publicity and inquiries and the design of various contact procedures.
>
> We recommend that the coordinating center obtain the Air Force minimum data set for consideration in the telephone contact.

11. Outcome Assessment

The questionnaire and, to a lesser extent, the medical examinations are mosaics of question segments, mostly drawn from existing instruments, blanketing many areas of possible health effects. The investigators propose to provide as much overlap in data collection as possible with other concurrent studies, particularly investigations of Australian veterans of Vietnam and U.S. Air Force Ranch Hands. This is a strength of the study and should be encouraged. Replication of any findings, whether positive or negative, will strengthen all the investigations.

While OTA appreciates the value of including questions from other studies, there is some unease about the lack of justification for the questions and the seeming lack of focus. There is a need for the investigators to relate questions to the purpose of the study. This exercise is the first step toward developing an overall scheme for interpreting the results. It is a difficult exercise even when dealing with objective information, and it is all the more difficult when dealing with so many largely subjective responses. The interpretive value of various answers and combinations of answers may be, next to the assignment of individuals to the low and high likelihood of exposure groups, the most controversial aspect of the study details. It is, therefore, important that the development of the analytical scheme be carried on in tandem with development of the likelihood of exposure index.

A fundamental point, discussed in our September 8 review of the first draft protocol, is reiterated in the current review: the investigators must specify at least some key outcomes they intend to look for. OTA does recognize, however, that there is merit in looking for as wide a range of outcomes as possible in view of the plethora of complaints alleged to be consequent to Agent Orange exposure. Allowance should be made for some looseness in data collection, for the examination of broad, open-ended hypothesis-seeking questions. The investigators could easily be faulted for failing to look for particular complaints after the study is completed. This does not alter the fact that decisions will have to be made to investigate thoroughly a small number of key conditions most likely to be associated with Agent Orange, and to exclude those for which little or no support exists. Decisions about key outcomes should be based on previous epidemiologic and animal studies of the components of Agent Orange and perhaps other toxic chemicals, if deemed relevant. The decisions should also take into account some of the more frequently-occurring effects reported in the popular press.

There is bound to be disagreement about the key endpoints chosen initially, but the sooner the initial list is drawn up, the greater the chance for constructive input from reviewers, and the happier everyone is likely to be with the final product. The question of key endpoints must be settled before the questionnaire and medical examinations can be made final.

We understand the seeming lack of focus in the questionnaire. The questionnaire has now been separated into a section dealing with demographic factors, Vietnam experience and the majority of confounders and a separate section, which can be administered at a different time, concerning the medical history. In addition, we have provided in the attached Table II, a list of the groups of questions which deal with specific factors and the reason for their inclusion in the questionnaire. This list may be helpful to the coordinating center in the evaluation of the questionnaire at the time of pilot testing.

As previously noted, the table included as Table I of this addendum gives the endpoints noted in the animal studies, the health effects reported in human studies and our own specification of those outcomes most likely to be seen or which we feel must be included in this study, regardless of their likelihood of occurrence. While we expect considerable debate about this list, it should serve as a starting point for discussion. An additional point about the questionnaire is the wide variety of complaints which have been reported in the popular press concerning the effects of Agent Orange. These are listed in a table in the appendix chapter of the protocol dealing with the popular press. We feel that these topics cannot be completely ignored in the collection of data for the study. Unfortunately the inclusion of such a range of effects also insures a relatively lengthy questionnaire. In the current form, with separation of the medical history section from the rest of the questions, the entire questionnaire should be more palatable because of the administration of segments in shorter time blocks.

We have not included broad open ended questions in the questionnaire for two major reasons: 1) our previous experience has been that diseases not specifically asked for in a questionnaire are not reported by the subjects. This is further confirmed by the established phenomenon that any individual's capacity for recognition exceeds his or her capacity for recall. 2) The difficulty of developing and applying coding schemes for open ended questions would greatly increase the cost of administering the questionnaire and would introduce an additional difficult problem in ensuring standardization.

a. Questionnaire

The veteran and spouse questionnaires are made up of questions about health, and non-health characteristics, broadly described as demographic, lifestyle and occupational descriptors. The questionnaires are made up, in large part, of questions and sections drawn from other questionnaires, including the Australian Agent Orange study, the Air Force's Ranch Hand questionnaire and several other general health and lifestyle questionnaires. The questionnaires were generally considered to be the weakest part of the protocol. There was strong feeling that a major overhaul is necessary both in substance and in form before the questionnaires can be used. There was some concern that the interview required to complete the questionnaire would take too long. This was tempered by recognition of the need to acquire hypothesis-seeking information which, of necessity, may be poorly delineated. At this time, overcollection is preferable to undercollection. The Panel strongly suggested arranging the sections or questions in the questionnaire and other data collection instruments hierarchically, from the inquiries most vital to those least likely to produce useful information. This hierarchy could guide eventual paring down of the questionnaire if deemed necessary after further field testing. A general suggestion was to encourage the study designers to enlist the help of experts in designing the questionnaires.

The Panel was unclear about the setting in which the questionnaire is to be administered. Some members expressed a preference for administering it, all or part, at some time prior to the medical examinations, and not necessarily at the examination site. If more convenient and numerous locations for the interview could be arranged, e.g. public schools or other public buildings, participation levels might be enchanced. Interviewing in the participant's home was not favored, since

his might discourage participation among a subgroup of veterans, including perhaps those who have not shared their Vietnam experiences with their families. This same concern, if it pertains to a large number of veterans, may pose a problem in attaining sufficient participation of wives.

Depending upon the length and content of the questionnaire that eventually is adopted, some thought might be given to "staging" its administration. This ties in with another issue concerning the training and background of interviewers. There might be merit in considering the use of trained medical personnel — nurses or physicians' assistants, for example — to administer the health segment, and other trained interviewers to cover the non-health questions. It might be possible, for instance, to administer the questions on demographics, lifestyle and occupation prior to the time of the medical examinations. This might be particularly advantageous if the questionnaire is long.

Concern was raised that, particularly in the health segment and in the questions dealing with exposures to chemicals both in and out of Vietnam, there was little or no allowance for spontaneity on the part of the participants. Valuable information might be volunteered if the opportunity exists for participants to fill in gaps left by specific questions.

The general health segment suffers from being too broad and sweeping, and the segments concerned with specific key areas do not go into enough depth. This is in large part a consequence of the lack of focus on specific key health outcomes related to Agent Orange. As presented in the questionnaire, the systems of the body

very unevenly covered. The language used for different systems varies from vague and possibly misleading vernacular to highly specific esoteric diagnoses. A potentially fruitful area of inquiry, infectious diseases, received no attention at all. Information about parasitic diseases, specifically, should be sought.

OTA feels strongly that both diagnoses and symptoms should be sought for all conditions of interest and that certain responses should trigger in-depth probes in key areas. The Panel suggested various models that the investigators might draw from for presenting diagnoses and symptoms, specifically the Kaiser Foundation medical history questionnaire, the Cornell Medical Index and the health history questionnaires of major insurance companies.

The questions relating to neurology are in need of revision. More emphasis uld be placed on functional questions in this area. For example, probing about specific skills that the participant possessed in the past compared with his abilities now could uncover changes in neurologic status. The questions should be restated and terms added to be more inclusive in describing sensations. These were not well-described.

The approach to malformations in offspring was considered deficient. The spouse questionnaire is not specific enough about exposures of the mother during each pregnancy, and no attempt is indicated to interview or obtain records of previous partners or spouses. Questions about smoking and drinking should be asked specific to each pregnancy. Questions about medications known to be teratogenic should be asked directly. No information about pregnancies resulting in perinatal deaths, often occurring in babies with birth defects, is gathered. This should be rrected. If a birth defect is reported by either the participant or spouse, an attempt should be made to verify the diagnosis via medical records.

See above comments.

The protocol recommends administering the questionnaire at the examination center during the course of the examination procedures. We feel that this procedure is mandatory. The administration of the questionnaire prior to the scheduled examination would probably increase the dropout rate during the interval between the interview and the conduct of the physical exam. We are generally uneasy about the use of trained medical personnel for administration of the medical history section because of the general finding that medically trained personnel are poor interviewers and have difficulty following precisely a standard protocol. Use of properly trained (in questionnaire administration) nurses or physicians assistants would have the advantage of better understanding of the medical conditions included. The danger is that these medically knowledgeable interviewers would make judgements about the "correctness" of the veteran's responses and introduce a potentially serious bias. We do, however, recommend that the results of the medical history section be provided to the examining physician at the time of physical examination.

The reviewers were concerned about lack of depth in many areas. Much of the lack of depth is deliberate since we felt that the veterans would generally have difficulty in answering specific technical questions. (Note that we have removed all questions about specific diagnostic tests from the revised questionnaire.) However, in all cases the veterans will be asked for the name and address of the diagnosing or treating physician or hospital. The necessary technical detail can then be obtained from this medical source.

We do not agree that information about tropical infections and parasitic diseases should be included in the questionnaire. Although it is likely that many veterans may have acquired parasites in Vietnam we are not aware of any basis that this is associated with exposure to Agent Orange. We feel, therefore, that inclusion of questions on these diseases would add complexity and length to an already long, complex questionnaire without adding commensurate relevant information.

Some of the scales from the Rand Health Insurance Study for physical and mental health status might be considered as additional data collection procedures because they have been well tested, and normative data will be available on a large population by the time this study is completed. We know, however, of no simple and useful method for assessing changes in functional level. We have added several questions from the NCHS questionnaires.

The administration of the spouse questionnaire to previous partners or spouses is strongly recommended in the protocol and reemphasized here. The verification of birth defects by use of medical records should certainly be included as should verification of any other reported condition.

b. Laboratory Tests

The laboratory tests included in the protocol were heavily criticized as inappropriate and generally not leading to any conclusions about exposure to toxic substances. OTA recognizes the difficulty in choosing appropriate laboratory tests, however, since none is specifically diagnostic for the effects of Agent Orange or its constituents. The point was stressed that the participants will be relatively young and healthy, and for the most part we should be looking for early markers of disease and not frank undiagnosed cases of most conditions. The selection of the study participants on whom the tests in Table 3 will be performed is not discussed. Just as for questionnaire and other medical examination items, the justification for laboratory tests should be included, and the conditions that can be detected by them, either alone or in conjunction with information from the questionnaire and physical examination, should be specified. In light of the recent publicity about melioidosis, some serological testing for evidence of exposure to infectious diseases might be considered. This is not advocated, however, if the tests available are not well standardized or accepted as meaningful.

An example of the potential difficulty in interpreting laboratory tests was brought up by one panel member. Laboratory values obtained from an individual might have no relevance whatsoever to an individual's exposure status in 1969. This is important because aberrations in levels of many enzymes, hormones, etc., are often reflective of acute rather than chronic conditions. For example, an elevated urine white blood cell count could be the result of a lower urinary tract infection occurring one week before the sample was drawn and not have any relevance to an

individual's Vietnam experience. Therefore, one aspect of the rationale for interpretation is to put into proper perspective the meaning of aberrant levels detected in laboratory tests.

Another aspect of interpreting these types of laboratory tests involves the reported result itself. Most laboratory tests have published reference ranges or so-called normal ranges, which are considered to be important clinical tools. There is, however, some controversy regarding their utility for epidemiologic study. What does it mean if the study group has more individuals with values outside a given reference range than the control group? Does it have biological significance or is it a consequence of the reference range's being too narrow for this group? In some cases, actual values can be reported (e.g., hematocrit, percent lymphocytes) and analyzed, circumventing the problem of the reference range. However, with variables such as urine protein, the values are usually reported as being within or outside the reference range and interpretation is difficult. Perhaps such variables should be considered only with respect to an individual's clinical presentation and not considered as epidemiologic outcomes.

Another related problem involves the possible finding of a significant difference between study and control groups which cannot be biologically explained. For example, what does it mean if the study group has significantly elevated red blood cell counts, a condition usually not considered detrimental? Will this be reported as a cause for concern?

There are, then, at least four areas pertaining to the analysis and interpretation of the laboratory aspects of the study which require guidelines for interpretation: the meaning of aberrant levels detected in laboratory tests, the significance and/or usefulness of reference ranges, clinical versus biologic interpretation of data, and a definition of areas of concern.

The laboratory tests recommended for this examination were developed with our internal medicine consultant in conjunction with the development of the physical exam and were designed to be complementary to that physical examination. It was further developed to ensure as much comparability as possible with the Air Force study. Further consideration of appropriate tests can be given by the Oversight Committee and coordinating center during development of the pilot study.

The selection of study participants for administration of the tests described in Table 3 are specified for each test in the table itself.

The interpretation of laboratory results can be made in two distinct ways, 1) clinical interpretation and 2) population interpretation. The clinical interpretation, in which the laboratory value is related to other examination information and a determination is made of clinical meaning for each individual, should be made by the examining physicians in conjunction with the coordinating center as outlined in the protocol. Appropriate notification of individuals and referral for appropriate care should be made as necessary. Normal ranges are useful in such clinical interpretations. For the population interpretation the distributions of laboratory values are determined for the comparison study groups. Since, as noted in the review, the participants will for the most part be young, healthy men we feel that the laboratory tests should be examined with the view of detecting biologic alterations which may have future implications for the health of individuals rather than relying on strictly clinical abnormalities. By the use of distributions of the laboratory values, the problem of normal ranges will not arise.

A cutoff value should be established for each laboratory procedure. This cutoff should be determined by the coordinating center in consultation with the appropriate laboratories and other expert consultants. To reduce laboratory errors, any value found outside the specified cutoff points should be retested on the same or, if possible, a new specimen.

The reviewers were concerned about what criteria would be used to determine which findings were cause for concern. We feel that any consistent differences in which the exposed group are "worse" than the unexposed and which cannot be explained in any other way should be considered cause for concern.

c. Physical Examination

The physical examination included in the protocol is adapted from that to be used in the Australian study, and it is a good starting point for the VA study. Panel members made a number of specific suggestions, included in this review in Attachment B. Some general points also were brought out. The physical exam should be "Americanized," though comparability with the Australian study should be preserved as much as possible. Systems for scoring items and examination techniques should be based on current American practice. Training for the medical personnel carrying out examinations should not be devoted to learning new scoring systems. Some of the items in the examination are too general, where specific conditions should be noted.

See the comments under the Agent Orange Working Group review.

d. Neurologic Examination, Psychologic Assessment and Neuropsychologic Assessment

The group of test instruments proposed to assess neurologic, psychologic and neuropsychologic status was generally considered strong. A number of improvements were suggested, the more specific of which are included in Attachment B.

The neurologic examination requires modification to focus more clearly on peripheral neuropathies. At present, some of the critical muscles are missed and appropriate examinations should be added. It was suggested that an audiogram be added as well. There are some questions requiring greater quantification and others requiring changes in explanations of the grading system. The question on mental status should be replaced with some objective measure, as the subjective remarks of the examiner would be difficult to interpret.

Regarding the psychologic assessment, the MMPI and SCL-90 have their strength in measuring depression and anxiety. An effect, if present, should be evident with these tests. SADS-RDC is not considered the "state-of-the-art" in many diagnostic categories, though for schizophrenia it is probably the best. NIMH is performing a cross-sectional screen on 15,000 individuals using a new scale called DIS, Supposedly it can differentiate schizophrenia, depression, phobias, obsessions, drug abuse, alcoholism and anti-social behavior with the last three items being the strongest. This obviously would be important in the veteran population. Since the scale for schizophrenia was weaker in DIS, the possibility of creating a hybrid between SADS and DIS might be considered. The DIS can be administered by a lay person and takes approximately 90 minutes.

The neuropsychologic test battery is well chosen for measuring effects of any brain damage if present. The sensitivity will be increased if results can be compared to test results from the veteran's induction examination. One Panel member

ıded a cautionary note about factors that must be considered in interpreting test results. In addition to age and education, native language is important. Verbal fluency in the controlled word associations and vocabulary are two examples that might be significantly altered by a native language other than English. The questionnaire at present does not include an inquiry about native language. Finally, it appears that these tests will take longer to administer than has been estimated in this protocol.

The Diagnostic Interview Schedule (DIS) is a structured interview with precoded, close-ended symptom items which yields DSM-III diagnoses; it is computer scorable and can also be used to generate Research Diagnostic Criteria (RDC) classifications, a precursor of DSM-III. The DIS is administered by lay interviewers whereas the Schedule for Affective Disorders and Schizophrenia (SADS) is administered by clinical interviewers. Therefore, the DIS is less expensive and more readily administered than the SADS. The strength of the SADS, however, lies in its reliance on the clinical expertise of the interviewer who makes the RDC ratings on the basis of the structured interview guide. The DIS is currently receiving extensive, full-scale field testing as part of the Epidemiological Catchment Area projects sponsored by NIMH, as well as being validated on clinical populations. At present the instrument has not been totally standardized, as there is a lack of consensus on the criteria for generating current diagnoses. The DIS could constitute an acceptable alternative to the SADS-RDC although the field testing and validation may not be completed in advance of this study. Since these two instruments differ so widely in method of data collection, creating a hybrid is probably not feasible.

We certainly agree that a question concerning native language should be included in the questionnaire and the question has been added. Those veterans identified as non-native English speaking should be analyzed as a separate group when comparing results of the neuropsychologic scales which involve language fluency. The estimated administration time for the neuropsychologic tests was developed by an experienced neuropsychologist. The estimates can be refined on the basis of experience from the pilot study.

e. Release of Medical Records to the Study

The protocol proposes that the study contractors request release of participants' medical records for use in the study. In general, there was a feeling that such records would have limited value. Concern was expressed that Agent Orange is such an emotional subject that a participant who presented himself to his family physician claiming ill effects from exposure might receive examinations and diagnoses different from a person who did not think he had been exposed to the herbicide. Additionally, it would be difficult to determine possible biases introduced by use of some medical records but not others. It was suggested that the time to make a final decision on this would be at the completion of the pilot test, when the yield from such an effort could be assessed.

Army induction examination records might be useful in establishing baseline values for some measurements. Those records suffer from many shortcomings, but they are collected in a routine manner, and they might be of value in the general health and psychologic areas. The usefulness of those records should be assessed.

If the effort is made to obtain medical records from participants, provision should be made for requesting release of children's medical records, as well. Such records would be of value in determining whether a birth defect might have resulted from exposure to toxic substances or from another cause. Likewise, medical records from ex-partners might be useful in the case of children borne by women other than the current spouse or partner.

We agree with these comments.

12. Data Analysis and Sample Size

The discussions of data analysis and sample size were well presented and thorough treatments, at least for certain aspects. However, there is no discussion of how confounding variables are to be handled in the analysis. This subject must be further developed.

The data analysis plan seem clearcut and logical. The notion of obtaining a handle on reporting bias is laudable. However, it is not clear just how a comparison of "those reporting exposure but not verified to have had exposure with those verified to have had exposure but not reporting exposure" (page 101) will provide the requisite information. Further, if this comparison shows some meaningful differences, what then will the investigators do in analyzing their results?

The remaining statistical analyses are generally straightforward, and and well presented, if not in full detail. Since there presently exists a fair degree of vagueness regarding the particular health outcomes implicated, the investigators cannot be faulted for their lack of detail regarding statistical analyses.

The sample size determination, made with reference to the limited information now available, is clear and pertinent to the proposed study. The requisite sample size, as the investigators indicate, can be more firmly determined following completion of the pilot study.

The choice of 0.01 and 0.05 for type I and type II error probabilities, respectively, is unusually severe. The investigators should consider relaxing the type I error at least, perhaps to the more customary 0.05 level. Adhering to a level of 0.01 seems to move this research study unnecessarily into a decisionmaking arena. Strength of association should be expressed by point estimates along with pertinent confidence intervals.

The choice of a 30% cutoff for combined nontraceability and refusal to participate raised concerns that such strictness might make the study impossible. An overall participation rate of 70%, which the investigators require, would be considered quite good for many studies but, according to the Panel, would likely be unachievable in this case. A somewhat lower participation rate was thought to be more realistic. Obtaining minimal information on essentially every participant at the time of the initial contact would reduce the impact of non-participation. On the other hand, adhering to the criterion of a difference in participation rates of no more than 15% between the high and low likelihood of exposure groups is considered appropriate.

22) The question of confounding variables is addressed in section D and E in the protocol section on data analysis. There are a number of ways in which confounding variables can be handled, or at least accounted for in analysis. For instance, various adjustment procedures, stratification and covariance analysis can be utilized. Logistic regression and log linear analysis, can also be employed.

The question concerning reported exposure versus verified exposure can be answered utilizing the fourfold table below of reported versus verified exposure - or sensitivity or specificity of reported exposure as a measure of verified exposure. (The letters represent the veterans in each cell.)

		Verified exposure: yes	Verified exposure: no	
Reported Exposure	yes	a	b	a+b
	no	c	d	c+d
		a+c	b+d	

In the usual fashion c represents false negatives and b false positives.

If the exposure was indeed damaging, then one would expect those with verified exposure, reported or not, to have "more" outcomes than those without exposure (i.e., disease rates among a+c greater than among b+d); the relative risk, given exposure would be greater.

One would also expect that the rates in a and c would be similar to each other, as would those in b and d. Therefore, one might expect the false negatives, c, to be meaningfully different from the false positives, b. In fact, such a difference might vindicate the verification procedures for exposure.

If the exposure was not damaging, then one would expect no difference between the exposed (a+c) and unexposed (b+d), hence no difference between the false negatives and false positives.

If, however, there is an impact associated with belief in exposure in the absence of actual impact, then one might expect that the relative risk given reported exposure would be greater (rate among a+b > among c+d). In this case the false positives might be expected to be substantially worse off than the false negatives. This type of difference might imply a differential reporting or recollection in the presence of a belief in exposure. Such a finding would call for a reexamination of the exposure verification procedures to assure that there is no error, and might call for reinterview of veterans to assure that the records do reflect their actual locations and experience.

If there is some impact associated with verified exposure and some impact associated with belief in exposure, then one would expect that the true positives (a) , who both believed themselves to be exposed and were exposed would have the highest rates (worst outcomes). The false negatives (c) and the false positives (b) would both have lower rates, the direction of their difference from each other depending on the risk associated with exposure and with belief in exposure. Those neither exposed nor reporting exposure (d) would have the most favorable outcomes.

In sum, a meaningful difference between false negatives and false positives has great importance as a finding in the study. The direction of the difference combined with comparisons with true positives and negatives will yield important evidence of relationships of exposure, belief and outcomes.

The reviewers suggest considering relaxing the type I error to a 0.05 level. We chose the level of 0.01 because of the seriousness of making an α error and for purposes of sample size computation. Once the study has been conducted the results can be reported with the actual significance levels and the interpretation of those levels can be made by to the reader.

The reviewers also feel that our criterion of an overall participation rate of 70% is likely to be unachieveable for this study. Our experience in a somewhat similar study tracing men from as long as 25 years ago and the experience reported by Eckland (Bruce K. Eckland, Retrieving Mobile Cases in Longitudinal Surveys, Public Opinion Quarterly, p. 51-64, Spring 1968), suggest that, with appropriate diligence and the wide variety of tracing resources available, more than 85% of the cohorts should be located. We feel that reduction of the overall location and participation rate to below 70% would leave the study results open to serious question.

Listed below are the specific comments from Attachment B. Our response or action concerning each comment is also given.

I. Comments on Protocol Text

page 11 "Time-bomb" idea - imponderable but not necessarily improbable.

We still feel this proposed mechanism is improbable.

page 15 para 2, l.4 "known very heavy exposure to Agent Orange." Even in Ranch Hand, exposure is presumed rather than known.

We agree, although the probability appears to be much higher.

page 20 para 1, l.2 "presumed highly . . . exposed." Even the higher exposure group will not necessarily be "highly" exposed. "Higher exposure group" might be more accurate.

"Higher exposure group" might be more accurate but every attempt should be made to establish a cohort with as high a likely exposure as possible.

page 25 Step 5, l.5 insert "likely," to read "number of likely exposures he encountered."

We agree.

II. Comments on Questionnaires

page 10 Question concerning agricultural exposures needs more attention. An agricultural specialist might be consulted to develop a set of questions which would fully probe possible exposures to agricultural chemicals. Lists of all generic and trade names of chemicals should be supplied. Hygiene habits after exposure to such chemicals should be probed as well.

We felt that additional detail would be too cumbersome and unlikely to yield good data. We have specified the general classes of chemicals of interest.

page 89, (e & f) Why are epilepsy, and convulsions or seizures separated when they are identical? How will it be rated if an individual answers yes to both versus just one?

Epilepsy, and convulsions or seizures are separated because many people will not respond positively to one or the other, particularly epilepsy. These can be combined in analysis as if they were one question.

page 89, (h) Head injury is often a problem of the past. It helps to determine severity by asking if loss of consciousness occurred, since such episodes are often treated in emergency rooms.

Done

page 95 Double vision and blindness in one eye are too limited; should include dimming of vision in both eyes? or one eye?

Revised

A question should be included regarding cramping in the calves since this is a common presentation in early peripheral neuropathy.

Done

Previous medication history is not covered. It is not enough to know what medications a person is currently taking.

We have included a question about past medication taken regularly for 3 months or longer

Sexual preference is not queried. It is important to ask about this since homosexuals disease patterns appear to be different from that of heterosexuals.

We do not feel that the responses would be accurate enough to be worth asking.

A question about cocaine use should be added.

Done

More questions dealing with "social health" should be included, covering marital history, migration, involvement with the criminal justice system, credit problems. These items could be verified through legal records.

Several questions have been added. Migration can be estimated from the residence history. We felt that many such questions would be considered offensive by the veterans. Note that an assessment of the veteran's financial status could be independently obtained by conducting routine credit checks. The coordinating center could establish an account with appropriate credit agencies for this purpose.

The reproductive section of the spouse questionnaire inquires about labor and delivery problems only for live births. This should be expanded to include all births.

Section revised

The spouse questionnaire should include questions specifically about use of anti-coagulants and spermicides, both of which may be teratogenic.

Done

III. Comments on Physical Examination

These comments were reviewed by a professor of Internal Medicine at UCLA and the necessary changes made according to his guidelines.

Urinalysis does not use American dip-stick categories of 1+ to 4+. Also, room to identify the type of cast is needed.

The urinalysis is part of the laboratory procedures and has been deleted here.

A.7.d. **"Nasal Mucosa Normal" is too general. There are specific abnormalities to be noted.**

See changes on form.

B.2. a&b. **Not sure that one can safely differentiate acute from chronic otitis externa on a single examination. Need more objective findings.**

See changes on form.

B.2. c. **Need a basic fundoscopic examination.**

Fundoscopic exam addeds as C5.

D.1. **Need an objective determination of lymphadenopathy.**

There is already a place for description of the lymphadenopathy. We are not sure what else was desired.

D.2. **Room is needed for description of abnormalities.**

Added.

E.4. **Gynaecomastia - unilateral or bilateral?**

Added.

E.5. **Clubbing needs to be added, here or elsewhere.**

Added under L4.

E.6. **Need respiratory rate.**

Added.

E.9. **This is an English-based classification, probably useful for this purpose. If used, we need anterior as well as posterior.**

Our consultant feels that there is considerable confusion now about the best way tc describe respiratory sounds. He feels the system should be left as is. We have added a check for anterior/posterior location.

F.4. **Need to describe how high jugular venous pressure is, not yes/no.**

Added.

F.8. **Need to distinguish ejection click from late systolic click. Also, splitting of S_1 and S_2 needs to be noted.**

Added.

F.9. Americans rate murmur on a scale of 1-6. Also needed is an opportunity to assess the murmur.

We agree that the scale could be changed but do not feel that it would add much.

F.10 a.b. These questions are very subjective. Should be asked only after questions of foot temperature, presence of ulcers or other skin changes. Pulses should precede any assessment of whether ischemia is present.

See changes on form. Patients can have small vessel disease with ischemia in the presence of normal pulses.

G. Probably need a question on whether guarding or tenderness of the abdomen. Also whether a pulsatile, enlarged aorta.

Questions on guarding/tenderness added. Category G.7. allows for description of other abdominal masses.

G.4. Need objective definition of hepatomegaly.

The objective measurement of liver span was in the form already.

G.5. Need objective definition of splenomegaly.

See changes on form.

J.a. Need to ask about prostatic nodules, rectal masses, hemorrhoids or other lesions.

See changes on form.

K. **Need room to describe positive findings.**

We do not see a need for any more description of the back.

K.8.a. **Pain where?**

See changes on form.

L.3. **Should include specific test for carpal tunnel syndrome.**

See changes on form.

M. **Need room to describe positive findings.**

A great many abnormalities are specifically questioned and room is provided under M12 for description of any more abnormalities.

M. 13. **Need objective definition of obesity.**

Since even bariatricians who deal with obesity have trouble defining exactly how obesity should be described we do not know how this should be further addressed. Note, however, that current height and weight are measured.

M.14. **What is the purpose of this question?**

This question was included to help interpret an abnormal glucose tolerance test which could be on the basis of lack of propoer carbohydrate loading.

Possible additions to physical examination.

-presence of xanthoma, xanthelasma
-presence of pallor.
-body habitus (e.g. Marfanoid)
-other endocrine-related conditions — feminization, body hair, striae, dorsal hump - fat distribution, Achilles reflex relaxation phase.

Xanthoma, xanthelasma, pallor and striae added under skin. Body habitus has been added as M.15. Deep tendon reflexes are examined in the neurologic exam. Feminization has been covered by questions on gynecomastia.

IV. Comments on Laboratory tests.

Tables 2 and 3 in the protocol were misplaced. There appears to have been some confusion as a result of this.

Semen analysis must be specifically defined since there are several semen parameters which may have biological relevance.

Defined in Table 2

Testosterone has not been shown to be a definitive predictor of testicular pathology or reproductive malfunction - most studies, however, have not distinguished between free or weakly bound testosterone (which is the biologically active steroid) and testosterone bound to sex-hormone binding globulin (inactive). The investigators should consider examining both total testosterone and free/weakly bound; studies which have considered the relative predictive value of sex hormones for testicular pathology have indicated that follicle-stimulating hormone has perhaps the most predictive value—albeit weak. The investigators should consider (1) the feasibility of conducting any sex hormone analyses at all since past studies do not suggest they are of great value and (2) if hormone analyses are included, follicle stimulating hormone and luteinizing hormone should be added since they also play important roles in the interactive relationships among the hypothalamus, anterior pituitary and the testis.

See Table 2. We would agree with adding free and total testosterone

A resting and step-electrocardiogram is proposed. It is hard to understand what would be identified from the electrocardiogram in this age group that could possibly be related to agent orange, nor the value of a simple exercise using a stool done in many centers in the United States.

3. We agree that a step-stool ECG would probably not be of much value. A treadmill ECG would be preferable. A thallium treadmill ECG would be still better but more costly. The relative merits of these tests can be further considered in the pilot test. The ECG is, like many other tests, necessary for a thorough evaluation of possible Agent Orange effects.

A renal screen is proposed, based on doing a simple urine analysis. It is unlikely that this would yield any useful information. Perhaps a dip-stick for protein would show something but a tremendous number of men in this age group will have protein in their urine early in the morning.

See Table 2. The renal screen includes a BUN and if that is abnormal a creatinine.

A series of measures are proposed for liver function, which also are essentially crude and unlikely to yield any useful information. Urinary porphyrins might be of interest because of the possibility of porphyria related to agent orange, but it would obviously make much more sense to look for patients with porphyria and determine whether they had been exposed to agent orange.

Elevated serum hepatic enzymes are a major postulated outcome and must be included. Urinary porphyrins were included (see Table 2).

The blood counts, again, offer no hope of any useful information.

We disagree. The comparison of population distributions could be of value and should be done.

Spirometry is proposed. It is unlikely that routine FEV, and FVC, considering the tremendous effects of cigarette smoking, and other environmental factors, would be of any use.

We disagree. Smoking histories and environmental exposures are collected in the questionnaire and can be incorporated into the analysis.

V. Comments on Neurologic Examination

The neurologic examination form has been revised.

Under tone, how does one include subtypes, such items as cogwheeling, etc.?

See revised form

Strength - must quantify; should use standard 0-5 scale. Peripheral neuropathies involve most distal muscles; therefore, must examine intrinsics of hand. Distal wrist extensors is fairly specific for lead neuropathy. In foot, extensor digitorum brevis (forms toes) is distal muscle usually affected first in peripheral neuropathy.

See revised form

Abnormal Movements - What does the grading system (1-4+) mean? It should be tabulated in the same fashion as the reflex responses.

See revised form

Mental Status - How can this be left open ended? A standardized mini-mental is one possibility. It would be very difficult to grade an examiner's subjective remarks.

Even when dealing with trained neurologists, each does the exam differently with grading systems dependent on his place of training.

See revised form

On page 55, under nerve conduction velocity, the sural is the only sensory measurement listed. Considering that even in toxic neuropathies which are predominantly motor, the sensory nerves may demonstrate electrical abnormalities first, both the ulnar and peroneal sensory latency and amplitude should be included. Amplitude is an important measurement since it reflects the number of axons involved in the action potential. Toxic neuropathies are usually axonal and therefore may demonstrate disease with a decreased amplitude before prolongation of the distal latency. Also it should be noted that the sural nerve may be congenitally absent.

We agree that the ulnar and peroneal sensory latencies and amplitudes should be included. However, after the pilot study the potential usefulness of all of the nerve conduction tests should be re-evaluated.

If electrodiagnostic abnormalities are found or clinical evidence of a neuropathy is present, conduction measurements should be extended to the median and posterior tibial. This will help differentiate entrapment neuropathies from polyneuropathies.

We agree.

Veterans Questionnaire
and
Hand Cards

VETERANS QUESTIONNAIRE

Fishing Expedition
Way to many questions
Will ⇒ chance bos –
then what –
Needs dummy questions
(eg neg response explored)
what Validation of bos? – Hosp record?

VETERAN

QUESTIONNAIRE FOR AGENT ORANGE

DATE OF INTERVIEW:_____

INTERVIEWER ID#:_____

PLACE OF EXAMINATION:_____

First, I would like to ask you a few general questions about you and your family. This information is important for statistical purposes, to see how people in this survey compare with the rest of the population.

1. What is your full name?

NAME:_____
FIRST MIDDLE LAST

2. What is your birthdate?

RECORD:_____
MONTH DAY YEAR

3. Where were you born?

RECORD:_____
CITY STATE

4. What was the highest grade in school you completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL: SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

5. With which of the following racial or ethnic backgrounds do you identify? Would you say:

Black,..... 1
Hispanic,..... 2
Asian, or..... 3
White?..... 4
OTHER..... 5
→ SPECIFY:_____

6. In what month and year did you enter the Armed Services?

RECORD:_____/_____
MONTH YEAR

7. What is your social security number?

RECORD:___ ___ ___/___ ___/___ ___ ___ ___

8. Please tell me the different cities you lived in for at least 2 months, starting with the place you were born.

PLACES RESIDED (CITY, STATE)	DATES OF RESIDENCE FROM	TO
1.		
2.		
3.		
4.		
5.		
6.		

9. How many sisters and brothers did you have in your family and what are their current ages? Do not include half or step sisters or brothers. IF DECEASED ASK FOR AGE AT DEATH AND CAUSE.

	AGE	CURRENT STATUS		CAUSE OF DEATH
		ALIVE	DECEASED	
Sisters		1	2	
		1	2	
		1	2	
		1	2	
NONE	0	1	2	
Brothers		1	2	
		1	2	
		1	2	
		1	2	
NONE	0	1	2	

10. Did you live with your natural parents during your childhood, or with step parents or guardians?

FATHER		MOTHER	
NATURAL	1	NATURAL	1
STEP	2	STEP	2
GUARDIAN	3	GUARDIAN	3
NONE	0	NONE	0

IF R DID NOT HAVE A FATHER OR MALE GUARDIAN DURING CHILDHOOD, GO TO Q14.

11. What was your father's (OR_____) major occupation during most of your childhood? (BE SPECIFIC - GET DETAILS)

_____

_____

12. What is his present occupation? (BE SPECIFIC - GET DETAILS)

_____

_____

WRITE "DECEASED" OR "RETIRED" IF APPROPRIATE

13. What was the highest grade in school he completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL (POST COLLEGE EDUCATION):

SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

NONE - 00

DON'T KNOW - 98

IF R DID NOT HAVE A MOTHER OR FEMALE GUARDIAN DURING CHILDHOOD, GO TO Q17.

14. What was your mother's (OR_____) major occupation during most of your childhood? (BE SPECIFIC - GET DETAILS)

_____

_____

15. What is her present occupation? (BE SPECIFIC - GET DETAILS)

_____

_____

WRITE "DECEASED" OR "RETIRED", IF APPROPRIATE

16. What was the highest grade in school she completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL (POST COLLEGE EDUCATION):

SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

NONE - 00

DON'T KNOW - 98

17. The next part of this questionnaire concerns jobs that you have held.

I am interested in all the different kinds of work you have done for a period of one month or more. Please include summer jobs or part-time jobs you may have held while you were going to school.

First, are you currently employed, either full or part-time?

YES..... 1

NO..... 2

A. IF YES -- I would like to start with your current job and work backward. What is your present job title?

IF NO -- I would like to start with your most recent job and work backward. What was your last job title?

RECORD IN APPROPRIATE COLUMN OF GRID. FOR EACH JOB ASK TITLE - COLUMN A, DUTIES - COLUMN B, AND KIND OF COMPANY INDUSTRY - COLUMN C AND RECORD.

CONFIDENTIAL

	17A. TITLE What is (was) your job title?	17B. DUTIES What are (were) your major duties in this job? (PROBE)	17C. KIND OF COMPANY What kind of company is (was) this? What type of industry was that in?
Current (or most recent) job.			
Before that?			
Before that?			
Before that?			

	17A. TITLE	17B. DUTIES	17C. KIND OF COMPANY
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			

18. On this card (HAND CARD 18) is a list of exposures that might affect your health. Please tell me about these or other substances you think might have been harmful to which you may have been exposed in any of these jobs. Let's start with your present/last job and work back. Were you exposed to any harmful substances on this job?

ASK FOR EACH JOB MENTIONED IN Q17.

IF YES TO ANY ASK FOR SUBSTANCE - COLUMN A, DATE STARTED JOB - COLUMN B, AND DATE ENDED JOB - COLUMN C.

IF NO ASK FOR START AND END DATES ONLY (B & C).

JOB	18A. What hazards were you exposed to? (RECORD SPECIFICS)	18B. When did you start this job?		18C. When did this job end?	
		MONTH	YEAR	MONTH	YEAR
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					

JOB	18A. What hazards were you exposed to?	18B. When did you start this job?		18C. When did this job end?	
		MONTH	YEAR	MONTH	YEAR
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					

19. Other than the jobs you have just told me about, have you ever worked either for pay or not on a farm or other agricultural setting?

YES.....ASK A & B..... 1

NO.....SKIP TO Q20..... 2

A. When and where did you do this work?

B. What chemicals were you exposed to?

DATES	WHERE	CHEMICALS

20. How many times have you been unemployed, if ever?

TIMES:_____

IF NEVER, SKIP TO Q22.

A. What were the reasons for these periods of unemployment?

_____

_____

_____

IF THE INTERVIEWEE IS CURRENTLY UNEMPLOYED (Q17) ASK THE FOLLOWING QUESTION.

21. How long have you been unemployed?

RECORD:_____

22. What sort of recreational activities do you participate in?

SWIMMING..... 1
HIKING..... 2
CAMPING..... 3
GOLF..... 4
TENNIS..... 5
GARDENING..... 6
OTHER..... 7
→SPECIFY: _____
_____
_____

23. Please look at this card again (HAND CARD 18-23). Read through the list of things you might have had contact with, either in a job or a hobby. Please tell me if you have worked with or been exposed to any of these things at least once a week for more than one month. Even though you may have mentioned them, we'd like you to tell us again. (RECORD INFORMATION EVEN IF PREVIOUSLY NOTED IN SECTION ON OCCUPATIONS.)

23. Exposure (RECORD SPECIFICS)	23A. When were you <u>first</u> exposed to this? (YEAR)	23B. When was the last time you were exposed to this? (YEAR)

24. We would like to know if you have had any medical complaints and how your health has been in general, over the past few weeks. As I read each statement, please tell me the answer which you think most nearly applies to you. Remember we want to know about present and recent complaints, not those that you had in the past.

First have you recently:

	Would you say:			
Been able to concentrate on whatever you're doing?	Better than usual	Same as usual	Less than usual	Much less than usual
Lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
Felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less than usual
Felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
Felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
Felt that you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
Been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much less able
Been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much less than usual

Been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
Been getting out of the house as much as usual?	More so than usual	Same as usual	Less than usual	Much less than usual
Been feeling on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well
Been satisfied with the way you've carried out your task?	Better than usual	About the same	Less well than usual	Much less well
Been taking things hard?	Not at all	No more than usual	Rather more than usual	Much more than usual
Found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
Found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been having restless, disturbed nights?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been managing as well as most people would in your shoes?	More so than usual	Same as usual	Rather less than usual	Much less than usual
Been able to feel warmth and affection for those near to you?	Better than usual	About same as usual	Less well than usual	Much less well
Been finding it easy to get on with other people?	Better than usual	About same as usual	Less well than usual	Much less well
Spent much time chatting with people?	More time than usual	About same as usual	Less than usual	Much less than usual

Been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
Felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
Been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much less hopeful
Felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual

25. I would like to ask you some questions about your family's health. Have your mother or father ever had any of these conditions:

	YES	FATHER: What was the disorder?	YES	MOTHER: What was the disorder?
Heart Disease.....				
High Blood Pressure.....				
Lung Disease.....				
Stroke.....				
Kidney Disease.....				
Diabetes.....				
Mental or Nervous Disease...				
Cancer or Tumour..... →What type?_____ _____				
Liver Disease.....				

26. Are your parents alive?

	YES	NO	Current age or age at death
Father.....			
Mother.....			

IF BOTH PARENTS ARE ALIVE, SKIP TO Q28.
IF ONE OR BOTH DECEASED, CONTINUE.

27. What did your (mother/father) die from?

	FATHER	MOTHER
Heart Attack.....	_____	_____
Heart Failure.....	_____	_____
High Blood Pressure....	_____	_____
Stroke.....	_____	_____
Cancer or Tumor.....	_____ Specific site: _____	_____ Specific site: _____
Kidney Disease.....	_____	_____
Diabetes.....	_____	_____
Accident or war.....	_____	_____
Pneumonia.....	_____	_____
Old Age.....	_____	_____
Asthma.....	_____	_____
Other.....	_____	_____

→SPECIFY:

_____

28. Have any of these diseases occurred in your blood relatives other than your parents? (Blood relatives are brothers and sisters with at least one parent in common, as well as grandparents, blood aunts and uncles.)

	RELATIONSHIP(S)
Heart Attacks.....	_____
Cancer.....	_____
High Blood Pressure....	_____
Asthma.....	_____
Liver Disease.....	_____
Depression/Nerves.....	_____

Now I am going to ask some questions about your everyday habits.

29. About how many hours do you sleep each night?

RECORD HOURS:_____

A. Do you usually take a nap during the day?

YES..... 1

→ How long do you usually sleep when you nap?

_____ / _____

MINUTES HOURS

NO..... 2

30. HAND CARD 30 TO R Please use the answers on this card for the next set of questions.

	ALMOST EVERY DAY	SOME-TIMES	RARELY	NEVER
How often do you eat breakfast? Would you say:	1	2	3	4
How often do you eat between meals?	1	2	3	4
How often do you participate in active sports?	1	2	3	4
How often do you swim or take long walks?	1	2	3	4
How often do you work in the garden?	1	2	3	4
How often do you do physical exercises, jog or run?	1	2	3	4
How often do you take weekend automobile trips?	1	2	3	4
How often do you hunt or fish?	1	2	3	4

31. Were you ever wounded in combat during your time in the service?

YES..... 1
NO.....SKIP TO Q32..... 2

A. In what years were you wounded?

RECORD:_____

B. What part(s) of you was (were) injured? CODE ALL MENTIONS.

HEAD..... 1
FACE..... 2
CHEST..... 3
ABDOMEN..... 4
LIMBS..... 5

C. What type of injury was it? Was it a: CODE ALL MENTIONS.

Bullet wound,..... 1
Schrapnel,..... 2
Knife wound, or..... 3
Impact trauma?..... 4
OTHER..... 5
→SPECIFY:_____

32. Were you hospitalized for any reason <u>other</u> than a combat wound while in the service?

YES..... 1

NO.....SKIP TO Q33..... 2

A. What was the problem?

_____

B. When were you hospitalized?

DATE:_____

C. Where were you hospitalized?

_____

D. Did the disease/condition completely resolve?

YES.....SKIP TO Q33..... 1

NO..... 2

E. Could you explain that?

_____

_____

_____

33. While serving in South Vietnam were you treated in a medical facility for any condition which did not require hospitalization?

YES..... 1

NO.....SKIP TO Q34..... 2

A. What were you treated for?

_____

_____

_____

B. When?

DATE(S):_____

_____

34. Have you ever been seriously injured other than in combat? (Serious injury means broken bone, or an injury requiring hospital admission, or injury causing significant disability.)

YES..... 1

NO.....SKIP TO Q35..... 2

A. What type of injury was that?

B. How did it occur?

C. In what year did it occur?

A. INJURY	B. MODE OF INJURY	C. YEAR OF INJURY

35. Have you ever had any surgical operations?

YES..... 1

NO.....SKIP TO Q36..... 2

A. What were they?

B. May I have the name and address of the hospital where it was performed?

C. Who was the surgeon who performed the operation?

36. Have you ever been admitted to a hospital for any <u>other</u> reason?

YES..... 1
NO.....SKIP TO Q37..... 2

A. Please tell me the hospital, their address, the year, and the relevant condition.

HOSPITAL:_____ CONDITION:_____
ADDRESS:_____ _____
YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____
ADDRESS:_____ _____
YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____
ADDRESS:_____ _____
YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____
ADDRESS:_____ _____
YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____
ADDRESS:_____ _____
YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____
ADDRESS:_____ _____
YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

37. Are you taking any prescribed medicines now, i.e. in the last month?

YES..... 1
NO.....SKIP TO Q38..... 2

A. Could you tell me the medicines and the reason you take them?

MEDICATION	CONDITION

38. How often in the last year have you taken excedrin, A.P.C., aspirin, empirin, or similar medication? Would you say:

Rarely,..... 1
Occasionally,..... 2
Once a month,..... 3
Once a week,..... 4
Several times a week,..... 5
Every day, or..... 6
Several times a day?..... 7

39. Has there been a period when you took these medications more often than in the past year?

YES..... 1
NO.....SKIP TO Q40..... 2

A. About what year was that?

RECORD:_____

B. How often did you take them? Would you say:

Once a month,..... 1
Once a week,..... 2
Several times a week,..... 3
Every day, or..... 4
Several times a day?..... 5

40. Did you ever take any drugs or pills to prevent malaria, prevent or treat tuberculosis, or treat fungal diseases?

YES..... 1
NO.....SKIP TO Q41..... 2

A. What were they for?

MALARIA..... 1
TUBERCULOSIS..... 2
FUNGUS..... 3

B. What was (were) the name(s) of the drug(s)?

_____

_____

_____

41. Have you had any infections (ear, nose, skin, eye) in the last year?

YES..... 1
NO.....SKIP TO Q42..... 2

A. How many?

RECORD #:_____

42. Have you ever had trouble with the healing of a wound or lesion?

YES..... 1
NO.....SKIP TO Q43..... 2

A. What was the site and nature of the wound or lesion?

_____

43. Have you ever regularly smoked cigarettes for at least three months?

YES..... 1
NO.....SKIP TO Q53..... 2

44. Do you smoke cigarettes now? Please include little cigars or brown cigarettes.

YES..... 1
NO.....SKIP TO Q46..... 2

A. On the average, do you smoke more than one cigarette per day?

YES (REGULAR SMOKER)..... 1
NO (OCCASIONAL SMOKER)...SKIP TO Q46.... 2

45. At the present time, what is the average number of cigarettes you smoke per day?

RECORD #:_____

46. How old were you when you began smoking cigarettes regularly?

RECORD AGE:_____

47. What is the average number of cigarettes you smoked per day since you began to smoke/when you smoked? Please give your best estimate.

RECORD #:_____

48. What is the maximum number of cigarettes you ever smoked per day for as long as a year?

RECORD #:_____

NEVER SMOKED FOR
ONE YEAR.....SKIP TO Q50.....97

49. For how many years did you smoke this number of cigarettes per day?

RECORD YEARS:_____

50. Have you ever attempted to stop smoking?

YES..... 1
NO.....SKIP TO Q53..... 2

A. What is the longest time you were able to stop?

RECORD #:_____ DAYS
_____ WEEKS
_____ MONTHS
_____ YEARS

51. How old were you when you stopped smoking cigarettes regularly?

RECORD AGE:_____

52. What was the main reason you stopped smoking?

HEALTH..... 1
ADVERSE PUBLICITY..... 2
OTHER..... 3
→SPECIFY:_____

53. Have you ever regularly smoked pipes or cigars for at least three months?

YES..... 1
NO.....SKIP TO Q55..... 2

54. Do you smoke pipes or cigars now?

YES..... 1
NO.....SKIP TO Q55..... 2

A. On the average, do you smoke at least one pipeful or cigar each day?

YES (REGULAR)..... 1
NO (OCCASIONAL)..... 2

55. Which do/did you smoke?

PIPE..... 1
CIGAR..... 2
BOTH..... 3

56. At the present time how many pipefuls or cigars do you usually smoke per day?

RECORD #:_____

DON'T SMOKE DAILY.....97

57. How old were you when you began smoking pipes or cigars regularly?

RECORD AGE:_____

58. What is the average number of pipefuls or cigars you smoked per day since you began to smoke/when you smoked? Please give your best estimate.

RECORD #:_____

59. What is the maximum number of pipefuls or cigars you ever smoked per day for as long as a year?

RECORD #:_____

NEVER SMOKED FOR
ONE YEAR.....SKIP TO Q61.....97

60. For how many years did you smoke this number of pipefuls or cigars per day?

RECORD YEARS:_____

61. Have you ever attempted to stop smoking?

YES..... 1
NO.....SKIP TO Q65..... 2

62. What is the longest time you were able to stop?

RECORD #:_____ DAYS
_____ WEEKS
_____ MONTHS
_____ YEARS

63. How old were you when you stopped smoking?

RECORD AGE:_____

64. What was the main reason you stopped smoking?

HEALTH..... 1
ADVERSE PUBLICITY..... 2
OTHER..... 3
→ SPECIFY:_____

65. Now let's talk about drinking alcoholic beverages, that is beer, wine, or mixed drinks. Did you ever drink alcoholic beverages on a fairly regular basis?

YES..... 1

NO.....SKIP TO Q67..... 2

A. When did you start drinking alcoholic beverages on a fairly regular basis?

RECORD:_____ DATE

OR

_____ AGE

B. Do you currently drink alcoholic beverages on a fairly regular basis?

YES.....SKIP TO Q66..... 1

NO..... 2

C. When did you last drink on a fairly regular basis?

RECORD:_____ DATE

OR

_____ AGE

66. You said that you (last drank on a fairly regular basis in DATE/are currently drinking on a fairly regular basis). How often did you drink alcohol during the last 3 months (that you did drink)? Would you say:

Every day,..... 6
4 to 6 days a week,..... 5
2 or 3 days a week,..... 4
Once a week,..... 3
2 or 3 days a month, or..... 2
Once a month?..... 1

A. On the days that you (drink/drank) about how many drinks (do/did) you have per day? That is, how many shots, cans or glasses?

RECORD #:_____ SHOTS
CANS
GLASSES

B. During the last three months which one of the following beverages did you drink most? Would you say:

Hard liquor,..... 1
Beer or ale, or..... 2
Wine or champagne?..... 3

67. Have you ever smoked marijuana regularly for a period of at least one month?

YES..... 1

NO.....SKIP TO Q69..... 2

A. When did you start smoking marijuana on a fairly regular basis?

RECORD DATE: _____ / _____
MONTH YEAR

B. These days, do you smoke marijuana fairly regularly?

YES..... 1

NO..... 2

IF "YES" TO Q67B - ENTER [0][0] [0][0] IN BOX OF Q67C AND SKIP TO Q68

IF "NO" TO Q67B - ASK Q67C

C. When did you last smoke marijuana on a fairly regular basis?

RECORD DATE: [ ][ ] [ ][ ]
MO. YR.

68. You said that you (last smoked marijuana on a fairly regular basis in (END DATE)/are currently smoking marijuana on a fairly regular basis). HAND CARD #68 Please look at this card and tell me which category best describes how often you smoked marijuana during the last three months (that you smoked on a fairly regular basis)?

EVERY DAY..... 6
4 TO 6 DAYS A WEEK..... 5
2 OR 3 DAYS A WEEK..... 4
ONCE A WEEK..... 3
2 OR 3 DAYS A MONTH..... 2
ONCE A MONTH..... 1

A. HAND CARD #68A On the days that you smoked marijuana, about how many joints did you smoke per day?

LESS THAN ONE A DAY..... 1
1 OR 2 A DAY..... 2
3 OR 4 A DAY..... 3
5 OR 6 A DAY..... 4
7 OR 8 A DAY..... 5
9 OR 10 A DAY..... 6
MORE THAN 10 A DAY..... 7
→HOW MANY?_____

69. Have you ever used barbiturates regularly for a period of at least one month? You might know barbiturates as "barbs," "downers," Nembutol, Seconal, Amytol, Doriden, Quealude, Methaqualone, "Sopors," Reds, Rainbows, or Yellow Jackets?

YES..... 1

NO.....SKIP TO Q70..... 2

A. When did you start using barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use barbiturates?

YES.....SKIP TO Q70..... 1

NO..... 2

C. When did you last use barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

70. Have you ever used amphetamines regularly for a period of at least one month? You might know amphetamines as "dexies," "uppers," "bennies," "diet pills," "speed," "crystals," methedrine, Benzadrine or Dexadrine.

YES..... 1

NO.....SKIP TO Q71..... 2

A. When did you start using amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use amphetamines?

YES.....SKIP TO Q71..... 1

NO..... 2

C. When did you last use amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

71. Have you ever used opiates regularly for a period of at least one month? You might know opiates as heroin, morphine, opium, codeine.

YES..... 1

NO.....SKIP TO Q72..... 2

A. When did you start using opiates?

RECORD: [ ][ ] [ ][ ]
MO. YR.

B. Do you still use opiates?

YES.....SKIP TO Q72..... 1

NO..... 2

C. When did you last use opiates?

RECORD: [ ][ ] [ ][ ]
MO. YR.

72. Have you ever used intravenous drugs, "shot up?"

YES.....ASK A..... 1
NO.....SKIP TO Q73..... 2

A. Which ones?

1._____

2._____

3._____

B. Did you start using intravenous drugs before or after you served in Vietnam?

BEFORE..... 1
AFTER..... 2

C. Do you still use them?

YES..... 1
NO..... 2

D. Did you ever share needles?

YES..... 1
NO..... 2

73. Have you ever had any changes in weight that were of concern to you?

YES..... 1
NO.....SKIP TO Q76..... 2

A. Have you ever had a weight change of more than 15 lbs. in six months?

YES..... 1
NO.....SKIP TO Q76..... 2

B. Was it because you were dieting?

YES..... 1
NO..... 2

C. Was it a:

	NO	YES	D. What year did this occur?	E. Is it a current problem?	
				YES	NO
a. Weight gain?.....	2 ASK b	1 ASK D	_____	1	2
b. Weight loss?.....	2	1 ASK D	_____	1	2

74. Did you seek medical care for this weight change?

YES..... 1
NO.....SKIP TO Q76..... 2

75. Where did you go for medical care regarding your weight change? Was it the:

Military medical service, or.....SKIP TO Q76.....	1
A private doctor/ hospital?.....ASK A.....	2

A. Please give me the name and address of the Doctor and/or Hospital you went to regarding your weight change.

_____

_____

_____

_____

76. Now, I would like to ask you some questions about your skin?

A. (HAND CARD #76) Please look at this card and tell me if you have ever had any problems with your skin? READ a-l AND CODE IN COLUMN A OF CHART.

IF NO TO ALL CONDITIONS.....SKIP TO Q77 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" IN COLUMN A - ASK: What year did this first occur? RECORD IN COLUMN B OF CHART.

C. Is the (...) a current problem or not? INSERT SKIN CONDITION R HAD/HAS IN COLUMN A FOR (...) - CODE ANSWER IN COLUMN C OF CHART.

D. Did you see a doctor about the (...) condition? INSERT CONDITION FOR (...) - CODE IN COLUMN D OF CHART.

IF R SAW A DOCTOR.....CONTINUE WITH E & F ALL OTHERS.....GO TO NEXT CONDITION

E. Where did you go for medical diagnosis and care for the (...) condition? Was it the Military Medical Service or some other doctor or hospital? INSERT CONDITION FOR (...) - RECORD IN COLUMN E OF CHART.

F. IF OTHER DOCTOR/HOSPITAL (NOT MILITARY) ASK: Please give me the name and address of the doctor or hospital you went to for the diagnosis and care you received for the (...) condition. RECORD IN COLUMN F OF CHART.

A. CONDITION			B. YEAR OCCURRED	C. CURRENT		D. SEE DOCTOR		E. WHAT DOCTOR	F. NAME/ADDRESS
	YES	NO		YES	NO	YES	NO		
a. Eczema	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
b. Acne	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
c. Psoriasis	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
d. Recurrent Pimples/ Boils	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	

e. Recurring rashes	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
f. Persistant rashes for longer than a month	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
g. Skin Cancer	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
h. Porphyria Cutanea Tarda	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
i. Spider Angiomata	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
j. Palmar Erythema	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
k. Caput Medusa	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
l. Xantholasma	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
m. Other Problems SPECIFY: _____	1	2	19_____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	
_____	1	2	19_____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	

77. Have you ever had acne?

YES..... 1
NO.....SKIP TO Q79..... 2

78. Have you ever had severe acne?

YES.....ASK A..... 1
NO.....SKIP TO Q79..... 2

A. In what year did you first have this severe acne?

RECORD:_____

If you had recurrences of severe acne in what years did these begin?

19__ __, 19__ __, 19__ __

NEVER HAD RECURRENCES.....99

B. Which parts of your body were affected by the severe acne? Was it your:

	YES	NO
Face?.....	1	2
Temples?.....	1	2
Behind or in ears?....	1	2
Shoulders?.....	1	2
Trunk?.....	1	2
Elsewhere?.....	1	2
SPECIFY:_____		
_____		

C. For how long did you have severe acne? Would you say:

Less than a month,..... 1
1-6 months,..... 2
7-12 months,..... 3
1-5 years, or..... 4
More than 5 years?..... 5

D. Is the acne still a problem?

YES..... 1
NO..... 2

79. Does your skin sunburn easily?

YES..... 1
NO..... 2

A. About how many times a year do you get a severe sunburn?

RECORD # TIMES:_____

80. Have you ever noticed any change in skin color apart from jaundice or suntan?

YES.....ASK A..... 1

NO.....SKIP TO C..... 2

A. In what year did you notice this change?

RECORD: 19 _____

B. Could you describe the change in skin color? Was it:

	YES	NO
Dark patches on your face?.....	1	2
Dark patches on your trunk or limbs?.	1	2
Light patches on your face?.....	1	2
Light patches on your trunk or limbs?	1	2

C. Have you noticed any change in the sensitivity of your skin to sunlight?

YES..... 1

NO.....SKIP TO Q81..... 2

D. In what was has your skin's sensitivity changed? Has it:

Increased, or..... 1

Decreased in sensitivity?..... 2

E. In what year did this change start?

RECORD: 19 _____

81. Apart from normal balding have you ever noticed a change in the hairiness of your head or body?

YES..... 1
NO.....SKIP TO Q82..... 2

A. What was the change? Was it:

	YES	NO
Unusual loss on head?.....	1	2
Unusual general loss?.....	1	2
Increase on face/neck?.....	1	2
General increase?.....	1	2

B. In what year did the change in hairiness first occur?

RECORD: 19 _____

82. Have you ever had problems with your ears in your adult life (over 16 yrs)? For example, discharge, ear ache or infection?

YES..... 1
NO.....SKIP TO Q83..... 2

A. In what year did you first have these problems?

RECORD: 19 _____

B. Do you still have ear trouble?

YES..... 1
NO..... 2

83. Have you ever had deafness or trouble hearing with one or both ears? Do not include problems during upper respiratory tract infection.

YES.....ASK A..... 1

NO.....SKIP TO C..... 2

A. Have you ever consulted a doctor about your loss of hearing?

YES..... 1

NO..... 2

B. When did you first have trouble hearing?

RECORD: 19 _____

C. Have you ever had an audiogram (hearing test)?

YES..... 1

NO..... 2

D. Have you ever had a job for a year or more where the noise level required that you speak much louder than you usually do?

YES..... 1

NO..... 2

84. Did you ever notice any change in the wax in your ears?

YES..... 1
NO.....SKIP TO Q85..... 2

A. How would you describe this change? Did it:

Increase,..... 1
Decrease, or..... 2
Change in consistency?..... 3

B. In what year did you first notice the change?

RECORD: 19 _____

C. Do you still have this problem?

YES.....ASK a..... 1
NO.....SKIP TO Q85..... 2

a. Where did you receive your diagnosis and care for the change in the wax in your ears? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME AND ADDRESS:

_____

_____

85. Do you now wear glasses or contact lenses?

YES..... 1
NO.....SKIP TO Q86..... 2

A. Do you wear glasses/contact lenses because you are:

	YES	NO
Farsighted?.....	1	2
Nearsighted?.....	1	2
Your age?.....	1	2
Astigmatism?.....	1	2
Some other reason?.....	1	2
SPECIFY:_____		
_____		

B. In what year did you start to wear glasses/contact lenses?

RECORD: 19_____

86. Has there been a time when you had more eyelid infections than you would have expected?

YES..... 1
NO.....SKIP TO Q87..... 2

A. In what year did you <u>first</u> have increased infections?

RECORD: 19_____

B. Are they still a problem?

YES..... 1
NO..... 2

87. Has a doctor ever told you that you had conjunctivitis?

YES..... 1
NO.....SKIP TO Q88..... 2

A. When did you first have conjunctivitis?

RECORD YEAR: 19_____

B. Do you still get conjunctivitis?

YES..... 1
NO..... 2

C. How often have you had conjunctivitis? Would you say:

Once only,..... 1
2 to 3 times,..... 2
Recurrently, or..... 3
Continuously?..... 4

a. Where did you receive your diagnosis and care for your eyes? Was it:

A Military Medical Service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME AND ADDRESS:

_____
_____
_____

88. Have you ever had migraines?

YES..... 1
NO.....SKIP TO Q89..... 2

A. In what year did you first suffer from migraines?

RECORD: 19_____

B. Have you been treated for migraines?

YES..... 1
NO.....SKIP TO D..... 2

C. Where did you receive your diagnosis and care for migraines? Was it:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME AND ADDRESS:

_____
_____
_____

D. Do you still have problems with migraine?

YES..... 1
NO..... 2

89. Have you ever been troubled by recurrent or persistent headaches over a period of time longer than a month, other than migraine?

YES..... 1

NO.....SKIP TO Q92..... 2

B. How bad are/were your headaches in general? Were they:

Severe enough to prevent work,..... 1

Moderate but you were able to continue work, or..... 2

Mild - Easily Relieved?..... 3

C. When you have a headache do you have other symptoms?

YES..... 1

NO.....SKIP TO Q90..... 2

D. What symptoms were the headaches associated with? Would you say:

	YES	NO
Flashes before the eyes?.....	1	2
Vomiting or nausea?.....	1	2
Numbness or tingling?.....	1	2
Sensitivity to bright light?....	1	2
Dizziness (spinning)?.....	1	2
Faintness?.....	1	2
Blurring of vision?.....	1	2
Weakness on one side of the body?	1	2

E. Are the headaches associated with sensations which have not been mentioned?

YES..... 1

NO.....SKIP TO Q90..... 2

F. What are they?

_____

_____

90. Where do/did you feel the headache, other than migraine, mainly? Is/was it in the:

	YES	NO
Front of your head?.....	1	2
Back of your head?.....	1	2
Left side?.....	1	2
Right side?.....	1	2
All over or around the head?.....	1	2

A. About what year were you first troubled by recurring headaches (other than migraine)?

RECORD: 19 _____

B. Do you still have problems with headaches?

YES..... 1
NO.....SKIP TO Q92..... 2

C. Have you consulted a doctor about these headaches?

YES..... 1
NO.....SKIP TO Q91..... 2

D. Where did you receive your diagnosis and care for headaches? Was it:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME AND ADDRESS:

_____
_____
_____

91. Have you had <u>any</u> special tests for your headaches?

YES..... 1
NO.....SKIP TO Q92..... 2

A. Were they:

	YES	NO
A skull X-ray?.....	1	2
A C.A.T. scan?.....	1	2
An E.E.G.?.....	1	2
A lumbar puncture?.....	1	2

IF YES, ASK FOR NAME AND ADDRESS OF PHYSICIAN OR HOSPITAL

NAME AND ADDRESS OF PHYSICIAN OR HOSPITAL PERFORMING TEST:

92. The next set of questions is about your heart and circulation.

A. Please look at this card (HAND CARD #92) and tell me if you have ever had any of the following conditions. READ a-j AND CODE IN COLUMN A OF CHART.

IF NO CONDITIONS...SKIP TO Q93 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) first occur? INSERT CONDITION FOR (...) - RECORD IN COLUMN B OF CHART.

C. Is the (...) a current problem? INSERT PROBLEM FOR (...) - CODE IN COLUMN C OF CHART.

D. Did you see the Military Medical Service or a doctor or hospital for the diagnosis and care for your (...)? INSERT PROBLEM FOR (...) - CODE IN COLUMN D OF CHART.

A. CONDITION	EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Heart attack	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
b. Angina	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
c. Heart failure	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
d. High blood pressure	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
e. Rheumatic fever	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
f. Disorders of the heart valves	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
g. Congenital heart disease	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
h. Clots in legs	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
i. Swelling of the ankles	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
j. Other heart conditions (SPECIFY) _____	1	2	19 _____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2

E. IF PRIVATE DOCTOR OR HOSPITAL, ASK: What is the name and address of the doctor/hospital you saw for diagnosis and care of (...)? RECORD IN COLUMN E OF CHART.

F. Are you currently under the care of a Military Medical Service or a private doctor or hospital for (...)? RECORD IN COLUMN F OF CHART.

G. IF PRIVATE DOCTOR/HOSPITAL: What is the name of the doctor/hospital you are currently under care for (...)? RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS	F. CURRENT CARE	G. NAME/ADDRESS CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

93. Have you ever had pain in the center of your chest which lasted longer than 30 minutes at a time?

YES..... 1
NO.....SKIP TO Q94..... 2

A. In what year did you first experience this chest pain?

RECORD: 19 _____

B. Has this chest pain recurred?

YES..... 1
NO.....SKIP TO Q94..... 2

C. Do you still experience this chest pain?

YES..... 1
NO.....SKIP TO Q94..... 2

D. Was/is chest pain brought on by any of the following:

	YES	NO
Walking on flat ground, up hills, on exertion like running?.....	1	2
Deep breathing or coughing?.....	1	2
Eating?.....	1	2
Change in position, e.g. stooping?.....	1	2
Other?.....	1	2
SPECIFY: _____		

E. Was/is chest pain associated with:

	YES	NO
Shortness of breath?.....	1	2
Sweating?.....	1	2
Feeling of tightness or pressure?.....	1	2
Breathing?.....	1	2
Pain in either arm?.....	1	2
Pain in jaw?.....	1	2
Other?.....	1	2
SPECIFY: _____		

94. Have you ever suffered from palpitations (unpleasant sensation of your heart beating)?

YES..... 1
NO.....SKIP TO Q95..... 2

A. In what year did the palpitations first occur?

RECORD: 19 _____

B. Do you still get palpitations?

YES..... 1
NO..... 2

C. Do/did the palpitations occur with:

	YES	NO
Exertion?.....	1	2
Emotion?.....	1	2

D. On some occasions did you feel that your heart:

	YES	NO
Missed beats?.....	1	2
Became irregular?.....	1	2
Beat slowly?.....	1	2
Beat very quickly?.....	1	2

95. Have you ever had shortness of breath or difficulty with breathing?

YES..... 1
NO.....SKIP TO Q96..... 2

A. When does this difficulty occur? Is it:

	YES	NO
On walking up a hill or flight of stairs?.....	1	2
On breathing in irritating air or substances?.....	1	2
At rest?.....	1	2
With wheezing?.....	1	2
Does it wake you at night?.....	1	2
Other?.....	1	2

→ SPECIFY:_____

_____

B. In what year did you first have difficulties with breathing?

RECORD: _____

C. Do you still have difficulty with breathing?

YES..... 1
NO..... 2

D. How do/did you relieve your shortness of breath? By:

	YES	NO
Taking medicine?.....	1	2
Resting?.....	1	2
Sitting upright?.....	1	2
Other?.....	1	2

→ SPECIFY:_____

_____

96. Have you suffered from:

	YES	NO
Varicose veins?.....	1	2
Pains in legs on walking any distance?.....	1	2

97. Have you seen a doctor about these symptoms?

YES..... 1

NO.....SKIP TO Q99..... 2

A. Where did you receive your diagnosis and care for these symptoms? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→ SPECIFY NAME AND ADDRESS:

_____

_____

_____

98. Have you had any special tests for your heart? Were they:

A. TEST	YES	NO	NAME OF PHYSICIAN OR HOSPITAL AND ADDRESS WHICH PERFORMED TEST
A chest X-ray?	1	2	
An electrocardiogram?	1	2	
An echocardiogram?	1	2	
A cardiac catheterization?	1	2	
Blood tests?	1	2	
Other? (SPECIFY) _____	1	2	

FOR EACH "YES" ASK NAME OF PHYSICIAN OR HOSPITAL AND ADDRESS WHICH PERFORMED TEST.

9 The next set of questions is about respiratory problems.

A. (HAND CARD #99) Please read this card and tell me if you have ever had any of the following: READ a-m AND CODE IN COLUMN A OF CHART.

IF NO TO ALL-SKIP TO Q100 ALL OTHERS - CONTINUE

B. FOR EACH "YES" ASK: In what year did (...) first occur? INSERT PROBLEM FOR (...) - RECORD IN COLUMN B OF CHART.

C. Is (...) a current problem? INSERT PROBLEM FOR (...) - RECORD IN COLUMN C OF CHART.

D. Are you on medication for your (...)? INSERT PROBLEM FOR (...) - RECORD IN COLUMN D OF CHART.

E. Did you see a Military Medical Service or other doctor or hospital for diagnosis and care for your (...)? INSERT PROBLEM FOR (...) - RECORD IN COLUMN E OF CHART.

F. IF OTHER DOCTOR OR HOSPITAL SEEN FOR DIAGNOSIS OR CARE, ASK: What is the name and address of the doctor/hospital you saw for diagnosis and care? RECORD NAME AND ADDRESS IN COLUMN F.

A. PROBLEM	EVER HAD YES	EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. TAKE MEDICATION YES	D. TAKE MEDICATION NO	E. DIAGNOSIS AND CARE	F. NAME AND ADDRESS
a. Sinusitis?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
b. Frequent nose bleeds?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
c. Frequent colds? (more than 3 a year)	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
d. Asthma?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
e. Chronic bronchitis?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
f. Emphysema?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	

g. T.B.?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
h. Bronchiectasis?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
i. Pleurisy?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
j. Pneumonia?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
k. Pneumonia more than once?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
l. Cancer of the lung?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
m. Other lung disease(s)? SPECIFY:									
____	1	2	19 ____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	
____	1	2	19 ____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	

100. Do you usually cough first thing in the morning in bad weather?

YES..... 1
NO..... 2

101. Do you usually cough at other times during the day and night in bad weather?

YES..... 1
NO..... 2

102. Do you cough first thing in the morning (when you get up) on more than 50 days in a year?

YES..... 1
NO.....SKIP TO Q105..... 2

103. For how many years have you had this cough? Would you say:

Less than 2 years,..... 1
2 to 5 years,..... 2
6 to 10 years, or..... 3
More than 10 years?..... 4

104. Do you usually bring up phlegm, sputum, or mucous from your chest first thing in the morning in bad weather?

YES..... 1
NO..... 2

105. Do you usually bring up phlegm, sputum, or mucous from your chest at other times during the day or night in bad weather?

YES..... 1
NO..... 2

106. Do you usually bring up phlegm from your chest first thing in the morning on more than 50 days in a year?

YES..... 1

NO.....SKIP TO Q108..... 2

107. For how many years have you raised phlegm, sputum, or mucous from your chest? Would you say:

Less than 2 years,..... 1

2 to 5 years,..... 2

6 to 10 years, or..... 3

More than 10 years?..... 4

108. In the past three years, have you had a period of increased cough and phlegm lasting for three weeks or more?

YES..... 1

NO.....SKIP TO Q110..... 2

109. Have you had more than one such three-week period?

YES..... 1

NO..... 2

110. Does your breath ever sound wheezing or whistling?

YES..... 1

NO.....SKIP TO Q112..... 2

111. On how many days has this happened during the past year?

RECORD # DAYS:_____

112. Have you ever had attacks of shortness of breath with wheezing?

YES..... 1
NO..... 2

113. During the past three years, how much trouble have you had with illnesses such as chest colds, bronchitis, or pneumonia? Would you say you have had a:

Great deal of trouble,..... 1
Some trouble, or..... 2
No trouble?.....SKIP TO Q116..... 3

114. During the past three years, how often were you unable to do your usual activities because of illness, such as chest colds, bronchitis, or pneumonia? Would you say:

Once,..... 1
Two to five times,..... 2
More than five times in the past three years, or..... 3
Never?..... 4

115. Have you had any of the following tests to investigate you chest conditions? If so, please tell me the name of the physician and the address or hospital which administered this test, chest X-ray, bronchoscopy, lung scan, or some other test.

TEST	YES	NO	NAME OF PHYSICIAN/HOSPITAL AND ADDRESS
Chest X-ray?	1	2	
Bronchoscopy?	1	2	
Lung scan?	1	2	
Other (SPECIFY) _____	1	2	

116. Have you ever had a diagnosis of diabetes?

YES..... 1
NO.....SKIP TO Q118..... 2

A. At what age was it diagnosed?

RECORD AGE:_____

117. What is your current treatment? Is it:

	YES	NO
Diet?.....	1	2
Pills?.....	1	2
Insulin?.....	1	2
None?.....	1	2

118. Have you ever had a diagnosis of thyroid trouble?

YES..... 1
NO.....SKIP TO Q119..... 2

A. Was this hypo- or hyperthyroid trouble?

HYPOTHYROID..... 1
HYPERTHYROID..... 2

119. Has a doctor ever told you that you have gout?

YES..... 1
NO.....SKIP TO Q120..... 2

A. At what age was the diagnosis made?

RECORD AGE:_____

B. What were the symptoms? Were they:

	YES	NO
Joint pain?.....	1	2
Kidney stones?.....	1	2
Other?.....	1	2

→SPECIFY:_____

_____

C. Has anyone else in your family ever had gout?

YES..... 1
NO.....SKIP TO E..... 2

D. What is their relationship to you?

RECORD:_____

E. Where did you receive your diagnosis and care for your gout? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME AND ADDRESS:

_____

_____

_____

120. Next, some questions regarding gastrointestinal conditions.

A. (HAND CARD #120) Please look at this card and tell me if you have ever had any of these problems. READ a-1 AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL CONDITIONS...SKIP TO Q121 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) condition first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Do you have the (...) condition currently? RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or a private doctor or hospital for this (...) condition? CODE APPROPRIATE ANSWER IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR OR HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for the (...) condition. RECORD IN COLUMN E OF CHART.

CONDITIONS	A. YES	A. NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS DOCTOR/HOSPITAL
a. Esophagitis?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Hiatus hernia?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Gastric or duodenal ulcer?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Crohns disease?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Bowel obstruction?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	

f. Diverticulitis?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Spastic or irritable colon?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
h. Ulcerative colitis?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
i. Anal problems or hemorrhoids?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
j. Dysentery?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
k. Malabsorption?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
l. Other gastro intestinal conditions? (SPECIFY) _____	1	2	19_____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	
_____	1	2	19_____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

1(A. (HAND CARD #121) Please look at this card(tell me if you ever had any of the following. (a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL..SKIP TO Q122
ALL OTHERS.....CONTINUE

B. In what year did (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or private doctor or hospital for the diagnosis and care of the (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR OR HOSPITAL ASK: Please give me the name and address of the doctor/hospital you saw for the (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS OF DOCTOR/HOSPITAL IN COLUMN E OF CHART.

CONDITION	A. YES	A. NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
a. Persistant indigestion or abdominal discomfort?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Bouts of abdominal pain?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Recurring bouts of feeling sick or vomiting?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Bouts of constipation (Normal=1 movement in 3 days to 3 in 1 day)	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Bouts of diarrhea?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Vomited blood?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Bleeding from the bowels?	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

122. Have you had any tests for these conditions? For example: READ a-e AND CODE. FOR EACH YES, ASK A.

TESTS	YES	NO	A. Please give me the name and address of physician or hospital which performed the (...) test.
a. Barium meal (swallow)?	1	2	
b. Barium enema?	1	2	
c. Laparoscopy?	1	2	
d. Endoscopy?	1	2	
e. Other? (SPECIFY) _____	1	2	

A. (HAND CARD #123) Please look at this card. tell me if you ever had any of the following. ASK a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q124 ALL OTHERS.....CONTINUE

B. In what year did (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or private doctor or hospital for the diagnosis and care of the (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR OR HOSPITAL ASK: Please give me the name and address of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

CONDITION	A. YES	A. NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
a. Hepatitis with or without jaundice?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Cirrhosis of the liver?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Jaundice?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Gall bladder disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Gallstones?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Pancreatitis?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Other diseases of the liver? (SPECIFY) ____	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

124. Have you had any tests for these conditions? For example: READ a-d AND CODE. FOR EACH "YES" ASK A.

TEST	YES	NO	A. Please give me the name and address of physician or hospital administering the (...) test.
a. Blood tests for the liver?	1	2	
b. Blood tests for the pancreas?	1	2	
c. Ultrasound?	1	2	
d. Other? (SPECIFY) _____	1	2	

125. Now some questions regarding renal conditions. By renal conditions we mean urinary, genital or kidney problems.

A. (HAND CARD #125) Please look at this card and tell me if you ever had any of the following. READ a-k AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q126
ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Kidney or bladder stones?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Kidney infection?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Nephritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Renal colic?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Bladder infection?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Disorders of the prostate?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Urethritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
h. Gonorrhea?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
i. Syphilis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
j. Herpes?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
k. Other problems? SPECIFY: ____	1	2	19____	1	2	Military/Medical.....1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you currently seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF SEEING PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you are seeing for the (...) problem. RECORD IN COLUMN G OF CHART.

E. NAME AND ADDRESS	F. CURRENT CARE	G. NAME/ADDRESS CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

126. Have you ever had an attack of painful or too frequent urination?

YES..... 1
NO.....SKIP TO Q127..... 2

A. When did this first occur?

RECORD YEAR:_____

B. Is it still a problem?

YES..... 1
NO..... 2

C. Have you seen a doctor about these symptoms?

YES..... 1
NO.....SKIP TO Q127..... 2

D. Did you see a:

Military medical service, or.....SKIP TO Q127..... 1

A private doctor/ hospital?.....ASK E..... 2

E. Please give me the name and address of the doctor/hospital.

_____

_____

_____

127. Do you have to get up more than once a night to pass urine?

YES..... 1
NO.....SKIP TO Q128..... 2

A. Is this a life-long habit?

YES.....SKIP TO Q128..... 1
NO..... 2

B. In what year did this habit change?

RECORD YEAR:_____

C. Have you seen a doctor about these symptoms?

YES..... 1
NO.....SKIP TO Q128..... 2

D. Did you see a:

Military medical service, or.....SKIP TO Q128..... 1
A private doctor/ hospital?.....ASK E..... 2

E. Please give me the name and address of the doctor/hospital.

_____
_____
_____

128. Have you ever passed blood in your urine?

YES..... 1
NO.....SKIP TO Q129..... 2

A. In what year did you first pass blood in your urine?

RECORD YEAR:_____

B. Do you still pass blood in your urine?

YES..... 1
NO..... 2

C. Have you seen a doctor about these symptoms?

YES..... 1
NO.....SKIP TO Q129..... 2

D. Did you see a:

Military medical service, or.....SKIP TO Q129..... 1
A private doctor/ hospital?.....ASK E..... 2

E. Please give me the name and address of the doctor/hospital.

_____

_____

_____

129. Have you had any special tests for urinary problems? READ a-c AND CODE. FOR EACH "YES" ASK A.

TEST	YES	NO	A. Please give me the name of physician or hospital administering test.
a. X-ray?	1	2	
b. Intravenous pyelogram (IVP)?	1	2	
c. Retrograde pyelogram?	1	2	

130. Now some questions regarding tumors and growths.

A. (HAND CARD #130) Please look at this card and tell me if you ever had any of the following. READ a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q131 ALL OTHERS.....CONTINUE

B. In what year was (...) diagnosed? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. ASK FOR ONLY a-d: What kind of a (...) was that? RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of the (...)? CODE IN COLUMN D OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. KIND	D. DIAGNOSIS AND CARE
a. A cancer?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
b. A tumor?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
c. A lump?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
d. A growth?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
e. A sarcoma (tumor of soft tissue)?	1	2	19____		Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
f. A tumor of the eye?	1	2	19____		Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
g. A tumor of the testes?	1	2	19____		Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

F. Are you <u>currently</u> seeing a Military Medical Service or private doctor/hospital for care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF CURRENTLY SEEING A PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you are currently seeing for the (...). INSERT CONDITION FOR (...). RECORD IN COLUMN G OF CHART.

E. NAME AND ADDRESS	F. CURRENT CARE	G. NAME/ADDRESS CURRENT DOCTOR/HOSPITAL
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	

131. Next, some questions regarding allergies.

A. (HAND CARD #131) Please look at this card and tell me if you have ever had any of these problems. READ a-f AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q132 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) condition first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or a private doctor/hospital for the diagnosis and care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for the (...)? INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

	A. EVER HAD YES	A. EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
a. Hives?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Other skin rashes?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Hayfever (Vasomotor rhinitis)?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Asthma?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Stomach upsets?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Other allergies? SPECIFY: _____	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

A. (HAND CARD #132) Please look at this card and tell me if you have ever had a diagnosis of any of the following diseases? READ a-w AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q132A ALL OTHERS.....CONTINUE

B. FOR ALL "YES" ASK: Did you see a Military Medical Service or a private doctor/hospital for the diagnosis and care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name of the doctor/hospital you went to for the (...) condition. RECORD NAME AND ADDRESS IN COLUMN C OF CHART.

D. Are you currently receiving treatment for (...) from a Military Medical Service or a private doctor/hospital? INSERT CONDITION FOR (...). RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you are currently seeing for the (...) condition. INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

CONDITION	A. EVER HAD YES	NO	B. DIAGNOSIS AND CARE	C. NAME AND ADDRESS	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
a. Lupus erythematosis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
b. Hashimoto's thyroiditis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
c. Rheumatoid arthritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
d. Vitiligo?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
e. Pernicious anemia?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK C	

f. Premature testicular failure?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
g. Addison's disease?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
h. Primary biliary cirrhosis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
i. Temporal arteritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
j. Idiopathic thrombocytopenic purpura?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
k. Ulcerative colitis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
l. Regional ileitis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
m. Hypoparathyroidism?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
n. Polymyositis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	

Q152 (cont.)

CONDITION	A. EVER HAD YES	NO	B. DIAGNOSIS AND CARE	C. NAME AND ADDRESS	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
o. Polymyalgia rheumatica?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
p. Periarteritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
q. Dermatomyositis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
r. Scleroderma?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
s. Pemphigus?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
t. Urticaria?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
u. Sjogren's syndrome?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	

v. Myasthenia gravis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
w. Glomerulo-nephritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 Doctor/Hosp..2 ASK E	

132A. Please look at the card again (HAND CARD #132) and tell me if anyone in your family, children, parents, aunts, uncles, etc. have ever been diagnosed for these diseases? READ a-w AND RECORD IN COLUMN I OF CHART.

A. IF "YES", ASK FOR RELATIONSHIP TO RESPONDENT.

CONDITION	I. YES	NO	II. RELATIONSHIP TO RESPONDENT
a. Lupus erythematosis?	1	2	
b. Hashimoto's thyroiditis?	1	2	
c. Rheumatoid arthritis?	1	2	
d. Vitiligo?	1	2	
e. Pernicious anemia?	1	2	
f. Premature testicular failure?	1	2	
g. Addison's disease?	1	2	
h. Primary biliary cirrhosis?	1	2	
i. Temporal arteritis?	1	2	
j. Idiopathic thrombocytopenic purpura?	1	2	
k. Ulcerative colitis?	1	2	
l. Regional ileitis?	1	2	
m. Hypoparathyroidism?	1	2	
n. Polymyositis?	1	2	
o. Polymyalgia rheumatica?	1	2	
p. Periarteritis?	1	2	
q. Dermatomyositis?	1	2	
r. Scleroderma?	1	2	
s. Pemphigus?	1	2	
t. Urticaria?	1	2	
u. Sjogren's syndrome?	1	2	
v. Myasthenia gravis?	1	2	
w. Glomerulonephritis?	1	2	

133. I would like to ask you about some nervous system disorders.

A. (HAND CARD #133) Please look at this card and tell me if you ever had any of the following. READ a-i AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q134 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	A. EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE
a. Stroke?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Encephalitis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Meningitis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Peripheral neuropathy (i.e. weakness, numbness, tingling of hands or feet)	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Epilepsy?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Convulsions or seizures?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Brain tumor?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
h. Head injury?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
i. Other (SPECIFY)? ↳_____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you currently seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF SEEING PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you are seeing for the (...) problem. RECORD IN COLUMN G OF CHART.

E. NAME AND ADDRESS	F. CURRENT CARE	G. NAME/ADDRESS CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

134. Have you <u>ever</u> had dizzy spells or blackouts (fits, faints or funny turns)?

YES..... 1
NO.....SKIP TO Q135..... 2

A. In what year did you first experience dizzy spells?

RECORD YEAR:_____

B. Do you still get dizzy spells, that is, in the last year?

YES..... 1
NO..... 2

C. How often did/do you have dizzy spells? Was/is it:

Once only,..... 1
Once a month or less often,..... 2
Several times a month,..... 3
Once a week,..... 4
Almost daily, or..... 5
Irregularly or in sprees?..... 6

D. Are/were the dizzy spells associated with:

	YES	NO
Headaches?.....	1	2
Nausea or vomiting?.....	1	2
Loss of balance?.....	1	2
Noise in the ears?.....	1	2
Difficulty with vision?.....	1	2
Certain head position?.....	1	2
Sense of spinning around?.....	1	2
Ear troubles?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1

NO.....SKIP TO Q135..... 2

F. Did you see a:

Military medical service, or.....SKIP TO Q135..... 1

A private doctor/ hospital?.....ASK G..... 2

G. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

H. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q135..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	
An E.E.G.?	1	2	
An E.M.G.?	1	2	
A C.A.T. scan of the skull?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

135. Have you ever had weakness or paralysis of any part of your body?

YES..... 1
NO.....SKIP TO Q136..... 2

A. Is/was the episode of weakness:

Short lived,..... 1
Recurrent or intermittent, or..... 2
Continuous?..... 3

B. How long did the episodes of weakness last? Would you say:

A few days at most,..... 1
1-3 months,..... 2
3-6 months,..... 3
6-12 months,..... 4
1-2 years, or..... 5
More than 2 years?..... 6

C. In what year did you first experience weakness in any part of your body?

RECORD YEAR:_____

D. Do you still experience this weakness, that is, in the last year?

YES..... 1
NO..... 2

E. Which part of your body is/was weak or lacking in power? Is/was it your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Leg or foot?.....	1	2
Both legs?.....	1	2
Hands and legs?.....	1	2
Both arms?.....	1	2
One side of the body?.....	1	2

F. Associated with the weakness, have you had:

	YES	NO
Double vision?.....	1	2
Imbalance?.....	1	2
Dizziness?.....	1	2
Difficulty with speech?....	1	2
Weakness in other parts of your body?.....	1	2
Blindness in one eye?.....	1	2

G. Have you seen a doctor about these symptoms?

YES.....ASK H..... 1

NO.....SKIP TO Q136..... 2

H. Did you see a:

Military medical service, or.....SKIP TO J..... 1

A private doctor/ hospital?.....ASK I..... 2

I. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

J. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q136..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	
An E.E.G.?	1	2	
An E.M.G.?	1	2	
A C.A.T. scan skull?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

136. Have you ever had numbness or loss of feeling of any part of your body?

YES..... 1
NO.....SKIP TO Q137..... 2

A. Was the numnbess or loss of feeling associated with weakness described previously?

YES.....SKIP TO Q137..... 1
NO..... 2

B. In what year did you first experience the numbness?

RECORD YEAR:_____

C. Do you still get numbness?

YES..... 1
NO..... 2

D. Which part of your body has/had been numb? Was it your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Leg or foot?.....	1	2
Both arms?.....	1	2
Both legs?.....	1	2
Hands and feet?.....	1	2
One side of the body?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q137..... 2

F. Did you see a:

Military medical service, or.....SKIP TO H..... 1
A private doctor/ hospital?.....ASK G..... 2

G. Please give me the name and address of the doctor/hospital you saw for your problem.

_____

_____

_____

H. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q137..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	
An E.E.G.?	1	2	
An E.M.G.?	1	2	
A C.A.T. scan of the skull?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

137. Have you ever suffered from persistent tingling or pins and ne

YES.....

NO.....SKIP TO Q138.....

A. Has the tingling been associated with the weakness or numbn described previously?

YES.....

NO.....

B. In what year did you first experience tingling or pins and

RECORD YEAR:_____

C. Do you still get tingling or pins and needles?

YES.....

NO.....

D. In which part of your body have you had pins and needles? in your:

	YES	N
Face?.....	1	2
Arm or hand?.....	1	2
Chest or abdomen?.....	1	2
Leg or foot?.....	1	2
Both arms?.....	1	2
Both legs?.....	1	2
Arms and legs?.....	1	2
One side of the body?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F.....

NO.....SKIP TO Q138.....

F. Did you see a:

Military medical service, or.....SKIP TO H..... 1

A private doctor/ hospital?.....ASK G..... 2

G. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

H. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q138..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	
An E.E.G.?	1	2	
An E.M.G.?	1	2	
A C.A.T. scan of the skull?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

138. Have you ever suffered from persistent or intermittent burning sensations in your muscles?

YES..... 1
NO.....SKIP TO Q139..... 2

A. Have these sensations been associated with weakness, numbness or tingling described previously?

YES.....SKIP TO Q139..... 1
NO..... 2

B. In what year did you first experience these sensations?

RECORD YEAR:_____

C. Are these sensations still a problem?

YES..... 1
NO..... 2

D. In which part of your body have you had these sensations? Was it your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Chest or abdomen?.....	1	2
Leg or foot?.....	1	2
Both arms?.....	1	2
Both legs?.....	1	2
One side of the body?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q139..... 2

F. Did you see a:

Military medical service, or.....SKIP TO H..... 1

A private doctor/ hospital?.....ASK G..... 2

G. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

H. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q139..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	
An E.E.G.?	1	2	
An E.M.G.?	1	2	
A C.A.T. scan of the skull?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

39. Have you ever suffered from persistent involuntary movements or tremors?

YES..... 1
NO.....SKIP TO Q140..... 2

A. Were the tremors associated with weakness, numbness or tingling described previously?

YES.....SKIP TO Q140..... 1
NO..... 2

B. In what year did you first experience the tremors?

RECORD YEAR:_____

C. Do you still have trouble with tremors?

YES..... 1
NO..... 2

D. Where do you experience the tremors mainly? Is it in your:

Hands,..... 1
Legs, or..... 2
Over your whole body?..... 3

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q140..... 2

F. Did you see a:

Military medical service, or.....SKIP TO H..... 1
A private doctor/ hospital?.....ASK G..... 2

G. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

H. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q140..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	_____ _____ _____
An E.E.G?	1	2	_____ _____ _____
An E.M.G.?	1	2	_____ _____ _____
A C.A.T. scan of the skull?	1	2	_____ _____ _____
Other special tests? SPECIFY: _____	1	2	_____ _____ _____

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

0. Have you had difficulty walking over a period of a month or more (excluding difficulty due to direct injury)?

YES..... 1

NO.....SKIP TO Q141..... 2

A. Do you still have any difficulty with walking?

YES..... 1

NO..... 2

B. In what year did you first experience difficulty walking?

RECORD YEAR:_____

C. Have you seen a doctor about these symptoms?

YES.....ASK D..... 1

NO.....SKIP TO Q141..... 2

D. Did you see a:

Military medical service, or.....SKIP TO F..... 1

A private doctor/ hospital?.....ASK E..... 2

E. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

F. Have you had any special tests for these conditions?

YES.....ASK a..... 1

NO.....SKIP TO Q141..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
A skull X-ray?	1	2	
An E.E.G?	1	2	
An E.M.G.?	1	2	
A C.A.T. scan of the skull?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

141. This set of questions is about reproduction.

A. (HAND CARD #141) Please look at this card and tell me if you ever had any of the following. READ a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q142 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Inflammation of the testes?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Tumor of the testes?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Hydrocoele?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Varicoele?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Hernia?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Sterility?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Other problem? SPECIFY:						
_____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
_____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you <u>currently</u> seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF PRIVATE DOCTOR/HOSPITAL CURRENTLY SEEN, ASK: Please give me the name and address of the doctor/hospital you are currently seeing for the (...). RECORD IN COLUMN G OF CHART.

E. NAME AND ADDRESS	F. CURRENT CARE	G. NAME/ADDRESS CURRENT DOCTOR/HOSPITAL
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2 Military/Medical.....1 Doctor/Hosp...ASK G...2	

142. Have you ever had any venereal disease or V.D. such as: READ a-c AND CODE IN COLUMN I OF CHART.

	I. YES	I. NO	II. FIRST OCCURRED MONTH - YEAR	III. SERVING S. VIETNAM YES	III. SERVING S. VIETNAM NO	IV. MONTH - YEAR WHILE SERVING
a. Syphilis?	1	2	_____ 19____	1	2	_____ 19____
b. Gonorrhea?	1	2	_____ 19____	1	2	_____ 19____
c. Clap?	1	2	_____ 19____	1	2	_____ 19____

IF ALL "NO"...SKIP TO Q143
ALL OTHERS.....CONTINUE

A. What month and year did you first have (...)? INSERT DISEASE FOR (...) - RECORD IN COLUMN II OF CHART ABOVE.

B. Did you have (...) while serving in South Vietnam? ASK FOR EACH "YES" IN COLUMN I - INSERT DISEASE FOR (...) - CODE IN COLUMN III OF CHART ABOVE.

C. What month and year did you have (...) while serving in South Vietnam? INSERT DISEASE FOR (...) - RECORD MONTH AND YEAR IN COLUMN IV OF CHART ABOVE.

143. Have you ever had the mumps?

YES.....ASK A..... 1
NO.....SKIP TO Q144..... 2

A. When did you have the mumps?

RECORD YEAR:_____

B. When you had the mumps did you have any swelling of the testicles at that time?

YES..... 1
NO..... 2
DK/DR..... 9

44. I would like to ask you some questions about fertility, i.e. your ability to father children.

A. Have you fathered <u>any</u> children or been responsible for a pregnancy?

YES..... 1
NO..... 2

B. Are you able to have an erection and ejaculate?

YES..... 1
NO..... 2

C. Do you have any reason to believe that you are <u>currently</u> unable to father children?

YES..... 1
NO.....SKIP TO G..... 2

D. Why do you believe you are currently unable to father children? Is it because:

	YES	NO
You have tried to have children without success?	1 ASK E	2
You have had a vasectomy?	1 SKIP TO H	2
You and your partner don't wish to have intercourse?	1 SKIP TO G	2
You have had a sperm count and it is low?	1 ASK G	2
Other reason? (SPECIFY) _____	1 SKIP TO G	2

E. For how long have you been trying to have children? Would you say:

Less than 6 months,..... 1
6 months to 1 year,..... 2
1 to 2 years, or..... 3
More than 2 years?..... 4

F. When you were trying to make your partner pregnant how often would you have intercourse? Would you say:

Daily,..... 1
Several times a week,..... 2
Once a week,..... 3
Twice a month,..... 4
Once a month, or..... 5
Less than once a month?..... 6

G. Are you currently avoiding having children?

Yes..... 1
NO.....SKIP TO I..... 2

h. Why are you avoiding having children? Is it because you are:

Planning not to have family,..... 1
Spacing family, or..... 2
Some other reason?..... 3
→SPECIFY:_____

I. Do you or your partner use contraception?

YES..... 1
NO.....SKIP TO K..... 2

J. (HAND CARD #144J) Please look at this card and tell me what method of contraception you and your partner usually use?

CONDOM.....01
PILL.....02
IUD.....03
TEMPERATURE.....04
DIAPHRAGM.....05
TUBAL LIGATION.....06
VASECTOMY.....07
RHYTHM.....08
OTHER.....09
→SPECIFY:_____

K. How would you rate your interest in sex at present? Would you say:

Increased interest for you,.....SKIP TO Q145..... 1
Normal for you, or..SKIP TO Q145..... 2
Decreased interest for you?.....ASK L..... 3

L. When did your interest first change?

RECORD YEAR:_____

145. How many children are you the natural father of? Please include children who do not live with you, children who are no longer living, and stillborn babies. Do not include step children, foster children or adopted children.

RECORD # OF CHILDREN:_____

NO CHILDREN.....SKIP TO Q147.....99

146. Have you fathered any children from your present wife or partner?

YES..... 1

NO.....SKIP TO Q147..... 2

NO PRESENT PARTNER..SKIP TO Q148..... 9

A. Now I would like to list all of your children from your present wife or partner. Please include children who do not live with you, children who are no longer living, and any stillborn babies. Starting with your oldest child, please give me the first and last names of each child. If the child is a boy or girl, the child's date of birth and whether the child is living, deceased or was stillborn. RECORD IN ROSTER - COLUMNS A-E.

CHILDREN FROM PRESENT WIFE(PARTNER)

A. GIVEN NAME	B. SURNAME	C. SEX M	F	DK	D. DATE OF BIRTH MONTH YEAR	E. LIVING	DE-CEASED	STILL-BORN
1.		1	2	9	____ 19____	1	2	3
2.		1	2	9	____ 19____	1	2	3
3.		1	2	9	____ 19____	1	2	3
4.		1	2	9	____ 19____	1	2	3
5.		1	2	9	____ 19____	1	2	3
6.		1	2	9	____ 19____	1	2	3
7.		1	2	9	____ 19____	1	2	3
8.		1	2	9	____ 19____	1	2	3
9.		1	2	9	____ 19____	1	2	3
10.		1	2	9	____ 19____	1	2	3
11.		1	2	9	____ 19____	1	2	3
12.		1	2	9	____ 19____	1	2	3

F. Do you know of anyone in your or your present wife's/partner's family who has had any stillbirths?

YES..... 1

NO.....SKIP TO Q147..... 2

a. Whose family was that? Was it:

Your family, or..... 1

Your wife's/partner's?..... 2

BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO WIFE/PARTNER:

_____

147. Now I need to ask a few questions about your present wife/partner.

NO WIFE/PARTNER...SKIP TO Q148.....99

A. How old is she?

RECORD AGE:_____

B. Please give me her date of birth?

RECORD:_____/_____
MONTH YEAR

C. What racial or ethnic group does she identify with?

RECORD:_____

D. How many years of school did she complete and receive credit for?

RECORD:_____

IF NO NATURAL CHILDREN SIRED.....SKIP TO Q152

148. Have you fathered <u>any</u> children from any <u>previous</u> wife or partner?

YES..... 1

NO.....SKIP TO INSTRUCTION BOX ABOVE Q149..... 2

A. As before, please give me the names and birth dates of these children, tell me whether each is a boy or girl, include children who are no longer living, and any stillbirths that you fathered from all <u>previous</u> marriages. RECORD IN ROSTER - COLUMNS A-E.

<u>CHILDREN FROM PREVIOUS PARTNER(S)</u>

A. GIVEN NAME	B. SURNAME	C. SEX M	F	DK	D. DATE OF BIRTH MONTH YEAR	E. LIVING	DE-CEASED	STILL-BORN
1.		1	2	9	____ 19____	1	2	3
2.		1	2	9	____ 19____	1	2	3
3.		1	2	9	____ 19____	1	2	3
4.		1	2	9	____ 19____	1	2	3
5.		1	2	9	____ 19____	1	2	3
6.		1	2	9	____ 19____	1	2	3
7.		1	2	9	____ 19____	1	2	3
8.		1	2	9	____ 19____	1	2	3
9.		1	2	9	____ 19____	1	2	3
10.		1	2	9	____ 19____	1	2	3
11.		1	2	9	____ 19____	1	2	3
12.		1	2	9	____ 19____	1	2	3

F. Do you know of anyone in your previous wife's/partner's family who has had any stillbirths?

YES..... 1

NO.....SKIP TO INSTRUCTION BOX ABOVE Q149..... 2

a. Who was it?

RELATIONSHIP TO PREVIOUS WIFE/PARTNER:

_____

G. Please give me the name and address of these children's mother(s).

MOTHER'S NAME:_____

ADDRESS:_____

_____

What are the first names of the children she and you had:

1._____
2._____
3._____
4._____

MOTHER'S NAME:_____

ADDRESS:_____

_____

FIRST NAMES OF CHILDREN:

1._____
2._____
3._____
4._____

H. FOR EACH MOTHER LISTED, ASK THE FOLLOWING QUESTIONS.

Name:_____

How old is she? RECORD AGE:_____

Can you give me her date of birth?

RECORD DATE:_____

What racial or ethnic group does she identify with?

RECORD:_____

How many years of school did she complete and receive credit for?

RECORD:_____

Name:_____

How old is she? RECORD AGE:_____

Can you give me her date of birth?

RECORD DATE:_____

What racial or ethnic group does she identify with?

RECORD:_____

How many years of school did she complete and receive credit for?

RECORD:_____

REFER TO ROSTERS 146 AND 148:

IF NO CHILDREN.....SKIP TO INTRO Q153
IF ANY DECEASED OR STILLBORN CHILDREN...ASK Q149
ALL OTHER.....SKIP TO Q150

149. Could you tell me something about the child(ren) who is (are) no longer living? Please give me the:

a. First name:_____

Date of death:_____

Place of death:_____

_____

Cause of death:_____

b. First name:_____

Date of death:_____

Place of death:_____

_____

Cause of death:_____

A. Could you tell me something about the stillbirth(s)? For example:

a. Date of birth:_____

Place of birth (name of hospital, city):

_____

Cause of stillbirth:_____

b. Date of birth:_____

Place of birth (name of hospital, city):

_____

Cause of stillbirth:_____

B. Now, about the children who are no longer living, please give me the child's name and the names and addresses of any doctors who knew this (these) child(ren), or hopsital where they were treated? First:

a. Given name of child:_____

Doctor's/Hospital's name:_____

_____

Address of Doctor/Hospital:_____

_____

b. Given name of child:_____

Doctor's/Hospital's name:_____

_____

Address of Doctor/Hospital:_____

_____

50. Were any of the children that you mentioned born with an abnormality or any physical or mental handicap (including those who are now dead)?

YES..... 1

NO.....SKIP TO Q151..... 2

DON'T KNOW..... 9

A. Please tell me the:

Given name of child:_____

Type of defect or handicap:_____

_____

a. Has the child received medical attention for this condition?

YES.....ASK b..... 1

NO.....SKIP TO NEXT CHILD OR D..... 2

b. Please give me the name of the doctor, hospital, or institution.

_____

_____

B. Given name of child: _____

Type of defect or handicap: _____

_____

a. Has the child received medical attention for this condition?

YES.....ASK b..... 1

NO.....SKIP TO NEXT CHILD OR D..... 2

b. Please give me the name of the doctor, hospital, or institution.

_____

_____

C. Given name of child: _____

Type of defect or handicap: _____

_____

a. Has the child received medical attention for this condition?

YES.....ASK B..... 1

NO.....SKIP TO D..... 2

b. Please give me the name of the doctor, hospital, or institution.

_____

_____

D. Has a close relative, either in <u>your family</u> or the <u>child's mother's family</u>, had a similar problem?

YES.....ASK a..... 1

NO.....SKIP TO Q151..... 2

DON'T KNOW.....SKIP TO Q151..... 9

a. Whose family was that? Was it:

Your family, or..... 1
The child's mother's family?..... 2
BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO CHILD'S MOTHER:

_____

51. Have any of the children you mentioned ever been diagnosed as having cancer, including leukemia or cancer of the blood?

YES..... 1

NO.....SKIP TO Q152..... 2

a. Please give me the:

Given name of child:_____

Type and site of malignancy:_____

Year of diagnosis:_____

Name of doctor or hospital who diagnosed and/or treated the child:

_____

A. Has a close relative either in <u>your family</u> or the <u>child's mother's family</u> had a similar problem?

YES.....ASK B..... 1

NO.....SKIP TO Q152..... 2

DON'T KNOW.....SKIP TO Q152..... 9

B. Whose family was that? Was it:

Your family, or..... 1

The child's mother's family?..... 2

BOTH..... 3

C. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO CHILD'S MOTHER:

_____

152. Did any pregnancy in which you were the partner end in a miscarriage or abortion?

YES.....ASK A..... 1
NO.....SKIP TO Q153..... 2
DON'T KNOW.....SKIP TO Q153..... 9

A. How many such pregnancies were there?

RECORD #:_____

a. In which year did the pregnancy end?

RECORD YEAR:_____

Name and address of hospital or doctor who treated her:

_____

_____

_____

b. Was the mother your present wife or partner?

YES.....SKIP TO d..... 1
NO.....ASK c..... 2

c. Could you tell me the name and current address of the mother?

_____

_____

_____

d. Do you know of anyone in your or the mother's family who has had pregnancies which ended in miscarriages or any other serious problems with the pregnancy?

YES..... 1
NO.....SKIP TO Q153..... 2

a. Whose family was that? Was it:

Your family, or..... 1
The mother's family?..... 2
BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO MOTHER:

_____

e. In which year did the pregnancy end?

RECORD YEAR:_____

Name and address of hospital or doctor who treated her:

_____

_____

_____

f. Was the mother your present wife or partner?

YES.....SKIP TO h..... 1
NO.....ASK g..... 2

g. Could you tell me the name and current address of the mother?

_____

_____

_____

h. Do you know of anyone in your or the mother's family who has had pregnancies which ended in miscarriages or any other serious problems with the pregnancy?

YES..... 1

NO.....SKIP TO Q153..... 2

a. Whose family was that? Was it:

Your family, or..... 1

The mother's family?..... 2

BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO MOTHER:

_____

w we have some questions about blood and glandular disorders.

153. Have you ever had a tendency to bleeding or bruising easily?

YES.....ASK A..... 1
NO.....SKIP TO Q154..... 2

A. In what year did this tendency first occur?

RECORD YEAR:_____

B. Is bleeding or bruising still a problem?

YES..... 1
NO..... 2

C. Is the tendency associated with any medications that you may have taken?

YES..... 1
NO..... 2

D. Do bleeding tendencies or blood disorders run in your family?

YES..... 1
NO..... 2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q154..... 2

F. Did you see a:

Military medical service, or.....SKIP TO Q154..... 1
A private doctor/ hospital?.....ASK G..... 2

G. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

H. Did you have any special tests for the blood problems?

YES.....ASK a..... 1

NO.....SKIP TO Q154..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERIN TEST
Blood tests?	1	2	_____ _____ _____
Bone marrow tests?	1	2	_____ _____ _____
Other special tests? SPECIFY: _____	1	2	_____ _____ _____

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

154. Have you ever suffered from a generalized gland enlargement?

YES.....ASK A..... 1
NO.....SKIP TO Q155..... 2

A. In what year did the gland enlargement first occur?

RECORD YEAR:_____

B. Are the enlarged glands still a problem?

YES..... 1
NO..... 2

C. Have you seen a doctor about these symptoms?

YES.....ASK D..... 1
NO.....SKIP TO Q155..... 2

D. Did you see a:

Military medical service, or.....SKIP TO Q155..... 1
A private doctor/ hospital?.....ASK E..... 2

E. Please give me the name and address of the doctor/hospital you saw for this problem.

_____
_____
_____

F. Did you have any special tests for the gland problems?

YES.....ASK a..... 1

NO.....SKIP TO Q155..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
Blood tests?	1	2	
Bone marrow tests?	1	2	
Other special tests? SPECIFY: _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

5. Have you had blood transfusions?

YES..... 1

NO.....SKIP TO Q156..... 2

A. Did a Military Medical Service or a private doctor/hospital administer the transfusion?

MILITARY MEDICAL SERVICE.....SKIP TO Q156..... 1

DOCTOR/HOSPITAL.....ASK B..... 2

B. Please give me the name of the doctor/hospital who administered the blood transfusion.

_____

_____

_____

156. Now these are some questions about bones and joints.

A. (HAND CARD #156) Please look at this card and tell me if you ever had any of the following. READ a-l AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q157 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Osteoarthritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Rheumatoid arthritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Gout?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Other arthritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Sciatica?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Disc trouble?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Spondylitis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
h. Lumbago?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
i. Systemic lupus erythematosis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
j. Scleroderma?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
k. Pagets disease?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
l. Other (SPECIFY) _____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you currently seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF PRIVATE DOCTOR/HOSPITAL CURRENTLY SEEN, ASK: Please give me the name and address of the doctor/hospital you are currently seeing for the (...). RECORD IN COLUMN G OF CHART.

E. NAME AND ADDRESS	F. CURRENT CARE	G. NAME/ADDRESS CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

157. Have you ever had an injury to a joint(s)?

YES..... 1
NO.....SKIP TO Q158..... 2

A. In what year did the initial injury occur?

RECORD YEAR:_____

B. Is the joint still a problem?

YES..... 1
NO..... 2

C. Have you seen a doctor about these symptoms?

YES.....ASK D..... 1
NO.....SKIP TO Q158..... 2

D. Did you see a:

Military medical service, or.....SKIP TO Q158..... 1
A private doctor/ hospital?.....ASK E..... 2

E. Please give me the name and address of the doctor/hospital you saw for this problem.

_____
_____
_____

F. Did you have any special tests for joints or bone problems?

YES.....ASK a..... 1

NO.....SKIP TO Q158..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
Blood tests?	1	2	
X-rays?	1	2	
Arthroscopy?	1	2	
Other (SPECIFY) _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

8. Apart from injury have you ever had hot painful, swollen or stiff joints?

YES..... 1
NO.....SKIP TO Q159..... 2

A. Which joints were affected?

ONE..... 1
SEVERAL SYMMETRICAL..... 2
SEVERAL ASYMMETRICAL..... 3

B. In what year did you first have painful or swollen joints?

RECORD YEAR:_____

C. Are these joints still a problem?

YES..... 1
NO..... 2

D. Have you seen a doctor about these symptoms?

YES.....ASK E..... 1
NO.....SKIP TO Q159..... 2

E. Did you see a:

Military medical service, or.....SKIP TO Q159..... 1
A private doctor/ hospital?.....ASK F..... 2

F. Please give me the name and address of the doctor/hospital you saw for this problem.

_____
_____
_____

G. Did you have any special tests for joints or bone problems?

YES.....ASK a..... 1

NO.....SKIP TO Q159..... 2

a. Did you have: READ EACH AND CODE IN COLUMN I.

TEST	I. YES	NO	II. NAME OF PHYSICIAN OR HOSPITAL ADMINISTERING TEST
Blood tests?	1	2	
X-rays?	1	2	
Arthroscopy?	1	2	
Other (SPECIFY) _____	1	2	

b. FOR EACH "YES" IN COLUMN I, ASK: Please give me the name and address of the doctor/hospital who administered the test(s). RECORD IN COLUMN II OF CHART.

159. next list is about gland disorders.

A. (HAND CARD #159) Please look at this card and tell me if you have ever had any of these problems. READ a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q160 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) condition first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or a private doctor/hospital for the diagnosis and care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name and address of the doctor/hospital you saw for the (...)? INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

CONDITION	A. EVER HAD YES	A. EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
a. Diabetes?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Overactive thyroid?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Underactive thyroid?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Pituitary gland disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Adrenal gland disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Parathyroid gland disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Other (SPECIFY) ↳____	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

60. Were you ever under care for mental or emotional problems such as a nervous breakdown, exhaustion, and so forth?

YES.....ASK A..... 1

NO.....SKIP TO Q161..... 2

A. Have you seen a doctor about this problem?

YES.....ASK B..... 1

NO.....SKIP TO Q161..... 2

B. Did you see a:

Military medical service, or.....SKIP TO Q161..... 1

A private doctor/ hospital?.....ASK C..... 2

C. Please give me the name and address of the doctor/hospital you saw for this problem.

_____

_____

_____

161. What were the dates of your military service?

ENTRY: _____ / _____
MONTH YEAR

SEPARATION: _____ / _____
MONTH YEAR

162. Did you enlist or were you drafted?

ENLISTED..... 1
DRAFTED..... 2

53. What were the locations of your military service? RECORD IN CHART BELOW. PROBE FOR COMPLETE LOCATION.

A. FOR EACH LOCATION, ASK: What was your company designation? PROBE FOR EACH LOCATION - RECORD IN COLUMN A OF CHART.

B. FOR EACH LOCATION, ASK: When were you in (...)? Please give me the month and year of arrival and the month and year you left (...). INSERT LOCATION FOR (...) - RECORD MONTH/YEAR R ARRIVED AND LEFT LOCATION IN COLUMN B OF CHART.

C. What were your duties when you were in (...)? INSERT LOCATION FOR (...). ASK FOR EACH LOCATION - RECORD IN COLUMN C OF CHART - PROBE FULLY FOR DUTIES.

LOCATIONS	A. COMPANY DESIGNATION	B. DATES FROM MO/YR	B. DATES TO MO/YR	C. DUTIES
1.		___ 19___	___ 19___	
2.		___ 19___	___ 19___	
3.		___ 19___	___ 19___	
4.		___ 19___	___ 19___	
5.		___ 19___	___ 19___	

164. Were you in any areas where any defoliants or weedkillers were used, for example, around the camp, back pack or truck spraying or air spraying by helicopter or airplane?

YES.....ASK A..... 1

NO.....SKIP TO Q166..... 2

A. When, that is, what months and years did the defoliant and weedkiller spraying occur? RECORD DATES IN COLUMN A OF CHART.

B. Please give me the name of the location of where you were when the defoliants and weedkillers were sprayed. RECORD LOCATION FOR EACH DATE IN COLUMN B OF CHART.

C. Please tell me if the defoliants or weedkillers were used by back pack or truck spraying or by helicopter or airplane spraying? RECORD IN COLUMN C OF CHART FOR EACH DATE.

D. Give me the names of the defoliants and weedkillers that were used. RECORD IN COLUMN D OF CHART FOR EACH DATE.

A. DATES MONTH/YEAR	B. LOCATION	C. SOURCE OF SPRAYING	D. NAME OF AGENT
____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
2. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
3. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
4. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	

65. Did you do any of the spraying yourself?

YES.....ASK A..... 1

NO.....SKIP TO Q166..... 2

A. What dates, month and year, did you do this spraying? RECORD IN COLUMN A OF CHART.

B. Please tell me where you did this spraying, the exact location. RECORD IN COLUMN B OF CHART FOR EACH DATE.

C. Please tell me if the defoliants or weedkillers were used by back pack or truck spraying or helicopter or plane spraying? CODE IN COLUMN C OF CHART.

D. Tell me the names of the defoliants and weedkillers that you used. RECORD NAMES IN COLUMN D OF CHART.

A. DATES MONTH/YEAR	B. LOCATION	C. SOURCE OF SPRAYING	D. NAME OF AGENT
1. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
2. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
3. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
4. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
5. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	

6. Did you ever handle drums of defoliant, load spraying equipment, maintain, clean or repair spraying equipment or participate in clean up of spills or leaks?

YES.....ASK A..... 1

NO.....SKIP TO Q167..... 2

A. What dates, month and year, did you handle, clean, repair, etc. drums of defoliant, spraying, equipment, etc.? RECORD IN COLUMN A.

B. Where did you do this? What was the location? RECORD IN COLUMN B OF CHART FOR EACH DATE.

C. What did you actually do? RECORD FULLY FOR EACH DATE IN COLUMN C.

A. DATES MONTH/YEAR	B. LOCATION	C. DUTIES
1. ____ 19____		
____ 19____		
3. ____ 19____		
4. ____ 19____		
5. ____ 19____		
6. ____ 19____		
____ 19____		

7. Were you ever under a spraying operation while it was going on?

YES.....ASK A..... 1

NO.....SKIP TO Q168..... 2

A. Please give me the dates, month and year, when you were under a spraying operation while it was going on. RECORD DATES IN COLUMN A OF CHART.

B. Where did this take place, tell me the location. RECORD FOR EACH DATE IN COLUMN B OF CHART.

C. Please tell me in detail, the type of defoliants used, type of spraying and any other details regarding the spraying operation. RECORD FULLY IN COLUMN C OF CHART FOR EACH DATE.

A. DATES MONTH/YEAR	B. LOCATION	C. DETAILS OF OPERATION
1. ____ 19____		
____ 19____		
3. ____ 19____		
4. ____ 19____		
5. ____ 19____		
6. ____ 19____		
____ 19____		

68. Now I would like to know the closest contact you had with any spraying operation such as defoliants, insecticides, etc.

A. As I read each of the following plese tell me if you were ever: READ a-d AND CODE IN COLUMN A.

IF ALL "NO".....SKIP TO Q169 ALL OTHERS - INCLUDING D.K. - CONTINUE

B. Please give me the date, month and year, that you (think you) were (...). INSERT APPROPRIATE a-d FOR (...). RECORD IN COLUMN B OF CHART.

C. Where were you, in other words, what city, state or country were you in when you (thought you) were (...)? INSERT a-d FOR (...). RECORD LOCATION R WAS AT IN COLUMN C OF CHART.

D. At the time you (thought you) were (...) was the spraying operation being done by back pack, truck, airplane, helicopter spraying, or some other way. INSERT a-d FOR (...) - CODE IN COLUMN D.

E. Please tell me the kind of defoliants, insecticides or sprays being used when you were (...)? INSERT a-d FOR (...) - CODE IN COLUMN E.

	A. YES	NO	D.K.	B. DATES	C. LOCATION	D. SOURCE OF SPRAYING	E. KIND
a. Drenched with spray?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 →_____	
b. Directly under spray but not drenched?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 →_____	
c. One who did the spraying?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 →_____	
d. Nearby spraying but not directly under?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 →_____	

9. Do you think you were exposed to "Agent Orange" while you served in Vietnam?

YES.....ASK A..... 1

NO.....SKIP TO Q170..... 2

DON'T KNOW.....ASK A..... 9

A. (Even though you're not sure) When do you think you were exposed to "Agent Orange?" Please give me the month and year?

RECORD DATE:_____/_____
MONTH YEAR

B. Where were you, what area of Vietnam, when you were exposed?

RECORD LOCATIONS:

1._____

2._____

3._____

C. How much of an exposure or dose do you think you got?

RECORD DOSE:_____

0. Please look at this card (HAND CARD #170) and give me the letter that comes closest to your income last year before taxes. Please include all sources, for example, wages, dividends, rentals, welfare, disability, etc.

A.	LESS THAN $3,000.....01	I.	$12,000 - $13,999.....09
B.	$3,000 - $3,999.....02	J.	$14,000 - $16,999.....10
C.	$4,000 - $4,999.....03	K.	$17,000 - $19,999.....11
D.	$5,000 - $5,999.....04	L.	$20,000 - $24,999.....12
E.	$6,000 - $6,999.....05	M.	$25,000 - $29,999.....13
F.	$7,000 - $8,499.....06	N.	$30,000 - $39,999.....14
G.	$8,500 - $9,999.....07	O.	$40,000 - $49,999.....15
H.	$10,000 - $11,999.....08	P.	$50,000 AND OVER.....16

REFUSED.....97
DON'T KNOW.....98

171. Do you own or rent your home (apartment)?

OWN..... 1
RENT..... 2
SOMETHING ELSE..... 3
→ SPECIFY:_____

2. We want to thank you for all the time you have given us. Your cooperation in this important study is vital to the success of the project. To complete our objectives in documenting your health status and health history we would like to contact the various hospitals, doctors or health care services you have mentioned in this interview so that we can look at your medical records. In order for us to do so, we need a signed release from you indicating your willingness to allow your medical records be made available to us. All information we collect will be kept strictly confidential and will be used for statistical and research purposes only. Your name or any details of your medical history will not be revealed. Are you willing to sign such a release?

YES.....GIVE CONSENT FORM

NO.....THANK AND TERMINATE

CONSENT FOR RELEASE OF MEDICAL RECORD INFORMATION

I hereby authorize the release of any medical records and information regarding my diagnosis and treatment to the investigators for the "Agent Orange Study."

_____ _____

SIGNATURE DATE

SOCIAL SECURITY # _____ _____ _____

SERVICE RECORD # _____

INTERVIEWER SIGNATURE_____

DATE:_____

VETERANS QUESTIONNAIRE HAND CARDS

CARD #18-23

A. CHEMICALS, CLEANING FLUIDS OR SOLVENTS (SPECIFY)

B. ASBESTOS, INSULATION MATERIAL

C. INSECTICIDES

D. PLASTICS OR RESINS (SPECIFY)

E. X-RAYS

F. ANESTHETIC GASES

G. RADIOACTIVITY, ISOTOPES

H. PETROLEUM PRODUCTS, FUELS, BENZENE (SPECIFY)

I. LEAD OR METAL SMELTING FUMES (SPECIFY)

J. HERBICIDES (PLANT KILLERS)

CARD #30

ALMOST EVERY DAY

SOMETIMES

RARELY

NEVER

CARD #68

EVERY DAY

4 TO 6 DAYS A WEEK

2 OR 3 DAYS A WEEK

ONCE A WEEK

2 OR 3 DAYS A MONTH

ONCE A MONTH

CARD #68A

LESS THAN ONE A DAY

1 OR 2 A DAY

3 OR 4 A DAY

5 OR 6 A DAY

7 OR 8 A DAY

9 OR 10 A DAY

MORE THAN 10 A DAY

CARD #76

A. ECZEMA

B. ACNE

C. PSORIASIS

D. RECURRENT PIMPLES/BOILS

E. PERSISTANT RASHES

F. SKIN CANCER

G. PORPHYRIA CUTANEA TARDA

H. SPIDER ANGIOMATA

I. PALMAR ERYTHEMA

J. CAPUT MEDUSA

K. XANTHOLASMA

L. OTHER PROBLEMS

CARD #92

A. HEART ATTACK

B. ANGINA

C. HEART FAILURE

D. HIGH BLOOD PRESSURE

E. RHEUMATIC FEVER

F. DISORDERS OF THE HEART VALVES

G. CONGENITAL HERAT DISEASE

H. CLOTS IN LEGS

I. SWELLING OF THE ANKLES

J. OTHER HEART CONDITIONS

CARD #99

A. SINUSITIS

B. FREQUENT NOSE BLEEDS

C. FREQUENT COLDS (MORE THAN 3 A YEAR)

D. ASTHMA

E. CHRONIC BRONCHITIS

F. EMPHYSEMA

G. T.B.

H. BRONCHIECTASIS

I. PLEURISY

J. PNEUMONIA

K. PNEUMONIA MORE THAN ONCE

L. CANCER OF THE LUNG

M. OTHER LUNG DISEASE(S)

CARD #120

A. ESOPHAGITIS

B. HIATUS HERNIA

C. GASTRIC OR DUODENAL ULCER

D. CROHNS DISEASE

E. BOWEL OBSTRUCTION

F. DIVERTICULITIS

G. SPASTIC OR IRRITABLE COLON

H. ULCERATIVE COLITIS

I. ANAL PROBLEMS OR HEMORRHOIDS

J. DYSENTERY

K. MALABSORPTION

L. OTHER GASTRO CONDITIONS

CARD #121

A. PERSISTANT INDIGESTION OR ABDOMINAL DOSCOMFORT

B. BOUTS OF ABDOMINAL PAIN

C. RECURRING BOUTS OF FEELING SICK OR VOMITING

D. BOUTS OF CONSTIPATION (NORMAL = 1 MOVEMENT IN 3 DAYS TO 3 IN 1 DAY)

E. BOUTS OF DIARRHEA

F. VOMITED BLOOD

G. BLEEDING FROM THE BOWELS

CARD #123

A. HEPATITIS WITH OR WITHOUT JAUNDICE

B. CIRRHOSIS OF THE LIVER

C. JAUNDICE

D. GALL BLADDER DISORDER

E. GALLSTONES

F. PANCREATITIS

G. OTHER DISEASES OF THE LIVER

CARD #125

A. KIDNEY OR BLADDER STONES

B. KIDNEY INFECTION

C. NEPHRITIS

D. RENAL COLIC

E. BLADDER INFECTION

F. DISORDERS OF THE PROSTATE

G. URETHRITIS

H. GONORRHEA

I. SYPHILIS

J. HERPES

K. OTHER PROBLEMS

CARD #130

A. A CANCER

B. A TUMOR

C. A LUMP

D. A GROWTH

E. A SARCOMA (TUMOR OR SOFT TISSUE)

F. A TUMOR OF THE EYE

G. A TUMOR OF THE TESTES

CARD # 131

A. HIVES

B. OTHER SKIN RASHES

C. HAYFEVER (VASOMOTOR RHINITIS)

D. ASTHMA

E. STOMACH UPSETS

F. OTHER ALLERGIES

CARD #132

A. LUPUS ERYTHEMATOSIS

B. HASHIMOTO'S THYROIDITIS

C. RHEUMATOID ARTHRITIS

D. VITILIGO

E. PERNICIOUS ANEMIA

F. PREMATURE TESTICULAR FAILURE

G. ADDISON'S DISEASE

H. PRIMARY BILIARY CIRRHOSIS

I. TEMPORAL ARTERITIS

J. IDIOPATHIC THROMBOCYTOPENIC PURPURA

K. ULCERATIVE COLITIS

L. REGIONAL ILEITIS

M. HYPOPARATHYROIDISM

N. POLYMYOSITIS

O. POLYMYALGIA RHEUMATICA

P. PERIARTERITIS

Q. DERMATOMYOSITIS

R. SCLERODERMA

S. PEMPHIGUS

T. URTICARIA

U. SJOGREN'S SYNDROME

V. MYASTHENIA GRAVIS

W. GLOMERULONEPHRITIS

CARD #133

A. STROKE

B. ENCEPHALITIS

C. MENINGITIS

D. PERIPHERAL NEUROPATHY (I.E. WEAKNESS, NUMBNESS, TINGLING OF HANDS OR FEET)

E. EPILEPSY

F. CONVULSIONS OR SEIZURES

G. BRAIN TUMOR

H. HEAD INJURY

I. OTHER

CARD #141

A. INFLAMMATION OF THE TESTES

B. TUMOR OF THE TESTES

C. HYDROCOELE

D. VARICOELE

E. HERNIA

F. STERILITY

G. OTHER PROBLEM

CARD #156

A. OSTEOARTHRITIS

B. RHEUMATOID ARTHRITIS

C. GOUT

D. OTHER ARTHRITIS

E. SCIATICA

F. DISC TROUBLE

G. SPONDYLITIS

H. LUMBAGO

I. SYSTEMIC LUPUS ERYTHEMATOSIS

J. SCLERODERMA

K. PAGETS DISEASE

L. OTHER

CARD #159

A. DIABETES

B. OVERACTIVE THYROID

C. UNDERACTIVE THYROID

D. PITUITARY GLAND DISORDER

E. ADRENAL GLAND DISORDER

F. PARATHYROID GLAND DISORDER

G. OTHER

CARD #170

A. LESS THAN $3,000

B. $3,000 - $3,999

C. $4,000 - $4,999

D. $5,000 - $5,999

E. $6,000 - $6,999

F. $7,000 - $8,499

G. $8,500 - $9,999

H. $10,000 - $11,999

I. $12,000 - $13,999

J. $14,000 - $16,999

K. $17,000 - $19,999

L. $20,000 - $24,999

M. $25,000 - $29,999

N. $30,000 - $39,999

O. $40,000 - $49,999

P. $50,000 AND OVER

VETERANS QUESTIONNAIRE HAND CARDS

CARD #40

EVERY DAY

4 TO 6 DAYS A WEEK

2 OR 3 DAYS A WEEK

ONCE A WEEK

2 OR 3 DAYS A MONTH

ONCE A MONTH

CARD #40A

LESS THAN ONE A DAY

1 OR 2 A DAY

3 OR 4 A DAY

5 OR 6 A DAY

7 OR 8 A DAY

9 OR 10 A DAY

MORE THAN 10 A DAY

CARD #49

A. ECZEMA

B. ACNE

C. PSORIASIS

D. RECURRENT PIMPLES/BOILS

E. PERSISTANT RASHES

F. SKIN CANCER

G. PORPHYRIA CUTANEA TARDA

H. SPIDER ANGIOMATA

I. PALMAR ERYTHEMA

J. CAPUT MEDUSA

K. XANTHOLASMA

L. OTHER PROBLEMS

CARD #58

A. HEART ATTACK

B. ANGINA

C. HEART FAILURE

D. HIGH BLOOD PRESSURE

E. RHEUMATIC FEVER

F. DISORDERS OF THE HEART VALVES

G. CONGENITAL HERAT DISEASE

H. CLOTS IN LEGS

I. SWELLING OF THE ANKLES

J. OTHER HEART CONDITIONS

CARD #63

A. SINUSITIS

B. FREQUENT NOSE BLEEDS

C. FREQUENT COLDS (MORE THAN 3 A YEAR)

D. ASTHMA

E. CHRONIC BRONCHITIS

F. EMPHYSEMA

G. T.B.

H. BRONCHIECTASIS

I. PLEURISY

J. PNEUMONIA

K. PNEUMONIA MORE THAN ONCE

L. CANCER OF THE LUNG

M. OTHER LUNG DISEASE(S)

CARD #82

A. ESOPHAGITIS

B. HIATUS HERNIA

C. GASTRIC OR DUODENAL ULCER

D. CROHNS DISEASE

E. BOWEL OBSTRUCTION

F. DIVERTICULITIS

G. SPASTIC OR IRRITABLE COLON

H. ULCERATIVE COLITIS

I. ANAL PROBLEMS OR HEMORRHOIDS

J. DYSENTERY

K. MALABSORPTION

L. OTHER GASTRO CONDITIONS

CARD #85

A. KIDNEY OR BLADDER STONES

B. KIDNEY INFECTION

C. NEPHRITIS

D. RENAL COLIC

E. BLADDER INFECTION

F. DISORDERS OF THE PROSTATE

G. URETHRITIS

H. GONORRHEA

I. SYPHILIS

J. HERPES

K. OTHER PROBLEMS

CARD #89

A. A CANCER

B. A TUMOR

C. A LUMP

D. A GROWTH

E. A SARCOMA (TUMOR OR SOFT TISSUE)

F. A TUMOR OF THE EYE

G. A TUMOR OF THE TESTES

CARD #90

A. HIVES

B. OTHER SKIN RASHES

C. HAYFEVER (VASOMOTOR RHINITIS)

D. ASTHMA

E. STOMACH UPSETS

F. OTHER ALLERGIES

CARD #91-92

A. LUPUS ERYTHEMATOSIS

B. HASHIMOTO'S THYROIDITIS

C. RHEUMATOID ARTHRITIS

D. VITILIGO

E. PERNICIOUS ANEMIA

F. PREMATURE TESTICULAR FAILURE

G. ADDISON'S DISEASE

H. PRIMARY BILIARY CIRRHOSIS

I. TEMPORAL ARTERITIS

J. IDIOPATHIC THROMBOCYTOPENIC PURPURA

K. ULCERATIVE COLITIS

L. REGIONAL ILEITIS

M. HYPOPARATHYROIDISM

N. POLYMYOSITIS

O. POLYMYALGIA RHEUMATICA

P. PERIARTERITIS

Q. DERMATOMYOSITIS

R. SCLERODERMA

S. PEMPHIGUS

T. URTICARIA

U. SJOGREN'S SYNDROME

V. MYASTHENIA GRAVIS

W. GLOMERULONEPHRITIS

CARD #93

A. STROKE

B. ENCEPHALITIS

C. MENINGITIS

D. PERIPHERAL NEUROPATHY (I.E. WEAKNESS, NUMBNESS, TINGLING OF HANDS OR FEET)

E. EPILEPSY

F. CONVULSIONS OR SEIZURES

G. BRAIN TUMOR

H. HEAD INJURY

I. OTHER

CARD #101

A. INFLAMMATION OF THE TESTES

B. TUMOR OF THE TESTES

C. HYDROCOELE

D. VARICOELE

E. HERNIA

F. STERILITY

G. OTHER PROBLEM

CARD #116

A. OSTEOARTHRITIS

B. RHEUMATOID ARTHRITIS

C. GOUT

D. OTHER ARTHRITIS

E. SCIATICA

F. DISC TROUBLE

G. SPONDYLITIS

H. LUMBAGO

I. SYSTEMIC LUPUS ERYTHEMATOSIS

J. SCLERODERMA

K. PAGETS DISEASE

L. OTHER

CARD #119

A. DIABETES

B. OVERACTIVE THYROID

C. UNDERACTIVE THYROID

D. PITUITARY GLAND DISORDER

E. ADRENAL GLAND DISORDER

F. PARATHYROID GLAND DISORDER

G. OTHER

Spouse Questionnaire
and
Hand Cards

SPOUSE QUESTIONNAIRE

SPOUSE

QUESTIONNAIRE FOR AGENT ORANGE

DATE OF INTERVIEW:_____

INTERVIEWER ID#:_____

PLACE OF EXAMINATION:_____

First, I would like to ask you a few general questions about you and your family. This information is important for statistical purposes, to see how people in this survey compare with the rest of the population.

1. What is your full name?

NAME:_____
FIRST MIDDLE LAST

2. What is your birthdate?

RECORD:_____
MONTH DAY YEAR

3. Where were you born?

RECORD:_____
CITY STATE

4. What was the highest grade in school you completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL: SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

With which of the following racial or ethnic backgrounds do you identify? Would you say:

Black,..... 1
Hispanic,..... 2
Asian, or..... 3
White?..... 4
OTHER..... 5
→ SPECIFY: _____

6. What is your social security number?

RECORD: ___ ___ ___/___ ___/___ ___ ___ ___

7. Please tell me the different cities you have lived in for at least 2 months, starting with the place you were born.

PLACES RESIDED (CITY, STATE)	DATES OF RESIDENCE FROM	TO
1.		
2.		
3.		
4.		
5.		
6.		

How many sisters and brothers did you have in your family and what are their current ages? Do not include half or step sisters or brothers. IF DECEASED ASK FOR AGE AT DEATH AND CAUSE.

	AGE	CURRENT STATUS		CAUSE OF DEATH
		ALIVE	DECEASED	
Sisters		1	2	
		1	2	
		1	2	
		1	2	
NONE	0	1	2	
Brothers		1	2	
		1	2	
		1	2	
		1	2	
NONE	0	1	2	

9. Did you live with your natural parents during your childhood, or with step parents or guardians?

FATHER		MOTHER	
NATURAL.....	1	NATURAL.....	1
STEP.....	2	STEP.....	2
GUARDIAN.....	3	GUARDIAN.....	3
NONE.....	0	NONE.....	0

IF R DID NOT HAVE A FATHER OR MALE GUARDIAN DURING CHILDHOOD, GO TO Q13.

10. What was your father's (OR_____) major occupation during most of your childhood? (BE SPECIFIC - GET DETAILS)

_____

_____

11. What is his present occupation? (BE SPECIFIC - GET DETAILS)

_____

_____

WRITE "DECEASED" OR "RETIRED" IF APPROPRIATE

12. What was the highest grade in school he completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL (POST COLLEGE EDUCATION):

SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

NONE - 00

IF R DID NOT HAVE A MOTHER OR FEMALE GUARDIAN DURING CHILDHOOD, GO TO Q16.

13. What was your mother's (OR_____) major occupation during most of your childhood? (BE SPECIFIC - GET DETAILS)

_____

_____

14. What is her present occupation? (BE SPECIFIC - GET DETAILS)

_____

_____

WRITE "DECEASED" OR "RETIRED", IF APPROPRIATE

15. What was the highest grade in school she completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL (POST COLLEGE EDUCATION):

SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

NONE - 00

16. The next part of this questionnaire concerns jobs that you have held.

I am interested in all the different kinds of work you have done for a period of one month or more. Please include summer jobs or part-time jobs you may have held while you were going to school.

First, are you currently employed, either full or part-time?

YES..... 1

NO..... 2

A. IF YES -- I would like to start with your current job and work backward. What is your present job title?

IF NO -- I would like to start with your most recent job and work backward. What was your last job title?

RECORD IN APPROPRIATE COLUMN OF GRID. FOR EACH JOB ASK TITLE - COLUMN A, DUTIES - COLUMN B, AND KIND OF COMPANY INDUSTRY - COLUMN C AND RECORD.

CONFIDENTIAL

	16A. TITLE What is (was) your job title?	16B. DUTIES What are (were) your major duties in this job? (PROBE)	16C. KIND OF COMPANY What kind of company is (was) this? What type of industry was that in?
Current (or most recent) job.			
Before that?			
Before that?			
Before that?			

	16A. TITLE	16B. DUTIES	16C. KIND OF COMPANY
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			
Before that?			

17. On this card (HAND CARD 17) is a list of exposures that might affect your health. Please tell me about these or other substances you think might have been harmful to which you may have been exposed in any of these jobs. Let's start with your present/last job and work back. Were you exposed to any harmful substances on this job?

ASK FOR <u>EACH JOB</u> MENTIONED IN Q16.

<u>IF YES</u> TO ANY ASK FOR SUBSTANCE - COLUMN A, DATE STARTED JOB - COLUMN B, AND DATE ENDED JOB - COLUMN C.

<u>IF NO</u> ASK FOR START AND END DATES ONLY (B & C).

<u>JOB</u>	17A. What hazards were you exposed to? (RECORD SPECIFICS)	17B. When did you start this job?		17C. When did this job end?	
		MONTH	YEAR	MONTH	YEAR
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					

JOB	17A. What hazards were you exposed to?	17B. When did you start this job?		17C. When did this job end?	
		MONTH	YEAR	MONTH	YEAR
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					
YES - ASK A,B,C NO - ASK B,C DK - ASK B,C					

18. Other than the jobs you have just told me, have you ever worked either for pay or not on a farm or other agricultural setting?

YES.....ASK A & B..... 1
NO.....SKIP TO Q19..... 2

A. When and where did you do this work?

B. What chemicals were you exposed to?

DATES	WHERE	CHEMICALS

19. Have you ever worked with or around anesthetic gases or radiation?

YES.....ASK A & B..... 1
NO.....SKIP TO Q20..... 2

A. When did you work with these?

B. Which anesthetic gases or radiation were you exposed to?

DATES	GASES/RADIATION

). Have you ever regularly smoked cigarettes for at least three months?

YES..... 1
NO.....SKIP TO Q30..... 2

21. Do you smoke cigarettes now? Please include little cigars or brown cigarettes.

YES..... 1
NO.....SKIP TO Q23..... 2

A. On the average, do you smoke more than one cigarette per day?

YES (REGULAR SMOKER)..... 1
NO (OCCASIONAL SMOKER)...SKIP TO Q23.... 2

). At the present time, what is the average number of cigarettes you smoke per day?

RECORD #:_____

23. How old were you when you began smoking cigarettes regularly?

RECORD AGE:_____

24. What is the average number of cigarettes you smoked per day since you began to smoke/when you smoked? Please give your best estimate.

RECORD #:_____

What is the maximum number of cigarettes you ever smoked per day for as long as a year?

RECORD #:_____

NEVER SMOKED FOR
ONE YEAR.....SKIP TO Q27.....97

26. For how many years did you smoke this number of cigarettes per day?

RECORD YEARS:_____

27. Have you ever attempted to stop smoking?

YES..... 1
NO.....SKIP TO Q30..... 2

A. What is the longest time you were able to stop?

RECORD #:_____ DAYS
_____ WEEKS
_____ MONTHS
_____ YEARS

28. How old were you when you stopped smoking cigarettes regularly?

RECORD AGE:_____

29. What was the main reason you stopped smoking?

HEALTH..... 1
ADVERSE PUBLICITY..... 2
OTHER..... 3
→SPECIFY:_____

Have you ever regularly smoked pipes or cigars for at least three months?

YES..... 1
NO.....SKIP TO Q32..... 2

31. Do you smoke pipes or cigars now?

YES..... 1
NO.....SKIP TO Q32..... 2

A. On the average, do you smoke at least one pipeful or cigar each day?

YES (REGULAR)..... 1
NO (OCCASIONAL)..... 2

32. Which do/did you smoke?

PIPE..... 1
CIGAR..... 2
BOTH..... 3

33. At the present time how many pipefuls or cigars do you usually smoke per day?

RECORD #:_____

DON'T SMOKE DAILY.....97

34. How old were you when you began smoking pipes or cigars regularly?

RECORD AGE:_____

35. What is the average number of pipefuls or cigars you smoked per day since you began to smoke/when you smoked? Please give your best estimate.

RECORD #:_____

36. What is the maximum number of pipefuls or cigars you ever smoked per day for as long as a year?

RECORD #:_____

NEVER SMOKED FOR
ONE YEAR.....SKIP TO Q38.....97

37. For how many years did you smoke this number of pipefuls or cigars per day?

RECORD YEARS:_____

38. Have you ever attempted to stop smoking?

YES..... 1
NO.....SKIP TO Q42..... 2

39. What is the longest time you were able to stop?

RECORD #:_____ DAYS
_____ WEEKS
_____ MONTHS
_____ YEARS

40. How old were you when you stopped smoking?

RECORD AGE:_____

41. What was the main reason you stopped smoking?

HEALTH..... 1
ADVERSE PUBLICITY..... 2
OTHER..... 3
→SPECIFY:_____

42. Now let's talk about drinking alcoholic beverages, that is beer, wine, or mixed drinks. Did you ever drink alcoholic beverages on a fairly regular basis?

YES..... 1
NO.....SKIP TO Q44..... 2

A. When did you start drinking alcoholic beverages on a fairly regular basis?

RECORD:_____ DATE

OR

_____ AGE

B. Do you currently drink alcoholic beverages on a fairly regular basis?

YES.....SKIP TO Q43..... 1
NO..... 2

C. When did you last drink on a fairly regular basis?

RECORD:_____ DATE

OR

_____ AGE

43. You said that you (last drank on a fairly regular basis in DATE/are currently drinking on a fairly regular basis). How often did you drink alcohol during the last 3 months (that you did drink)? Would you say:

Every day,..... 6
4 to 6 days a week,..... 5
2 or 3 days a week,..... 4
Once a week,..... 3
2 or 3 days a month, or..... 2
Once a month?..... 1

A. On the days that you (drink/drank) about how many drinks (do/did) you have per day?

RECORD #:_____

B. During the last three months which one of the following beverages did you drink most? Would you say:

Hard liquor,..... 1
Beer or ale, or..... 2
Wine or champagne?..... 3

Have you ever smoked marijuana regularly for a period of at least one month?

YES..... 1

NO.....SKIP TO Q46..... 2

A. When did you start smoking marijuana on a fairly regular basis?

RECORD DATE: ____/____
MONTH YEAR

B. These days, do you smoke marijuana fairly regularly?

YES..... 1

NO..... 2

IF "YES" TO Q44B - ENTER [0][0] [0][0] IN BOX OF Q44C
AND SKIP TO Q45

IF "NO" TO Q44B - ASK Q44C

C. When did you last smoke marijuana on a fairly regular basis?

RECORD DATE: [ ][ ] [ ][ ]
MO. YR.

45. You said that you (last smoked marijuana on a fairly regular basis in the (END DATE)/are currently smoking marijuana on a fairly regular basis). HAND CARD #45 Please look at this card and tell me which category best describes how often you smoked marijuana during the last three months (that you smoked on a fairly regular basis)?

EVERY DAY..... 6
4 TO 6 DAYS A WEEK..... 5
2 OR 3 DAYS A WEEK..... 4
ONCE A WEEK..... 3
2 OR 3 DAYS A MONTH..... 2
ONCE A MONTH..... 1

A. HAND CARD #45A On the days that you smoked marijuana, about how many joints did you smoke per day?

LESS THAN ONE A DAY..... 1
1 OR 2 A DAY..... 2
3 OR 4 A DAY..... 3
5 OR 6 A DAY..... 4
7 OR 8 A DAY..... 5
9 OR 10 A DAY..... 6
MORE THAN 10 A DAY..... 7
→HOW MANY?_____

46. Have you ever used barbiturates regularly for a period of at least one month? You might know barbiturates as "barbs," "downers," Nembutol, Seconal, Amytol, Doriden, Quaalude, Methaqualone, "Sopors," Reds, Rainbows, or Yellow Jackets?

YES..... 1

NO.....SKIP TO Q47..... 2

A. When did you start using barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use barbiturates?

YES.....SKIP TO Q47..... 1

NO..... 2

C. When did you last use barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

47. Have you ever used amphetamines regularly for a period of at least one month? You might know amphetamines as "dexies," "uppers," "bennies," "diet pills," "speed," "crystals," methedrine, Benzadrine or Dexadrine.

YES..... 1

NO.....SKIP TO Q48..... 2

A. When did you start using amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use amphetamines?

YES.....SKIP TO Q48..... 1

NO..... 2

C. When did you last use amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

48. Have you ever used opiates regularly for a period of at least one month? You might know opiates as heroin, morphine, opium, codeine.

YES..... 1

NO.....SKIP TO Q49..... 2

A. When did you start using opiates?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use opiates?

YES.....SKIP TO Q49..... 1

NO..... 2

C. When did you last use opiates?

RECORD: ☐☐ ☐☐
MO. YR.

49. Have you <u>ever</u> used intravenous drugs, "shot up?"

YES.....ASK A..... 1
NO.....SKIP TO Q50..... 2

A. Which ones?

1._____

2._____

3._____

Next we have some questions about your health.

50. First, how tall are you?

RECORD: _____ / _____
FEET INCHES

51. What is your present weight?

RECORD: _____
LBS.

52. Have you ever had any endocrine or hormone problems such as diabetes or thyroid problems (too much or too little)?

YES.....ASK A-D..... 1

NO.....SKIP TO Q53..... 2

A. What is/was the problem?

B. When did the problem first occur?

C. How was the (...) problem treated? (PROBE)

D. Do you still have the (...) problem?

ASK A-D FOR EACH PROBLEM MENTIONED AND RECORD IN APPROPRIATE COLUMN OF CHART.

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED	D. PROBLEM STILL PRESENT	
			YES	NO
			1	2
			1	2
			1	2
			1	2

53. Do you have any chronic medical conditions? By that I mean something which keeps coming back or which requires constant medical treatment?

YES.....ASK A-C..... 1

NO.....SKIP TO Q54..... 2

A. What is/are the condition(s)/

B. When did (...) condition first occur?

C. How has (...) condition been treated? (PROBE)

ASK A-C FOR EACH CONDITION MENTIONED AND RECORD IN APPROPRIATE COLUMN OF CHART.

A. CONDITION	B. DATE FIRST OCCURRED	C. HOW TREATED

54. Now I would like to ask some questions about your reproductive system and any pregnancies you may have had.

At what age did your period first start?

RECORD AGE:_____

55. Other than when you were pregnant, have there been times when you were not having periods or your periods were irregular?

YES.....ASK A-D..... 1

NO.....SKIP TO Q56..... 2

A. What was the problem?

B. When did this first occur?

C. How was it treated? (PROBE)

D. Is it still a problem?

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED	D. PROBLEM STILL PRESENT	
			YES	NO
			1	2
			1	2
			1	2
			1	2

56. Have you ever had fibroids or any other problems with your uterus or womb?

YES.....ASK A-C..... 1
NO.....SKIP TO Q57..... 2

A. What was the problem?
B. When did this occur?
C. How was it treated? (PROBE)

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED

57. Have you ever taken birth control pills?

YES..... 1
NO.....SKIP TO Q58..... 2

A. What dates did you take them?

START DATE	STOP DATE

58. Have you ever been hospitalized for any reason other than childbirth?

YES.....ASK A-C..... 1
NO.....SKIP TO Q59..... 2

A. Why were you hospitalized?
B. When were you hospitalized?
C. What treatement were you given? (PROBE)

A. PROBLEM	B. DATE	C. TREATMENT

59. How would you rate your health today? Would you say it is:

Excellent,..... 1
Good,..... 2
Fair, or..... 3
Poor?..... 4

60. Have you ever suffered from mental or emotional problems such as a nervous breakdown, exhaustion, and so forth?

YES.....ASK A-C..... 1

NO.....SKIP TO Q61..... 2

A. What was the problem?

B. When did this happen?

C. What kind of treatment did you receive?

A. PROBLEM	B. DATE	C. TREATMENT

61. Have you ever felt you were under severe or unusual stress?

YES.....ASK A-C..... 1

NO.....SKIP TO Q62..... 2

A. What was the problem?

B. When did this happen?

C. What did you do about it?

A. PROBLEM	B. DATE	C. WHAT YOU DID

62. Please look at this card (HAND CARD #62) and for each item tell me if you have ever had the problem, and if so, at what age it began and the nature of the problem. First:

	PROBLEM YES	PROBLEM NO	AGE AT ONSET	NATURE OF PROBLEM
Ulcers or other stomach or intestinal problems?	1	2		
Epilepsy or other nervous system disorders?	1	2		
Heart disease?	1	2		
Recurrent urinary system disorders (kidney or bladder trouble)?	1	2		
Chronic lung disease such as tuberculosis or emphysema?	1	2		
Venereal disease?	1	2		
Major nutritional disturbances?	1	2		
High blood pressure?	1	2		

63. Have you ever taken any of the following types of medications regularly and, if so, when?

	YES	NO	DATE
Thyroid medication?	1	2	
Steroids (cortisone)?	1	2	
Anti-arthritic or rheumatoid preparations?	1	2	
Anti-allergy preparations?	1	2	
Tranquilizers?	1	2	
Anti-depressants?	1	2	
Appetite depressants?	1	2	
Anti-convulsants?	1	2	

64. Have you ever been pregnant?

YES.....SKIP TO Q66..... 1

NO..... 2

65. Was there ever a time when you were trying to become pregnant and could not do so?

YES.....SKIP TO Q68..... 1

NO.....SKIP TO INSTRUCTION ABOVE Q70..... 2

66. How many times have you been pregnant?

RECORD #:_____

67. Was there ever a period of time when you were trying to become pregnant, and either could not do so, or it took more than six months to do so?

YES..... 1

NO.....SKIP TO Q70..... 2

68. What is the most number of months or years at one stretch that you tried to become pregnant?

RECORD #:_____ MONTHS

_____ YEARS

69. Did your doctor feel that the delay in this pregnancy may have resulted from medical or other difficulties?

YES.....ASK A..... 1

NO.....SKIP TO INSTRUCTION BOX ABOVE Q70..... 2

A. What was the suspected cause for this delay of pregnancy?

_____

70. Next, I am going to ask you some questions about (each of your pregnancy(ies). I am interested in all of your pregnancies, even if they ended in a miscarriage or abortion.

A. When did your (first, second, etc.) pregnancy end? RECORD MONTH AND YEAR IN COLUMN A OF CHART.

B. What was the birth/due date for this infant? RECORD MONTH AND YEAR IN COLUMN B OF CHART.

C. How many months did this pregnancy last? RECORD NUMBER OF MONTHS IN COLUMN C OF CHART.

D. Did you have any problems during this pregnancy such as infection, unusual bleeding, swelling, high blood pressure, or vomiting? RECORD ANSWER IN COLUMN D OF CHART.

Q66 # OF PREGS. _____

	A. MO/YR	B. BIRTH/ DUE DATE	C. # MONTHS	D. PROBLEMS	E. HAVE MEASLES
First pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Second pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Third pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Fourth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Fifth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Sixth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Seventh pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2
Eighth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 → _____ NO.....2	YES.....1 NO.....2

E. Did you have german measles during this pregnancy or were you exposed to a known case of german measles during this pregnancy? RECORD IN COLUMN E OF CHART. 193b

F. Were you taking any medications or drugs during this pregnancy? RECORD IN COLUMN F OF CHART.

G. How much weight did you gain during this pregnancy? RECORD NUMBER OF POUNDS IN COLUMN G OF CHART.

H. Did this pregnancy end with the birth of a live baby that lived at least one month? RECORD IN COLUMN H OF CHART.

Ha. How did it end? USE CODES IN BOX BELOW. IF ABORTION ASK Hb - ALL OTHERS GO TO NEXT PREGNANCY. RECORD IN COLUMN Ha OF CHART.

Hb. Was there any reason to think that the baby might have had a birth defect? RECORD IN COLUMN Hb OF CHART.

1. LB< 1 month	2. Stillborn	4. Abortion
	3. Miscarriage	5. Ectopic

- CODES FOR COLUMN Ha

F. MEDICATIONS/DRUGS	G. WEIGHT (LBS)	H. LIVE BABY	Ha. HOW END	Hb. REASON FOR BIRTH DEFECT
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO....ASK Ha..........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)..........1 → ______ NO....................2	______	YES...GO TO NEXT......1 → NAME: ______ NO....ASK Ha..........2	______	YES (SPECIFY)......1 → ______ NO................2

71. A. Did you have any problems with your labor or delivery with your (...) pregnancy? DO NOT ASK FOR PREGNANCIES NOT ENDING IN LIVE BIRTH. INSERT FIRST, SECOND, ETC. FOR (...). RECORD IN COLUMN A OF CHART.

194b

B. Was this a girl or boy? RECORD IN COLUMN B OF CHART.

C. How much did he/she weigh at birth? RECORD WEIGHT IN COLUMN C OF CHART.

D. What was his/her length at birth? RECORD LENGTH IN INCHES IN COLUMN D OF CHART.

E. Were there any congenital abnormalities or birth defects in the baby? RECORD IN COLUMN E OF CHART.

F. Did this child have difficulty at the time of delivery? RECORD IN COLUMN F OF CHART.

G. Did the child stay in the nursery after your discharge from the hospital? RECORD IN COLUMN G OF CHART.

A. PROBLEMS	B. GIRL/ BOY	C.	D. LENGTH	E. ABNORMALITIES OR DEFECTS	F. DIFFICULT DELIVERY	G. NURSER
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES... NO....
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES... NO....
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES... NO....
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES... NO....
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES... NO....
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES...1 NO....2
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES...1 NO....2
YES (SPECIFY)....1 → ____ NO..............2	GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)..1 → ____ NO............2	YES (SPECIFY)..1 → ____ NO............2	YES...1 NO....2

RECORD IN COLUMN H OF CHART.

I. Is this child alive at present? RECORD IN COLUMN I OF CHART.

J. Has this child had any serious illnesses such as cancer or leukemia? RECORD IN COLUMN J OF CHART.

K. What was the date of the child's death? RECORD MONTH AND YEAR IN COLUMN K OF CHART.

L. What was the cause of death? RECORD IN COLUMN L OF CHART.

M. FOR DEATH, BIRTH DEFECT, STILLBORN, MISCARRIAGE, OR ABORTION WITH A SUSPECTED BIRTH DEFECT, ASK: Please give me the name and address of the doctor involved with this pregnancy? REFER TO Q70Ha & b, Q71E, Q71L. RECORD IN COLUMN M OF CHART.

H. BREASTFEED (DATES)	I. ALIVE	J. ILLNESSES	K. DATE OF DEATH	L. CAUSE OF DEATH	M. DOCTOR'S NAME/ADDRESS
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO NEXT PREG OR Q72..2	MO____ YR____		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ________ NO..GO TO Q72.......2	MO____ YR____		

IF YES TO Q70Hb OR Q71E.....ASK Q72
IF NONE.....SKIP TO Q73

72. I notice that you had _____ baby(ies) with congenital abnormalities or birth defects. Do you know of anyone in your or the father's family who has had a similar problem?

YES.....ASK A..... 1
NO.....SKIP TO Q73..... 2

A. Who was that?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

73. Do you know of anyone in your or the father's family who has had miscarriages or stillbirths, or any other serious problems with a pregnancy?

YES.....ASK A..... 1
NO.....SKIP TO Q74..... 2

A. Who was that?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

74. Do you know of anyone in your or the father's family who has had a child with serious childhood illness, mental retardation, developmental problems or the like?

YES.....ASK A..... 1

NO.....SKIP TO Q75..... 2

A. Who was that and what was the problem?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

75. Were any of the pregnancies you have mentioned conceived while your husband was on leave from South Vietnam?

YES.....ASK A..... 1

NO.....SKIP TO Q76..... 2

A. Which one?

RECORD PREGNANCY #:_____

The last few questions are about your husband's or partner's health and will be useful in helping us to get a clear picture of his health generally.

76. Compared to other men his age, how would you rate the health of your husband or partner over the past 5 years? Would you say:

Very good,..... 1

Good,..... 2

Fair,..... 3

Poor, or..... 4

Very poor?..... 5

77. Has there been a major change in the health of your husband or partner over the past 10-15 years?

YES.....ASK A..... 1
NO.....SKIP TO Q78..... 2

A. Could you describe this change and give reasons why you think this change has occurred?

_____

_____

_____

_____

78. Compared to other men his age, how much of the time has your husband or partner been happy over the past 5 years? Would you say:

All of the time,..... 1
Most of the time,..... 2
Some of the time,..... 3
A little of the time, or..... 4
None of the time?..... 5

79. Has there been a major change in the behavior of your husband or partner over the past 10-15 years?

YES.....ASK A..... 1
NO.....SKIP TO Q80..... 2

A. Could you describe this change and give reasons why you think this change has occurred?

_____

_____

_____

_____

_____

80. Does the present behavior of your hsuband or partner prevent a normal family life?

YES.....ASK A..... 1

NO.....SKIP TO Q81..... 2

A. In what way does the present behavior of your husband or partner prevent a normal family life?

_____

_____

_____

_____

81. Would you please tell me anything else about your husband's or partner's health and/or behavior we have not mentioned and which you think may be of significance?

_____

_____

_____

_____

IF R IS NOT CURRENTLY MARRIED TO SAMPLED VETERAN...ASK Q'S 82 & 83

IF R IS CURRENTLY MARRIED TO SAMPLED VETERAN...THANK AND TERMINATE

82. Please look at this card (HAND CARD #82) and give me the letter that comes closest to your total family income last year before taxes. Please include all sources, for example, wages, dividends, rentals, welfare, disability, etc.

A.	LESS THAN $3,000.....01	I.	$12,000 - $13,999.....09
B.	$3,000 - $3,999.....02	J.	$14,000 - $16,999.....10
C.	$4,000 - $4,999.....03	K.	$17,000 - $19,999.....11
D.	$5,000 - $5,999.....04	L.	$20,000 - $24,999.....12
E.	$6,000 - $6,999.....05	M.	$25,000 - $29,999.....13
F.	$7,000 - $8,499.....06	N.	$30,000 - $39,999.....14
G.	$8,500 - $9,999.....07	O.	$40,000 - $49,999.....15
H.	$10,000 - $11,999.....08	P.	$50,000 AND OVER.....16

REFUSED.....97
DON'T KNOW.....98

83. Do you own or rent your home (apartment)?

OWN..... 1
RENT..... 2
SOMETHING ELSE..... 3
→ SPECIFY:_____

SPOUSE QUESTIONNAIRE HAND CARDS

CARD #13D-14

A. CHEMICALS, CLEANING FLUIDS OR SOLVENTS (SPECIFY)

B. ASBESTOS, INSULATION MATERIAL

C. INSECTICIDES

D. PLASTICS OR RESINS (SPECIFY)

E. X-RAYS

F. ANESTHETIC GASES

G. RADIOACTIVITY, ISOTOPES

H. PETROLEUM PRODUCTS, FUELS BENZENE (SPECIFY)

I. LEAD OR METAL SMELTING FUMES (SPECIFY)

J. HERBICIDES (PLANT KILLERS)

CARD #18

EVERY DAY

4 TO 6 DAYS A WEEK

2 OR 3 DAYS A WEEK

ONCE A WEEK

2 OR 3 DAYS A MONTH

ONCE A MONTH

CARD #18A

LESS THAN ONE A DAY

1 OR 2 A DAY

3 OR 4 A DAY

5 OR 6 A DAY

7 OR 8 A DAY

9 OR 10 A DAY

MORE THAN 10 A DAY

CARD #36

ULCERS OR OTHER STOMACH OR INTESTINAL PROBLEMS

EPILEPSY OR OTHER NERVOUS SYSTEM DISORDERS

HEART DISEASE

RECURRENT URINARY SYSTEM DISORDERS (KIDNEY OR BLADDER TROUBLE)

CHRONIC LUNG DISEASE SUCH AS TUBERCULOSIS OR EMPHYSEMA

VENERAL DISEASE

MAJOR NUTRITIONAL DISTURBANCES

HIGH BLOOD PRESSURE

CARD #13D-14

A. CHEMICALS, CLEANING FLUIDS OR SOLVENTS (SPECIFY)

B. ASBESTOS, INSULATION MATERIAL

C. INSECTICIDES

D. PLASTICS OR RESINS (SPECIFY)

E. X-RAYS

F. ANESTHETIC GASES

G. RADIOACTIVITY, ISOTOPES

H. PETROLEUM PRODUCTS, FUELS BENZENE (SPECIFY)

I. LEAD OR METAL SMELTING FUMES (SPECIFY)

J. HERBICIDES (PLANT KILLERS)

CARD #18

EVERY DAY

4 TO 6 DAYS A WEEK

2 OR 3 DAYS A WEEK

ONCE A WEEK

2 OR 3 DAYS A MONTH

ONCE A MONTH

CARD #17

A. CHEMICALS, CLEANING FLUIDS OR SOLVENTS (SPECIFY)

B. ASBESTOS, INSULATION MATERIAL

C. INSECTICIDES

D. PLASTICS OR RESINS (SPECIFY)

E. X-RAYS

F. ANESTHETIC GASES

G. RADIOACTIVITY, ISOTOPES

H. PETROLEUM PRODUCTS, FUELS BENZENE (SPECIFY)

I. LEAD OR METAL SMELTING FUMES (SPECIFY)

J. HERBICIDES (PLANT KILLERS)

CARD #45

EVERY DAY

4 TO 6 DAYS A WEEK

2 OR 3 DAYS A WEEK

ONCE A WEEK

2 OR 3 DAYS A MONTH

ONCE A MONTH

CARD #45A

LESS THAN ONE A DAY

1 OR 2 A DAY

3 OR 4 A DAY

5 OR 6 A DAY

7 OR 8 A DAY

9 OR 10 A DAY

MORE THAN 10 A DAY

CARD #62

ULCERS OR OTHER STOMACH OR INTESTINAL PROBLEMS

EPILEPSY OR OTHER NERVOUS SYSTEM DISORDERS

HEART DISEASE

RECURRENT URINARY SYSTEM DISORDERS (KIDNEY OR BLADDER TROUBLE)

CHRONIC LUNG DISEASE SUCH AS TUBERCULOSIS OR EMPHYSEMA

VENERAL DISEASE

MAJOR NUTRITIONAL DISTURBANCES

HIGH BLOOD PRESSURE

CARD #82

A. LESS THAN $3,000.....01

B. $3,000 - $3,999.....02

C. $4,000 - $4,999.....03

D. $5,000 - $5,999.....04

E. $6,000 - $6,999.....05

F. $7,000 - $8,499.....06

G. $8,500 - $9,999.....07

H. $10,000 - $11,999.....08

I. $12,000 - $13,999.....09

J. $14,000 - $16,999.....10

K. $17,000 - $19,999.....11

L. $20,000 - $24,999.....12

M. $25,000 - $29,999.....13

N. $30,000 - $39,999.....14

O. $40,000 - $49,999.....15

P. $50,000 AND OVER.....16

Physical Examination

PHYSICAL EXAMINATION

D.O.B. ..... |_|_| Day |_|_| Month 19|_|_| Year

PLACE OF EXAMINATION _____

EXAMINER _____

TODAY'S DATE ..... |_|_| Day |_|_| Month 19|_|_| Year

TIME COMMENCED ..... |_|_|_|_|

HEIGHT ..... |_|_|_| cms

WEIGHT ..... |_|_|_| Kg

VISUAL ACUITY ..... Right
Left

URINALYSIS

a. pH (*Enter in box*) ..... |_|_|

	NEG	TRACE	POS	NOT KNOWN
b. PROTEIN	☐	☐	☐	☐
c. GLUCOSE	☐	☐	☐	☐
d. KETONES	☐	☐	☐	☐
e. BLOOD	☐	☐	☐	☐

f. R.B.Cs ..... |_|_|_|

g. W.C.C. ..... |_|_|_|

h. CASTS ..... |_|_|_|

A. HEAD, MOUTH, TEETH

(OTHER THAN EYES, CRANIAL NERVES)

A.1 HAIR

	NO	YES
a. FRONTAL BALDNESS	☐	☐
b. OTHER BALDNESS	☐	☐
c. SCALP ALOPECIA	☐	☐
d. FACIAL ALOPECIA	☐	☐

A.2 FACIAL SKIN

	NO	YES
a. ACNE	☐	☐
b. ACNEIFORM SCARS	☐	☐
c. OTHER SCARS	☐	☐
d. ABNORMAL PIGMENTATION	☐	☐
e. OTHER SKIN ABNORMALITY	☐	☐

Describe: _____

_____

A.3 LIPS

	NO	YES
a. ANGULAR STOMATITIS	☐	☐
b. CHEILOSIS	☐	☐

A.4 GINGIVA

	NO	YES
a. MARGINAL GINGIVITIS	☐	☐
b. BLEEDING GUMS	☐	☐

A.5 TONGUE

	NO	YES
a. FISSURES	☐ 1	☐ 2
b. PAPILLARY ATROPHY OR ATROPHIC GLOSSITIS	☐ 1	☐ 2
c. LEUKOPLAKIA	☐ 1	☐ 2

A.6 TEETH

	YES	NO
a. FULL SET OF TEETH, EITHER NATURAL OR ARTIFICIAL *(disregard wisdom teeth)*	☐ 1	☐ 2

b. NUMBER OF TEETH MISSING AND NOT REPLACED BY PROSTHESES ☐☐ (Enter Number)

	SATISFACTORY	UNSATISFACTORY
c. MAINTENANCE OF TEETH OR DENTURES *Tick only one box*	☐ 1	☐ 2

A.7 NOSE

a. NOSTRILS PATENT
(If YES, skip to A.8 If NO, examine each nostril with a speculum)..... YES R ☐ 1 L ☐ 1 NO R ☐ 2 L ☐ 2

b. NASAL POLYP..... YES R ☐ 1 L ☐ 1 NO R ☐ 2 L ☐ 2

c. OTHER PATHOLOGY..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

*Describe:*_____

OFFICE USE ☐☐☐☐

d. Nasal Mucosa Normal NO ☐ YES ☐

A.8 TEMPORAL BRUITS..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

A.9 OTHER SCARS..... NO ☐ 1 YES ☐ 2

*Describe:*_____

OFFICE USE ☐☐☐☐

B. EARS

B.1 PINNAE..... NORMAL R ☐ 1 L ☐ 1 ABNORMAL R ☐ 2 L ☐ 2
If normal, skip to B2.

a. OPERATIVE SCAR..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

b. OTHER ABNORMALITY..... R ☐ 1 L ☐ 1 R ☐ 2 L ☐ 2

*Describe:*_____

OFFICE USE ☐☐☐☐

B.2 AUDITORY CANALS ..... NORMAL R ☐ 1 L ☐ 1 — ABNORMAL R ☐ 2 L ☐ 2
If normal, skip to B.3

a. ACUTE OTITIS EXTERNA ..... NO R ☐ 1 L ☐ 1 — YES R ☐ 2 L ☐ 2

b. CHRONIC OTITIS EXTERNA ..... R ☐ 1 L ☐ 1 — R ☐ 2 L ☐ 2

c. CANAL OCCLUDED PARTIALLY OR COMPLETELY ..... R ☐ 1 L ☐ 1 — R ☐ 2 L ☐ 2
If not occluded, skip to B.3

d. IS OCCLUSION PARTIAL OR COMPLETE? ..... PARTIAL R ☐ 1 L ☐ 1 — COMPLETE R ☐ 2 L ☐ 2

e. IS CERUMEN THE CAUSE OF THE OCCLUSION? ..... NO ☐ 1 — YES ☐ 2

g. OTHER CAUSE OF OCCLUSION ..... NO ☐ 1 — YES ☐ 2
Describe: _____
_____

OFFICE USE ☐☐☐☐

B.3 TYMPANIC MEMBRANE ..... VISIBLE R ☐ 1 L ☐ 1 — NOT VISIBLE R ☐ 2 L ☐ 2
If not visible, skip to C.1

a. IS THE TYMPANIC MEMBRANE NORMAL? ..... NORMAL R ☐ 1 L ☐ 1 — ABNORMAL R ☐ 2 L ☐ 2
If normal, skip to C.1

b. *Describe any abnormality, including scarring:* _____
_____

OFFICE USE ☐☐☐☐

C. EYES

C.1 BLEPHARITIS

a. CURRENT ..... NO R ☐ 1 L ☐ 1 — YES R ☐ 2 L ☐ 2

b. SCARRING ..... R ☐ 1 L ☐ 1 — R ☐ 2 L ☐ 2

C.2 PTOSIS ..... NO R ☐ 1 L ☐ 1 — YES R ☐ 2 L ☐ 2

C.3 CORNEAE, SCLERAE, CONJUNCTIVAE

	NORMAL	ABNORMAL
a. CONJUNCTIVAE	R ☐ 1	R ☐ 2
	L ☐ 1	L ☐ 2
b. SCLERAE	R ☐ 1	R ☐ 2
	L ☐ 1	L ☐ 2
c. CORNEAE	R ☐ 1	R ☐ 2
	L ☐ 1	L ☐ 2

*If any abnormalities, describe:*_____

OFFICE USE ☐☐☐☐

C.4 PUPILS AND IRISES

Are the pupils equal, circular, concentric, and reactive (directly and consensually) to light, and to accommodation?

	NORMAL	ABNORMAL
	R ☐ 1	R ☐ 2
	L ☐ 1	L ☐ 2

*If abnormal, describe:*_____

OFFICE USE ☐☐☐☐

D. NECK, THYROID

D.1 LYMPHADENOPATHY

	NO	YES
a. CERVICAL	☐ 1	☐ 2
b. SUPRACLAVICULAR	☐ 1	☐ 2

*If yes to D.1a and/or D.1b, describe side(s), site(s), consistency, presence of tenderness:*_____

OFFICE USE ☐☐☐☐

D.2 THYROID

a. SIZE

WHO classification, groups 0-3 (Write 0-3)..... ☐

If Thyroid is normal on palpation, skip to D.3.

If Abnormal, answer D.2b-D.2e

	NO	YES
b. PRESENCE OF NODULES	☐ 1	☐ 2
c. ENLARGEMENT OF ISTHMUS	☐ 1	☐ 2
d. TENDERNESS	☐ 1	☐ 2
e. PRESENCE OF BRUIT	☐ 1	☐ 2

D.3 OTHER NECK ABNORMALITIES

NO	YES
☐ 1	☐ 2

*Describe:*_____

OFFICE USE ☐☐☐☐

E. CHEST AND RESPIRATORY SYSTEM

E.1 AXILLARY LYMPHADENOPATHY ..... NO ☐ 1 YES ☐ 2

If yes, describe side(s), site(s), consistency, presence of tenderness: _____

_____

_____

OFFICE USE ☐☐☐☐

E.2 TRACHEAL DEVIATION ..... NO R ☐ 1 YES TO R ☐ 2 TO L ☐ 3

E.3 BEADING OF RIBS ..... NO ☐ 1 YES ☐ 2

E.4 BREASTS

a. GYNAECOMASTIA ..... NO ☐ 1 YES ☐ 2

b. MASSES ..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

E.5 CYANOSIS ..... NO ☐ 1 YES ☐ 2

E.6 DYSPNOEA AT REST ..... NO ☐ 1 YES ☐ 2

E.7 CHEST FORM ..... NORMAL ☐ 1 ABNORMAL ☐ 2

If abnormal, describe: _____

_____

OFFICE USE ☐☐☐☐

E.8 SCARS — THORAX

a. SURGICAL ..... NO ☐ 1 YES ☐ 2

b. OTHER WOUNDS ..... NO ☐ 1 YES ☐ 2

If yes to E.8a and/or E.8b, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

E.9 AUSCULTATION ..... NORMAL ☐ 1 ABNORMAL ☐ 2

If normal, skip to E.10

If abnormal, enter findings:

	UPPER ZONE	MID ZONE	LOWER ZONE
a. DIMINISHED BREATH SOUNDS	R ☐ 1	R ☐ 2	R ☐ 3
	L ☐ 1	L ☐ 2	L ☐ 3
b. ABSENT BREATH SOUNDS	R ☐ 1	R ☐ 2	R ☐ 3
	L ☐ 1	L ☐ 2	L ☐ 3
c. BRONCHIAL BREATH SOUNDS	R ☐ 1	R ☐ 2	R ☐ 3
	L ☐ 1	L ☐ 2	L ☐ 3
d. RALES	R ☐ 1	R ☐ 2	R ☐ 3
	L ☐ 1	L ☐ 2	L ☐ 3
e. RHONCHI	R ☐ 1	R ☐ 2	R ☐ 3
	L ☐ 1	L ☐ 2	L ☐ 3
f. WHEEZE	R ☐ 1	R ☐ 2	R ☐ 3
	L ☐ 1	L ☐ 2	L ☐ 3

E.10 OTHER ABNORMAL CHEST FINDINGS ..... NO ☐ 1 YES ☐ 2

If yes, describe: _____

_____

OFFICE USE ☐☐☐☐

F. CARDIOVASCULAR

F.1 RADIAL PULSE

a. RATE/MIN ..... RATE ☐☐☐

b. RHYTHM ..... REGULAR ☐ 1 IRREGULAR ☐ 2

F.2 BLOOD PRESSURE (Sitting Right Arm)

Enter mm/Hg in boxes ..... SYSTOLIC ☐☐☐

DIASTOLIC ☐☐☐

F.3 DEPENDENT OEDEMA ..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

F.4 ELEVATED JUGULAR VENOUS PRESSURE ..... NO ☐ 1 YES ☐ 2

F.5 CAROTID PULSES

		YES	NO
a.	NORMAL, SYMMETRICAL	☐ 1	☐ 2
	If yes, skip to F.6		
	If no, answer F.5b and F.5c below		
		NO	YES
b.	DIMINISHED PULSE	R ☐ 1	R ☐ 2
		L ☐ 1	L ☐ 2
		NO	YES
c.	BRUIT	R ☐ 1	R ☐ 2
		L ☐ 1	L ☐ 2

F.6 CARDIAC APICAL IMPULSE

		YES	NO		
a.	PALPABLE	☐ 1	☐ 2		
	If not palpable, skip to F.7				
	If palpable, answer F.6b and F.6c below.				
		4	5	6	7
b.	LIES WITHIN INTERCOSTAL SPACE NUMBER	☐ 1	☐ 2	☐ 3	☐ 4
		MEDIAL TO MCL	AT MCL	LATERAL TO MCL	
c.	RELATION TO MIDCLAVICULAR LINE (MCL)	☐ 1	☐ 2	☐ 3	

F.7 PRAECORDIAL THRILLS

		NO		YES
a.	THRILL(s) PRESENT	☐ 1		☐ 2
	If no thrills, skip to F.8			
	If thrills present, answer F.8b and F.8c below			
		NO		YES
b.	SYSTOLIC THRILL	☐ 1	BASE	☐ 2
			APEX	☐ 3
		NO		YES
c.	DIASTOLIC THRILL	☐ 1	BASE	☐ 2
			APEX	☐ 3

F.8 HEART SOUNDS (other than MURMURS)

		NORMAL	ABNORMAL	
a.	1ST HEART SOUND	☐ 1	Accentuated	☐ 2
			Diminished	☐ 3
		NORMAL	ABNORMAL	
b.	2ND HEART SOUND	☐ 1	Accentuated	☐ 2
			Diminished	☐ 3
		ABSENT	PRESENT	
c.	OTHER HEART SOUNDS	☐ 1	☐ 2	
	If present describe: _____			
	_____	☐ S3		
	_____	☐ S4		
		☐ Click		

F.9 MURMUR(s) ..... NO ☐ 1 YES ☐ 2

If no murmurs, skip to F.10

If murmurs found, answer F.9a and F.9b

a. TIMING, INTENSITY, LOCATION OF MURMUR(S)

		SYSTOLIC		
		SOFT	MODERATE	LOUD
SYSTOLIC	APEX	☐ 1	☐ 2	☐ 3
	LEFT STERNAL EDGE	☐ 1	☐ 2	☐ 3
	PULMONARY AREA	☐ 1	☐ 2	☐ 3
	AORTIC AREA	☐ 1	☐ 2	☐ 3

		DIASTOLIC		
		SOFT	MODERATE	LOUD
DIASTOLIC	APEX	☐ 1	☐ 2	☐ 3
	LEFT STERNAL EDGE	☐ 1	☐ 2	☐ 3
	PULMONARY AREA	☐ 1	☐ 2	☐ 3
	AORTIC AREA	☐ 1	☐ 2	☐ 3

b. Shape

☐ Holosystolic
☐ Crescendo
☐ Decrescendo

F.10 LOWER LIMB ISCHAEMIA

Check dorsalis pedis, popliteal and femoral pulses

a. IS THERE EVIDENCE OF LOWER LIMB ISCHAEMIA?..

	NO	YES
R	☐ 1	☐ 2
L	☐ 1	☐ 2

If no ischaemia, skip to F.11

b. IF ISCHAEMIA IS SUSPECTED, INDICATE CHARACTER OF PULSES:

		NORMAL	DIMINISHED	ABSENT
FEMORAL PULSES	R	☐ 1	☐ 2	☐ 3
	L	☐ 1	☐ 2	☐ 3
POPLITEAL PULSES	R	☐ 1	☐ 2	☐ 3
	L	☐ 1	☐ 2	☐ 3
DORSALIS PEDIS PULSES	R	☐ 1	☐ 2	☐ 3
	L	☐ 1	☐ 2	☐ 3

F.11 VARICOSE VEINS

		NO	YES
LOWER LIMBS	R	☐ 1	☐ 2
	L	☐ 1	☐ 2

G. ABDOMEN

G.1 SCARS — ABDOMEN

	NO	YES
a. SURGICAL	☐ 1	☐ 2
b. WOUND	☐ 1	☐ 2

If yes to G.1a and/or G.1b, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

	NO	YES
G.2 ABDOMINAL DISTENSION	☐ 1	☐ 2

If distended, what is the apparent cause of the distension? (e.g. obesity): _____

_____

_____

OFFICE USE ☐☐☐☐

	NO	YES
G.3 HERNIAS	☐ 1	☐ 2

If no abdominal hernia(s), skip to G.4

If hernia(s) present, indicate site:

	NO	YES
R. Groin	☐ 1	☐ 2
L. Groin	☐ 1	☐ 2
Incisional	☐ 1	☐ 2
Umbilical	☐ 1	☐ 2

	NO	YES
G.4 HEPATOMEGALY	☐ 1	☐ 2

If no hepatomegaly, skip to G.5

If Hepatomegaly found, answer G.4a, G.4b, G.4c & G.4d

	ABSENT	PRESENT	
a. PRESENCE OR ABSENCE OF TENDERNESS	☐ 1	☐ 2	
b. SIZE		Moderately Enlarged	☐ 1
		Grossly Enlarged	☐ 2

Span in RML ____cm.

c. HARDNESS	Soft	☐ 1
	Firm	☐ 2
	Hard	☐ 3
d. TEXTURE	Smooth	☐ 1
	Nodular	☐ 2

G.5 SPLENOMEGALY ..... NO ☐ 1 YES ☐ 2

If no splenomegaly, skip to G.6

If splenomegaly found, indicate size: .....

Moderately Enlarged ☐ 1

Grossly Enlarged ☐ 2

G.6 INGUINAL LYMPHADENOPATHY ..... NO ☐ 1 YES ☐ 2

If inguinal lymphadenopathy present, describe side(s), consistency, presence of tenderness: _____

_____

_____

OFFICE USE ☐☐☐☐

G.7 OTHER ABDOMINAL MASSES ..... NO ☐ 1 YES ☐ 2

If yes, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

H. SCROTUM

H.1 PRESENCE OR ABSENCE OF TESTES ..... PRESENT R ☐ 1 L ☐ 1 ABSENT R ☐ 2 L ☐ 2

H.2 HYDROCOELE ..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

H.3 NODULE OF TESTIS OR EPIDIDYMIS ..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

H.4 TUMOUR ..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

If yes, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

H.5 VARICOCOELE ..... NO R ☐ 1 L ☐ 1 YES R ☐ 2 L ☐ 2

H.8 OTHER SCROTAL ABNORMALITY ..... NO ☐ 1 YES ☐ 2

If yes, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

J. RECTAL EXAM

a. Prostate
- ☐ enlarged
- ☐ tender
- ☐ firm

b. Hemacult ☐ Positive ☐ Negative

K. THE BACK, INCLUDING CERVICAL SPINE

K.1 SCOLIOSIS ..... NO ☐ 1 YES ☐ 2

K.2 KYPHOSIS ..... NO ☐ 1 YES ☐ 2

K.3 LORDOSIS ..... NO ☐ 1 YES ☐ 2

K.4 SACRO-ILIAC JOINTS TENDERNESS ..... NO: R ☐ 1 L ☐ 1 YES: R ☐ 2 L ☐ 2

K.5 OTHER SITES OF TENDERNESS IN THE BACK, INCLUDING CERVICAL SPINE ..... NO ☐ 1 YES ☐ 2

If yes, describe: _____

_____

OFFICE USE ☐☐☐☐

K.6 MOBILITY OF CERVICAL SPINE

	NORMAL	RESTRICTED	PAINFUL
a. HEAD NODDING	☐ 1	☐ 2	☐ 3
b. FLEXION	☐ 1	☐ 2	☐ 3
c. EXTENSION	☐ 1	☐ 2	☐ 3
d. LATERAL FLEXION TO THE RIGHT	☐ 1	☐ 2	☐ 3
e. LATERAL FLEXION TO THE LEFT	☐ 1	☐ 2	☐ 3
f. ROTATION TO THE RIGHT	☐ 1	☐ 2	☐ 3
g. ROTATION TO THE LEFT	☐ 1	☐ 2	☐ 3

K.7 MOBILITY OF THORACOLUMBAR SPINE

	NORMAL	RESTRICTED	PAINFUL
a. FLEXION	☐ 1	☐ 2	☐ 3
b. EXTENSION	☐ 1	☐ 2	☐ 3
c. LATERAL FLEXION TO THE RIGHT	☐ 1	☐ 2	☐ 3
d. LATERAL FLEXION TO THE LEFT	☐ 1	☐ 2	☐ 3
e. ROTATION TO THE RIGHT	☐ 1	☐ 2	☐ 3
f. ROTATION TO THE LEFT	☐ 1	☐ 2	☐ 3

K.8 STRAIGHT-LEG-RAISING TEST

	NO	YES
a. PAIN ON STRAIGHT-LEG RAISING	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2

If no pain, skip to K.9
If painful, answer K.8b

	NO	YES
b. IS PAIN INCREASED WITH DORSIFLEXION OF FOREFOOT?	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2

	YES	NO
K.9 SCARS	☐ 1	☐ 2

If yes, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

L. JOINTS

In describing any abnormalities, note swelling, deformity, pain on motion, Herberden's nodes where appropriate, and any other abnormalities

	NORMAL	ABNORMAL
L.1 SHOULDERS	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2

If abnormal, describe: _____

_____

OFFICE USE ☐☐☐☐

	NORMAL	ABNORMAL
L.2 ELBOWS	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2

If abnormal, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

L.3 WRISTS ..... NORMAL R ☐ 1 L ☐ 1 ABNORMAL R ☐ 2 L ☐ 2

If abnormal, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

L.4 HANDS

		NORMAL	ABNORMAL
a.	METACARPO-PHALANGEAL JOINTS	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2
b.	PROXIMAL INTER-PHALANGEAL JOINTS	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2
c.	DISTAL INTER-PHALANGEAL JOINTS	R ☐ 1 L ☐ 1	R ☐ 2 L ☐ 2

If abnormal in 4a-c, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

L.5 HIPS ..... NORMAL R ☐ 1 L ☐ 1 ABNORMAL R ☐ 2 L ☐ 2

If abnormal, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

L.6 KNEES ..... NORMAL R ☐ 1 L ☐ 1 ABNORMAL R ☐ 2 L ☐ 2

If abnormal, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

L.7 ANKLES ..... NORMAL R ☐ 1 L ☐ 1 ABNORMAL R ☐ 2 L ☐ 2

If abnormal, describe: _____

_____

_____

OFFICE USE ☐☐☐☐

	NORMAL	ABNORMAL
L.8 FEET	R ☐ 1	R ☐ 2
	L ☐ 1	L ☐ 2

*If abnormal, describe:*_____

OFFICE USE ☐☐☐☐

M. SKIN, OBESITY

	NO	YES
M.1 ACNE (Other than facial)	☐ 1	☐ 2
M.2 ACNEIFORM SCARRING (Other than facial)	☐ 1	☐ 2
M.3 ABNORMAL PIGMENTATION	☐ 1	☐ 2

*If yes describe:*_____

OFFICE USE ☐☐☐☐

	NO	YES
Hirsutism	☐	☐

Describe_____

	NO	YES
M.4 BLEMISHES	☐ 1	☐ 2
M.5 PETECHIAE	☐ 1	☐ 2
M.6 BRUISING	☐ 1	☐ 2
M.7 SPIDER NAEVI	☐ 1	☐ 2
M.8 FOLLICULAR KERATOSES	☐ 1	☐ 2

M.9 ACROPACHY ..... NO ☐ 1 YES ☐ 2

M.10 OEDEMA ..... NO ☐ 1 YES ☐ 2
(Other than dependent oedema already noted)

M.11 SCARS ..... NO ☐ 1 YES ☐ 2
(Other than those already noted)
If yes, describe: _____
_____
_____

OFFICE USE ☐☐☐☐

M.12 OTHER SKIN ABNORMALITIES ..... NO ☐ 1 YES ☐ 2
If yes, describe: _____
_____
_____

OFFICE USE ☐☐☐☐

	NO	YES
Caput Medusa	☐	☐
jaundice	☐	☐
palmar erythema	☐	☐

M.13 OBESITY ..... NO ☐ 1 YES ☐ 2

M.14 DIET

	NO	YES
Low carbohydrate	☐	☐

Please complete the physical examination summary before discussing the medical examination with the subject.

***Summary* — physical examination**

Do you think from this examination and your impressions that this person may have, or may have had the following conditions?

		1 NO	2 YES	DEGREE OF CERTAINTY (1 = uncertain 5 = completely certain)
1.	**Dermatologic problems**			
	• Severe Acne or acneiform scarring	☐	☐	1 2 3 4 5
	• Porphyria Cutanea Tarda	☐	☐	1 2 3 4 5
2.	**Ears** other.	☐	☐	1 2 3 4 5
	• Infections	☐	☐	1 2 3 4 5
	• Change in amount or consistency of cerumen	☐	☐	1 2 3 4 5
3.	**Eyes**	1	2	
	• Blepharitis	☐	☐	1 2 3 4 5
	• Recurrent eye infections	☐	☐	1 2 3 4 5
5.	**Cardiovascular disease**	☐	☐	1 2 3 4 5
	Specify: _____			
6.	**Chest findings suggestive of chronic lung disease**	1	2	
	• Chronic obstructive airways disease	☐	☐	1 2 3 4 5
	• Localised respiratory disease	☐	☐	1 2 3 4 5
	Specify _____			
7.	**Liver Disease**	1	2	
	• Hepatitis	☐	☐	1 2 3 4 5
	• Cirrhosis	☐	☐	1 2 3 4 5
	• Hepatic/biliary disease other.	☐	☐	1 2 3 4 5
	Specify if known: _____			
8.	**Renal/Urinary Problems**	1 ☐	2 ☐	1 2 3 4 5
	Specify if known: _____			
9.	**Gastrointestinal Conditions**	1 ☐	2 ☐	1 2 3 4 5
	I. Specify: _____			
	II. Specify: _____			
10.	**Neoplasia**	1 ☐	2 ☐	1 2 3 4 5
	Specify: _____			
11.	**Anaemia**	1 ☐	2 ☐	1 2 3 4 5
12.	**Scars**	1	2	
	• Gunshot wounds	☐	☐	1 2 3 4 5
	• Surgical	☐	☐	1 2 3 4 5
	Specify: _____			

	1	2	
13. **Psychological Problems**			
i. Depression	☐	☐	1 2 3 4 5
ii. Emotional Instability	☐	☐	1 2 3 4 5
iii. Other	☐	☐	1 2 3 4 5
Specify: _____			
	1	2	
14. **Diabetes**	☐	☐	1 2 3 4 5
15. **Thyroid Dysfunction**	☐	☐	1 2 3 4 5
Specify: _____			

Are there any other conditions that this person suffers from?

DEGREE OF CERTAINTY

1. _____ 1 2 3 4 5
2. _____ 1 2 3 4 5
3. _____ 1 2 3 4 5
4. _____ 1 2 3 4 5

Are there any other comments you wish to make?

_____

_____

_____

_____

EXAMINER'S SIGNATURE.....

TIME AT COMPLETION..... ☐☐:☐☐

NEUROLOGICAL EXAMINATION

HEAD AND NECK - Normal to Palpations/Inspection ☐Y ☐N Specify Scar ☐
Asymmetry ☐ Depression ☐
Carotid Bruit ☐No ☐R ☐L
Neck Range of Motion ☐ Normal or Decreased to ☐ Left ☐ Right ☐ Forward ☐ Backward

TRUNK

MOTOR SYSTEM - Handedness Right ☐ Left ☐

Gait ☐ Normal or ☐ Broad Based ☐ Ataxic ☐Small Stepped ☐Other-Specify

Associated Movements ☐Arm Swing ☐Normal or Abnormal ☐R ☐L

Muscle Status (strength, tone, volume, tenderness, fibrillations)
Bulk ☐ Normal ☐Abnormal

Tone Upper Extremities ☐Normal or ☐Increased ☐Decreased
☐Right ☐Left

Lower Extremities ☐Normal or ☐Increased ☐Decreased
☐Right ☐Left

Strength - Distal wrist extensors ☐Normal ☐Decreased
Ankle/Toe Dors/Flexors ☐Normal ☐Decreased ☐R ☐L
Proximal Deltoids ☐Normal ☐Decreased ☐R ☐L
Hip Flexors ☐Normal ☐Decreased ☐R ☐L

Abnormal Movements (tremors, tics, choreas, etc.) Fasiculations ☐No ☐Yes (1-4+)
Tenderness ☐No ☐Yes (1-4+)

Tremor ☐No ☐Yes - Specify
Upper Extremity ☐R ☐L ☐Resting ☐Essential ☐Intention
Lower Extremity ☐R ☐L ☐Other

Coordination (a) Equilibratory - Eyes Open
Eyes Closed - Romberg ☐Positive (Abnormal) ☐Negative (Normal)
Right Foot Left Foot

(b) Nonequilibratory (F to N; F to F; H to K) Finger-to-nose-to-finger
☐Normal ☐Abnormal ☐Right ☐Left ☐Both
Heel-Knee-Shin ☐Normal ☐Abnormal ☐Right ☐Left ☐Both
(c) Succession Movements (including check, rebound, posture-holding)
If indicated, check ☐Normal ☐Abnormal ☐R ☐R

Rapidly alternative movements ☐Normal ☐Abnormal ☐R ☐L ☐Both

Skilled Acts (a) Praxis
(b) Handwriting. If indicated, ☐Normal ☐Abnormal
(c) Speech (articulation, aphasia, agnosia) Grossly ☐Normal
☐Abnormal - Specify Dysarthria ☐
Aphasia ☐

Reflexes (0-absent; 1-sluggish; 2-active; 3-very active; 4-transient clonus; 5-sustained clonus)

Superficial	R	L	Deep	R	L	Other	R	L	Abnormal	R	L
									Babinski		
Biceps			Patellar								
Triceps											
			Achilles								
Remarks											

MENINGEAL IRRITATION Spurling Maneuver of Neck ☐Normal ☐Abnormal
☐R ☐L ☐Both
Straight Leg Raising ☐Normal ☐Abnormal ☐R ☐L ☐Both

NERVE STATUS (tenderness, tumors, etc.)

SENSORY SYSTEM (tactile, pain, vibration, position. If positive sensory signs are present, summarize below and indicate details on Anatomical Figure, Std. Form 531)

Light Touch ☐Normal ☐Abnormal
Pin Prick ☐Normal ☐Abnormal (Map on Anatomical Figure)
Vibration (at ankle, 128 hz tuning fork): ☐Normal ☐Abnormal ☐R ☐L ☐Both
Position (Great toe): ☐Normal ☐Abnormal ☐R ☐L ☐Both

CRANIAL NERVES

I R Smell ☐Present ☐Absent
L Smell ☐Present ☐Absent

II Fundus R Normal ☐ Abnormal ☐ Disk Pallor/atrophy
☐Exudate ☐Papilledema ☐Hemorrhage

Fundus L Normal ☐ Abnormal ☐ Disk pallor/atrophy
☐Exudate ☐ Papilledema ☐Hemorrhage

Fields (to confrontation)
Right ☐Normal ☐Abnormal Left ☐Normal ☐Abnormal

III Normal ☐ ☐Abnormal - Specify
IV
VI
Pupils-Size (mm) Equal ☐ Unequal ☐ Difference mm____
Shape, position Round ☐ Other ☐ ☐R ☐L
Light, Reaction Normal ☐ Abnormal ☐ ☐R ☐L
Position of Eyeballs

Movements R L

Nystagmus Rotary ☐ Horizontal ☐ Vertical ☐
(Draw position)

Ptosis R☐ L☐

V Motor R Clench Jaw - Symmetric ☐ Deviated ☐ R☐ L☐
L

Sensory R Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐
L Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐

Corneal Reflex R L

VII Motor R Normal smile ☐Yes ☐No Palpebral Fissure ☐Yes ☐No
L Normal smile ☐Yes ☐No Palpebral Fissure ☐Yes ☐No

IX Palate and Uvula
X Movement Normal ☐ Deviation to ☐R ☐L

Palatal Reflex R ☐Normal ☐Abnormal
L ☐Normal ☐Abnormal

XII Tongue-Protruded-Central ☐ R☐ L☐
Atrophy ☐No ☐Yes

MENTAL STATUS (alert, clear, cooperative, etc.) Gross abnormalities: ☐No ☐Yes - Specify

Neurological Examination

NEUROLOGICAL EXAMINATION

HEAD AND NECK - Normal to Palpations/Inspection ☐Y ☐N Specify Scar ☐
Asymmetry ☐ Depression ☐
Carotid Bruit ☐No ☐R ☐L
Neck Range of Motion ☐ Normal or Decreased to ☐ Left ☐ Right ☐ Forward ☐ Backward

TRUNK

MOTOR SYSTEM - Handedness Right ☐ Left ☐

Gait ☐ Normal or ☐ Broad Based ☐ Ataxic ☐Small Stepped ☐Other-Specify

Associated Movements ☐Arm Swing ☐Normal or Abnormal ☐R ☐L

Muscle Status (strength, tone, volume, tenderness, fibrillations)
Bulk ☐ Normal ☐Abnormal

Tone Upper Extremities ☐Normal or ☐Increased ☐Decreased
☐Right ☐Left

Lower Extremities ☐Normal or ☐Increased ☐Decreased
☐Right ☐Left

Strength - Distal wrist extensors ☐Normal ☐Decreased
Ankle/Toe Dors/Flexors ☐Normal ☐Decreased ☐R ☐L
Proximal Deltoids ☐Normal ☐Decreased ☐R ☐L
Hip Flexors ☐Normal ☐Decreased ☐R ☐L

Abnormal Movements (tremors, tics, choreas, etc.) Fasiculations ☐No ☐Yes (1-4+)
Tenderness ☐No ☐Yes (1-4+)

Tremor ☐No ☐Yes - Specify
Upper Extremity ☐R ☐L ☐Resting ☐Essential ☐Intention
Lower Extremity ☐R ☐L ☐Other

Coordination (a) Equilibratory - Eyes Open
Eyes Closed - Romberg ☐Positive (Abnormal) ☐Negative (Normal)

Right Foot Left Foot

(b) Nonequilibratory (F to N; F to F; H to K) Finger-to-nose-to-finger
☐Normal ☐Abnormal ☐Right ☐Left ☐Both
Heel-Knee-Shin ☐Normal ☐Abnormal ☐Right ☐Left ☐Both

(c) Succession Movements (including check, rebound, posture-holding)
If indicated, check ☐Normal ☐Abnormal ☐R ☐R

Rapidly alternative movements ☐Normal ☐Abnormal ☐R ☐L ☐Both

Skilled Acts (a) Praxis

(b) Handwriting. If indicated, ☐Normal ☐Abnormal

(c) Speech (articulation, aphasia, agnosia) Grossly ☐Normal
☐Abnormal - Specify Dysarthria ☐
Aphasia ☐

Reflexes (0-absent; 1-sluggish; 2-active; 3-very active; 4-transient clonus; 5-sustained clonus)

Deep	R	L	Deep	R	L	Other	R	L	Abnormal	R	L
									Babinski		
Biceps			Patellar								
Triceps											
			Achilles								
Remarks											

MENINGEAL IRRITATION Spurling Maneuver of Neck ☐Normal ☐Abnormal
☐R ☐L ☐Both
Straight Leg Raising ☐Normal ☐Abnormal ☐R ☐L ☐Both

NERVE STATUS (tenderness, tumors, etc.)

SENSORY SYSTEM (tactile, pain, vibration, position. If positive sensory signs are present, summarize below and indicate details on Anatomical Figure, Std. Form 531)

Light Touch ☐Normal ☐Abnormal
Pin Prick ☐Normal ☐Abnormal (Map on Anatomical Figure)
Vibration (at ankle, 128 hz tuning fork): ☐Normal ☐Abnormal ☐R ☐L ☐Both
Position (Great toe): ☐Normal ☐Abnormal ☐R ☐L ☐Both

CRANIAL NERVES

I R Smell ☐Present ☐Absent
L Smell ☐Present ☐Absent

II Fundus R Normal ☐ Abnormal ☐ Disk Pallor/atrophy
☐Exudate ☐Papilledema ☐Hemorrhage

Fundus L Normal ☐ Abnormal ☐ Disk pallor/atrophy
☐Exudate ☐ Papilledema ☐Hemorrhage

Fields (to confrontation)
Right ☐Normal ☐Abnormal Left ☐Normal ☐Abnormal

III Normal ☐ ☐Abnormal - Specify
IV
VI
Pupils-Size (mm) Equal ☐ Unequal ☐ Difference mm____
Shape, position Round ☐ Other ☐ ☐R ☐L
Light, Reaction Normal ☐ Abnormal ☐ ☐R ☐L
Position of Eyeballs

Movements R L

Nystagmus Rotary ☐ Horizontal ☐ Vertical ☐
(Draw position)

Ptosis R☐ L☐

V Motor R Clench Jaw - Symmetric ☐ Deviated ☐ R☐ L☐
L

Sensory R Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐
L Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐

Corneal Reflex R L

VII Motor R Normal smile ☐Yes ☐No Palpebral Fissure ☐Yes ☐No
L Normal smile ☐Yes ☐No Palpebral Fissure ☐Yes ☐No

IX Palate and Uvula

X Movement Normal ☐ Deviation to ☐R ☐L

Palatal Reflex R ☐Normal ☐Abnormal
L ☐Normal ☐Abnormal

XII Tongue-Protruded-Central ☐ R☐ L☐
Atrophy ☐No ☐Yes

MENTAL STATUS (alert, clear, cooperative, etc.) Gross abnormalities: ☐No
☐Yes - Specify

Psychological Assessment

PYSCHOLOGICAL ASSESSMENT

Three alternatives for assessing psychological disorder are presented below and evaluated: clinical interview rating, comprehensive personality assessment, and current symptomatology.

1. Clinical Interview Rating

Purpose. This procedure involves a structured interview designed to elicit information in order to make diagnostic decisions according to standardized operational criteria.

Rationale. Different types of psychiatric disorder, including subtypes of depressive disorder, differ not only in their distribution in the population but in their etiology as well. The natural history, clinical course, indicated treatment modality, prognosis, and response to treatment are specific to diagnostic categories. Thus, specific diagnosis is preferable to the relatively undifferentiated identification of high levels of symptomatology achieved by screening checklists. This procedure was designed in part to improve the generally low reliability of routine clinical psychiatric diagnostic procedures.

Method. The Research Diagnostic Criteria (RDC) consists of a set of specific diagnostic criteria for a selected group of functional psychiatric disorders.[1] There are 25 major diagnostic categories, many of which are further subdivided into nonmutually exclusive subtypes, such as major depressive disorder which has 11 such subtypes. These diagnostic categories are shown in Table 1. The RDC, like other current research diagnostic procedures, requires a distribution of a minimum number of symptoms which meet a minimum standard of severity and further requires that the symptoms are not explainable by physical illness or another

TABLE 1

Table 1.—Research Diagnostic Criteria Diagnoses
Schizophrenia
Acute—chronic
Paranoid
Disorganized
Catatonic
Mixed (undifferentiated)
Residual
Schizo-affective disorder—manic
Acute—chronic
Mainly schizophrenic
Mainly affective
Schizo-affective disorder—depressed
Acute—chronic
Mainly schizophrenic
Mainly affective
Depressive syndrome superimposed on residual schizophrenia
Manic disorder
Hypomanic disorder
Bipolar with mania (bipolar I)
Bipolar with hypomania (bipolar II)
Major depressive disorder
Primary
Secondary
Recurrent unipolar
Psychotic
Incapacitating
Endogenous
Agitated
Retarded
Situational
Simple
Predominant mood
Minor depressive disorder with significant anxiety
Intermittent depressive disorder*
Panic disorder
Generalized anxiety disorder with significant depression
Cyclothymic personality*
Labile personality*
Briquet's disorder (somatization disorder)*
Antisocial personality*
Alcoholism
Drug use disorder
Obsessive compulsive disorder
Phobic disorder
Unspecified functional psychosis
Other psychiatric disorder
Schizotypal features*
Currently not mentally ill
Never mentally ill*

* These conditions are diagnosed on a longitudinal or lifetime basis. All other conditions are diagnosed on the basis of current or past episodes of psychopathology.

NOTE: Tables 1 and 2 from Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteris: Rationale and reliability. Archives of General Psychiatry 1978; 35:773-782.

psychiatric diagnosis.[2] For example, the inclusion and exclusion criteria for major depressive disorder are summarized in Table 2. TABLE 2

The Schedule for Affective Disorders and Schizophrenia (SADS) is a structured interview guide with rating scales designed specifically for collecting information relevant to the diagnostic categories of the RDC. The 78 page protocol contains over 200 scales and check-list items and requires 90-120 minutes to complete. Since many of the items require a fairly sophisticated knowlege of manifest psychopathology, the ratings should be done by clinical personnel with some professional background. Part I of the SADS collects information on any current episode and the prior week; part II collects information concerning past episodes.

All diagnoses for the SADS-RDC are judged as either not present, probable or definite. For affective disorders it also distinguishes episodic disorders which involve a sustained disturbance clearly distinguished from previous functioning from intermittent and chronic disorders which do not have a clear onset and in which there are recurrent periods of disorder separated by normal periods.[3]

The reliability of the SADS-RDC has been shown to be quite high, even under test-retest conditions where a much lower reliability is expected.[1,3] It has been used successfully in clinical populations,[4] and has proved to be acceptable in community populations encompassing a wide range of socioeconomic, age, race, and ethnic groups.[3,5]

Table 2. RDC Criteria for Major Depressive Disorder

A. One or more distinct periods with dysphoric mood or pervasive loss of interest or pleasure. The disturbance must be prominent and relatively persistent but not necessarily the most dominant symptom.

B. At least five of the following are required as part of the episode for definite and four for probable.
   1. poor appetite or weight loss or increased appetite or weight gain
   2. sleep difficulty or sleeping too much
   3. loss of energy, fatigability or tiredness
   4. psychomotor agitation or retardation
   5. loss of interest or pleasure in usual activities including social contact or sex
   6. feeling of self-reproach or excessive or inappropriate guilt
   7. complaints or evidence of diminished ability to think or concentrate
   8. recurrent thoughts of death or suicide, or any suicidal behavior.

C. Duration of dysphoric features at least one week (definite if lasted more than two weeks, probable if one to two weeks).

D. Sought or was referred for help from someone during dysphoric period, took medication, or had impairment in functioning with family, at home, at school, at work or socially.

E. None of the exclusionary criteria which suggest schizophrenia is present.

F. Does not meet the criteria for schizophrenia, residual subtype.

2. Comprehensive Personality Assessment

Purpose. This procedure is designed to identify clinically relevant aspects of personality which have been relatively stable over time.

Rationale. This procedure is intended to provide a standardized, quantitative assessment of personality with predictive utility in an actuarial sen e.

Method. The Minnesota Multiphasic Personality Inventory (MMPI) measures 26 areas of personality traits and attitudes of which nine are scales of personality characteristics indicative of clinical syndromes. These include depressive affect; manic affect; obsessive and compulsive states; delusions, hallucinations, illusions, ideas of reference; phobias; and, sadistic, masochistic trends.[6] The instrument consists of 550 statements which are self-administered and which require 30-90 minutes to complete. Subjects are scored on individual scales and profile scores may be used to separate diagnostic groups. The scale has been widely used on clinical and normal populations and extensive normative data is available, particularly for the MMPI-D Depression subscale.[7]

3. Current Symptomatology

Purpose. This procedure provides for the rapid identification of high levels of current psychiatric symptomatology.

Rationale. This procedure is primarily intended for screening purposes and for comparison of groups in terms of level of symptomatology. In addition, various scales are used to assess changes in symptom level among individuals previously diagnosed. The procedure itself is not intended to provide a precise psychiatric diagnosis. In addition, the focus tends to be on

disorder as a current state rather than as an enduring personality trait. Although generally intended to measure specific types of disorder, such as depression, the scales tend to be highly associated with one another suggesting that they assess a general form of nonspecific, mild psychiatric disorder of the depressive-anxiety type.[8] The primary advantage of these scales is that they are easy to administer and are generally sensitive to current levels of impairment.

Method. Considering both comprehensiveness and previous research applications, the Hopkins Symptom Checklist (SCL-90) represents the instrument of choice.[9] Subjects self-report the occurrence of 90 symptom items during the last week using a five point rating scale. The inventory assesses nine primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Substantial standardization and psychometic data are available for the scales which comprise this inventory.[10]

Evaluation

The three assessment procedures summarized above represent radically different approaches. First, they are intended to assess different aspects of psychological disorder: psychiatric diagnosis, personality functioning, and current psychiatric symptomatology, respectively. While diagnosis is preferable for the reasons listed above, the number of individuals falling into each diagnostic category will be limited, particularly for relatively rare conditions, making comparisons across populations difficult.

This especially true with respect to current as opposed to lifetime diagnosis. On the other hand, the symptom method has the advantage of yielding a larger classification as "impaired", but these individuals will typically represent a relatively heterogeneous group with respect to underlying diagnosis, with the implication that different etiological patterns will be present. Thus the decision here is in part a function of the number of individuals studied. With a relatively small population the symptom checklist is probably desirable; as the sample size increases the use of the diagnostic interview becomes more appropriate from a statistical viewpoint. On the other hand, the diagnostic interview is considerably more expensive than either the personality or symptom assessment both in terms of the actual monetary costs and in terms of professional time involved. If the diagnostic interview is undertaken, some form of preliminary screening may be desirable.

The differences between the personality and symptom assessment methods are less marked. The major distinction lies in personality trait versus symptom state. The first seeks to assess relatively long-term disorders in functioning while the latter is directed towards current functioning. Presumably the symptom measures are more reactive to recent events than are the personality measures. This distinction may be of more analytic than practical utility. To the extent that the focus is on relatively stable, enduring forms of disorder, however, then the personality assessment is preferable. The symptom checklist, however, is more clearly directed towards the identification of disorder of a diagnostic type than are the personality measures. That is, they assess

symptoms associated with clinical syndromes which would be considered relevant to a diagnosis, whereas the items on the MMPI frequently lack any inherent meaning in and of themselves and are of import only in terms of actuarial prediction.

Finally, all three forms of assessment are subject to certain potential forms of distortion and bias. The two self-report measures may incorporate response bias including selective presentation of self, social desirability, acquiesence, etc. The clinical interview is subject to distortion in the reports to the interviewer and in the interviewer's interpretation of these reports. The use of standardized measures in all three instances which have been extensively studied from this perspective, however, should tend to minimize this type of problem.

REFERENCES

1. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: Rationale and reliability. Archives of General Psychiatry 1978;35:773-782.
2. Robins LN, Helzer JE, Croughan J, Ratcliff KS: National Institute of Mental Health Diagnostic Interview Schedule. Archives of General Psychiatry 1981; 38: 381-389.
3. Weissman MM, Myers JK: Affective disorders in a US urban community. Archives of General Psychiatry 1978; 35: 1304-1311.
4. Endicott J, Spitzer RL: Use of the Research Diagnostic Criteria and the Schedule for Affective Disorders and Schizophrenia to study affective disorder. American Journal of Psychiatry 136; 1979: 52-56.
5. Vernon SW, Roberts RE: Use of the SADS-RDC in a tri-ethnic community survey. Archives of General Psychiatry, in press.
6. Miller DC: Handbook of Research Design and Social Measurement. New York: Longman, 1977.
7. Rehm LP: Assessment of depression. In Hersen M, Bellack AS (eds.) Behavioral Assessment. New York: Pergamon Press,1981. pp246-295.
8. Dohrenwend BP, Shrout PE, Egri G, Mendelsohn FS: Nonspecific psychological distress and other dimensions of psychopathology: Measures for use in the general population. Archives of General Psychiatry. 1980; 37:12229-1236.
9. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L: The Hopkins Symptom Checklist (HSCL): A measure of psrimary symptom dimensions. Pharmacopsychiat 7; 1974: 79-110.
10. Derogatis LR: SCL-90 Administration, scores and procedures manual-I. Johns Hopkins University, 1977.

Neuropsychological Assessment

4

NEUROPSYCHOLOGICAL ASSESSMENT

Clinical neuropsychology is concerned with the assessment of the behavioral manifestations of brain dysfunction. It enhances clinical neurological observation by adding precision and increased sensitivity to the measurement, as well as defining normal variance which makes the diagnosis of defects more precise. Neuropsychological assessment can be especially useful in assessment of mild impairments due to early brain disease or diffuse brain damage. Neuropsychological assessment involves measurement and description of various cognitive abilities, including memory, language, abstract reasoning, ability to concentrate, orientation, visuospatial and visuomotor skills. By evaluating performance in these areas, it is possible to aid in the diagnosis of the neurological problem, as well as to differentiate between neurological and psychological symptoms. Neuropsychological assessment is often considered to be a special form of the neurological evaluation. Since it focuses only on behavioral manifestations, it is possible to be more precise and refined in the evaluation.

Toxic substances have been found to affect cognitive functioning in various ways, dependent upon the type of toxin. However, there are some symptoms which are common to many of the toxins. These include impairment of alertness, poor concentration, disorientation, memory loss, emotional disturbances (heightened or flattened affect, irritability, instability, etc.), speech disturbances, headaches and slowed motor speed and incoordination of movement. Clinical neuropsychology is well-suited to evaluating the presence and extent of these types of disturbances.

The neurological effects of this Agent Orange are not presently known, therefore, it is necessary to assess all aspects of cognitive functioning, including intellect, language, perceptual-motor abilities and memory. The presence and extent of any deficits can be determined by a comprehensive, thorough neuropsychological examination.

In order to assess the deficits, the individual's performance can be compared to either his prior performance (Army Classification Battery) or the average ability expected of a person of that age and educational level. In most tests, comparison to premorbid levels of functioning is preferred. The premorbid performance can be approximated by the various examinations given in schools and the armed forces.

The battery consists of various tests that measure intelligence, language, memory, visual-spatial and visual-motor abilities and general level of functioning.

Intellectual ability will be assessed with the Wechsler Adult Intelligence Scale (WAIS) (1). This test samples many types of intellectual functions, including language, memory and visuo-spatial abilities. There is a large amount of information available concerning the WAIS, and normative data are available on various populations. This test can be used to compare the subject's current performance to his premorbid performance in several ways. First of all, the scores derived from this test can be compared to other intelligence tests given previously. Secondly, performance on several of the subtests is not usually impaired in mild and moderate brain damage and can be used to estimate premorbid functioning. Therefore, intellectual deterioration can be determined from this comparison. The WAIS provides other valuable information in evaluating specific deficits because some of the subtests are very sensitive to certain types of impairment ([2]).

The WAIS consists of 11 subtests:

1. Information - This subtest is a measure of general knowledge and is usually a good estimate of premorbid intellectual ability.

2. Comprehension - This subtest consists of common sense questions and interpretation of proverbs. It gives some indication of the individual's social reasoning and ability to think in the abstract dimension.

3. Arithmetic - This subtest consists of 14 oral math problems increasing in difficulty. This tests not only immediate memory and concentration, but also the ability to manipulate numbers mentally and keep track of the various operations required.

4. Similarities - The subject is asked to explain the relationship of word pairs (e.g., apple, pear). This also is a good measure of general intellectual ability, the "g" or global intelligence factor.

5. Digit Span - This subtest has two sections. In the first, a list of numbers must be repeated in the sequence it was given, and in the second, the list must be reversed. This tests not only immediate auditory memory, but, in the backward version, the ability to keep track of new items of information and reverse them from memory.

6. Vocabulary - There are 40 words arranged in order of difficulty. This subtest tends to be one of the least affected subtests with diffuse or nonfocal brain damage, and therefore, it is regarded as a good indicator of premorbid intellectual ability.

7. Digit Symbol - This is a coding task requiring the subject to match symbols with numbers. It is a test of motor persistence and speed, ability to sustain attention and visual-motor coordination.

8. Picture Completion - There are 21 incomplete pictures in this subtest, and the subject must point out the missing detail.

9. Block Design - The subject must duplicate designs made by the examiner with red- and white-colored blocks. This tests visuo-spatial organization.

10. Picture Arrangement - This test consists of a cartoon which must be arranged into a meaningful story. It is thought to reflect social sophistication and ability to organize events sequentially.

11. Object Assembly ("jigsaw type") - This is another measure of visual-spatial reasoning. The subject is asked to assemble jigsaw-type puzzles of familiar objects (e.g., elephant).

As previously mentioned, results of the WAIS can be compared with results of the Army Classification Battery in order to provide estimates of pre-exposure intellectual functioning. An added feature of the WAIS is that it contains measures of old information ("crystallized intelligence"), as well as measures of new learning ability ("fluid intelligence"). The latter is believed to be selectively impaired in most cases of diffuse cerebral dysfunction.

General cognitive functioning will be assessed, not only from previously described subtests of the WAIS, but also from results of nonverbal tests. The Porteus mazes tests (2) the ability of the subject to plan ahead and evaluate the consequences of his moves in his completion of this maze task. The test is carefully designed to have a "low floor" and "high ceiling," so that subjects at all levels of intellectual functioning can be reliably tested.

The Raven Progressive Matrices (3) test is a series of pattern-matching end abstract reasoning tasks in a multiple choice format. The matrices increase in difficulty and have been shown to be of great diagnostic value, as well as clinical utility in cases of malingering and other so-called "functional disorders." This test is also considered to be of great value in evaluating diffuse cerebral dysfunction.

Memory will be assessed in the battery, because memory deficits are one of the most frequently occurring problems with many types of brain damage. The Wechsler Memory Scale is an excellent measure since it assesses three types of memory: immediate, short- and long-term. The Wechsler Memory Scale (4,5) consists of seven subtests.

The Personal and Current Information and Orientation section tests the subject's knowledge of current events and assesses long-term memory for personal information. The Logical Memory section tests short-term memory. The subject must listen to each of two paragraphs and then try to retell the story immediately after the reading, including as many details as possible. The Associate Learning Task also tests short-term memory. It consists of word pairs, some easy (baby-cries) and some hard (cabbage-pin). The subject is read the list of pairs, and then given the first word of each pair, must recall the other. Three trials are given. Immediate memory is tested in the auditory modality by the Digit Span subtest (similar to the WAIS) and in the visual modality by the Visual Repro task. The subject is shown a geometric design for ten seconds and is then asked to draw it from memory. This test has been given to many subjects, and norms on various populations are available.

The Benton Visual Retention test (6) is a widely-used test of visual, immediate memory and should be used to supplement the WMS. It consists of several sets of geometric designs with varying administration techniques. Visual-motor abilities will also be studied in this proposal. These abilities are complex, consisting of the integration of visual input and motor output. Integrity of this function will be determined by several tests.

The Bender Gestalt (7) requires copying of nine geometric designs. It is a measure of complex visuographic integration[1] and is a sensitive indicator of brain damage. The Block Design and Object Assembly subtests of the WAIS also measure visual-motor abilities and will be included in the evaluation.

Verbal functioning and language abilities will also be assessed. The Token Test (8,9) is very sensitive to subtle language deficits which may not be apparent in the subjects conversational speech. It consists of a series of commands to which the subject must move the appropriate tokens in response. The tokens are round and square, large and small and red, yellow, green, white or blue.

The Controlled Word Association task (10,11) consists of three word-naming tests in which the subject is asked to list as many words as he can think of which begin with a certain letter. This is a reliable measure of verbal fluency.

The ability to produce words in a certain category is often decreased dramatically in cases of brain damage, and therefore, the use of this measure will uncover relatively subtle deficits in language functioning.

All of the tests described above can be given by research technicians and can be scored by a Master's level psychologist.

The time requirements are as follows:

1. WAIS, 1½-2 hrs.
2. Tokent Test, 5 min.
3. Controlled Word Association, 5 min.
4. Bender Gestalt, 10 min.
5. Raven Progressive Matrices, 20 min.
6. Wechsler Memory Scale, 20 min.
7. Benton Visual Retention Test, 15 min.
8. Porteus Maze Test, 10 min.

It is recommended that a neuropsychologist be used as a consultant to the project. His/her responsibilities would be in training the research technicians in supervising psychological personnel and in providing modifications to the proposed battery, if changes are found to be necessary in pilot testing.

References

1. Matarazzo, V.D. Wechler's Measurement and Appraisal of Adult Intelligence (5th ed.), Baltimore: Williams & Wilkins, 1972.

2. Lezak, M.D. Neuropsychological Assessment, New York: Oxford University Press, 1976.

3. Archibald, Y.M., Wepman, J.M. and Jones, L.V. Performance on nonverbal cognitive tests following unilateral cortical injury to right and left hemispheres. J. of Nervous and Mental Disease, 1967, 145, 25-36.

4. Hulicka, I.M. Age differences in WMS scores. Journal of Genetic Psychology, 1966, 109, 135-145.

5. Wechsler, D. A standardized memory scale for clinical use. Vol. 4, 1945, 19, 87-95.

6. Benton, A.L. Revised visual retention test. New York: Psychological Corporation, 1974.

7. Bender, L. A visual motor Gestalt test and its clinical use. American Orthopsychiatric Association Research Monographs, 1938, #3.

8. Boller, F. and Vignolo, L.A. Latent sensory aphasia in hemisphere-damaged patients: An experimental study with the Token Test. Brain, 1966, 89, 815-831.

9. Di Renzi, E. and Vignolo, L.A. The Token Test: A sensitive test to detect disturbances in aphasics. Brain, 1962, 85, 665-678.

10. Benton, A.L. The measurement of aphasic disorders. In: A. Cáceres Velasquez, Aspectos patólogicos del lengage. Lima: Centro Neuropsicologico, 1973a.

11. Borkowski, J.G., Benton, A.L. and Spreen, Q. Word fluency and brain damage. Neuropsychologia, 1967, 5, 135-140.

A

APPENDIX A

GLOSSARY

GLOSSARY

Terms

Antipersonnel gas — Any gas designed to kill, injure or obstruct personnel (e.g. teargas).

Battalion — Tactical military unit, consisting of headquarters and four companies. In Vietnam, Army battalions each had specific areas of operation; all four companies would be stationed within range of their hardest hitting weapons, which were usually stationed at battalion headquarters.

Bias — Systematic error which leads to a distortion of the relationship between two variables in an epidemiologic study.

BIRLS file — VA computerized information file; Veterans and Beneficiaries Identification and Records Location System.

Blind known standard — Used to test the validity of a laboratory procedure. Samples of known value are sent to a laboratory for blind evaluation; the reported value and the true value are compared.

Blind split sampling — Used to test the reliability of a laboratory procedure. A sample is split into two; both are sent to a laboratory for blind evaluation as two independent samples; the reported values for the two splits are compared.

Cacodylic acid	An arsenic containing herbicide. The sodium salt of cacodylic acid was used to formulate Agent Blue.
Carcinogenic	Causing cancer.
Case	Subject in a case-control study who is selected on the basis of having some particular disease.
Case-control study	Also known as a retrospective study. Epidemiologic study in which case subjects are selected on the basis of having a particular disease and control subjects are selected on the basis of absence of the disease.
Chloracne	An acneform eruption of the skin caused by exposure to various chemicals, including dioxin.
Chloroquine	Drug used for the prophylaxis and treatment of malaria.
Cohort	A group of individuals who share certain characteristics (e.g., similar exposure to Agent Orange).
Cohort study	Also known as prospective study. The study population is selected on the basis of known exposure and known non-exposure to some agent. This population is followed into the future and the occurrence of disease is observed.
Company	Military unit; subdivision of a battalion; approximately 180-200 men per company.
Company Morning Reports	Daily reports at the company level which lists significant events relating to individuals such as transfers, temporary duty assignments, R and R, etc.

Confounding factors

In epidemiology, factors which may distort the apparent relationship between two variables under study.

Congenital defects

Defects existing at the time of birth.

Control group — A comparison group. In a case-control study, the control group consists of those without the disease of interest; in a cohort study, the control group consists of those without the exposure of interest.

Cross-sectional Study

(or Survey). Epidemiologic study in which the current health status of a population is assessed and compared to (usually) current exposure status.

Dapsone — Drug used as a supplement to chloroquine/primaquine malaria prophylaxis against chloroquine-resistant falciparum malaria.

Dioxin — In this protocol, dioxin refers to 2,3,7,8 - TCDD.

Epidemiology
Epidemiologic Study

The study of the distribution and determinants of stages of health in human populations.

Follow-up study — Another term for cohort study.

half life — The time in which half of a beginning quantity of material will be altered or degraded.

HERBS tape — Acronym for the computerized records of herbicide spray operations in South Vietnam.

Historical Cohort (nonconcurrent cohort) — Variant of the cohort study design. Exposure has taken place in the past and the study population is assembled from past records. The study population is followed to some subsequent point in time to observe for disease outcome.

Hypoplasia — Underdevelopment of tissue or an organ, usually due to a decreased number of cells.

Involution — A lessening of the size of a tissue caused by a reduction in the number of its component cells, without degeneration.

Malathion — O, o-dimetryldithiophosphate; an organophosphorous compound used in Vietnam as an insecticide to control mosquito populations.

Matching — The process of selecting comparison group members so they are similar to study group members on specific suspected confounding factors.

Miscarriage — Spontaneous expulsion of the products of pregnancy before the middle of the second trimester.

Misclassification — Occurs in epidemiologic studies when an individual is assigned an incorrect value for a study parameter.

Morbidity — Non-fatal disease.

Nephropathy — Disease of the kidney.

Neuropathy — Disorder of the nervous system.

Nonscientific Media

Magazines, newspapers, popular books, brochures, films, congressional testimonies; popular press.

Nosologist — A specialist in the classification of diseases.

Odds ratio — An estimate of risk calculated in a case-control study design.

Operation Ranch Hand

The U.S. Air Force herbicide spray operation in Vietnam from 1962 to 1971.

Picloram — An herbicide used in combination with 2,4-D to form Agent White.

Popular Press — Synonym for nonscientific media. Magazines, newspapers, films, brochures, popular books, congressional testimonies.

Porphyria Cutanea Tarda

Disorder of porphyrin metabolism which includes skin lesions.

Proportionate Mortality (or morbidity) Analysis

Analysis which compares the relative importance of a specific cause of death (or disease) to the total number of deaths (or diseases in a population).

Reliability — Precision or repeatability of a test. Consistency of results when a test is performed more than once on the same individual or sample under the same conditions is a measure of reliability.

Risk Ratio — Ratio of disease rates for those with and without the hypothesized causal factor.

Secular trend — A gradual change over a relatively long period of time (years or decades).

Stillbirth — The birth of an infant which is not alive at birth.

Study group — A general term for the group of subjects in an epidemiologic study with the disease or the exposure of interest.

Teratogenic — Causing physical defects in offspring in utero.

"Time-bomb" theory

Theory reported in the popular press which has been proposed to explain the plausibility of delayed Agent Orange health effects following weight loss. Reportedly, dioxin is stored in fat; upon weight loss dioxin is released into the blood stream.

Tracing Methodology

Tracing Mechanism

Methods used to locate members of a group of interest.

Validity — Accuracy of a test relative to "truth". How close a reported test value is to the true value is a measure of validity.

Veteran — Person who served in, and was discharged from, U.S. military service (except those who were discharged dishonorably).

Vietnam era veteran — Veteran who served during the time of the Vietnam era, August 5, 1964 to May 7, 1975. Includes those who served in areas other than Vietnam.

"Vietnam experience" — The sum of the exposures and influences that a soldier experienced during the Vietnam war.

Vietnam veteran — Veteran who served in Vietnam during the time of the Vietnam era.

Abbreviations

2,3,7,8 - TCDD — 2,3,7,8 - tetrachlorodibenzo-p-dioxin. A contaminant of 2,4,5-T, and therefore, a contaminant of Herbicides Green, Pink, Purple and Orange.

2,4 - D — 2,4 - dichlorophenoxy acetic acid. A component of Herbicides Orange, Pink and White.

2,4,5 - T — 2,4,5 - trichlorphenoxy acetic acid. A component of Herbicides Green, Pink, Purple and Orange.

C 123	Type of aircraft used by the Air Force in Operation Ranch Hand to spray herbicides in South Vietnam.
cm	centimeter
ha	hectare
kg	kilogram
lb	pound
LD 50	Abbreviation for median lethal dose, the dose that is fatal to 50% of exposed animals.
MACV	Military Assistance Command, Vietnam
MOS	Military Occupational Specialty. Occupation classification code used by U.S. Army.
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion

TCDD	In this protocol, 2,3,7,8 tetrachlorodbenzo-p-dioxin. (See 2,3,7,8 - TCDD).
UTM	Universal Transvers Mercator. A grid system used by the military based on the transverse mercator projection applied to maps of the earth's surface extending to 84 north and 80 south.

B

APPENDIX B

RESEARCH METHODS

III. Research Methods

A. Uses and limitations of Epidemiology

Epidemiology is a branch of Public Health Science which deals with the cause of disease by studying the ways in which disease varies by population characteristics. It is the only practical method by which effects of external agents on the health of humans in natural settings can be studied. Because epidemiology focusses on people in their natural activities, it is distinct from the laboratory sciences which can assign subjects (animals) to controlled exposure conditions. Epidemiology must take account of the self-selection and other selective pressures which place people in exposed or unexposed situations. Thus while being the only means for adequately studying the effect of external agents on humans, epidemiology does not provide the type of clear cause and effect results which can be obtained through the use of the more traditional experiemntal laboratory sciences. On the other hand, because of the differences in anatomy, physiology and metabolism between humans and any other animal species, animal studies will never adequately answer the questions concerning effects of human exposure. In addition, problems of multiple exposures which people encounter but which are not characteristic of laboratory animal studies must be considered.

B. Establishing Causality

The ultimate goal of scientific studies is usually

to establish a cause and effect relationship. Because of the self-selection and other problems encountered in epidemiologic studies, establishing causality is difficult. Epidemiologists have developed a set of guidelines to assist in this process. These include (but are not limited to):

1. Proper time relationship between variables: the suspected cause should preceed the suspected outcome.

2. Consistency: the same association is found in different sutdies done under different conditions.

3. Strength of association: the stronger the association, i.e., the larger the difference between the exposed and unexposed (usually measured by the ratio of their rates), the greater the likelihood of a causal relationship.

4. Biologic plausibility: the hypothesis of a causal relationship is strengthened if the relationship is biologically plausible. (A lack of biologic plausibility may, of course, reflect a deficit in the level of understanding of the biology.)

The most important of these epidemiologically is generally considered to be number 2. (Establishing the proper time sequence is obviously important but generally relatively easy to do.) In the case of Agent Orange, the fact that a study of U.S. ground troops will be one of several studies allows the important opportunity for confirmation of findings. In addition, we propose, in section IV, a series of studies which in the aggregate will help to build

the necessary "multiple evidence".

C. Epidemiologic Study Designs

Epidemiologic study designs generally fall into two broad categories: experimental and observational studies. Since the investigators in a study of Agent Orange have no control over the assignment of subjects to exposure category, the study will be of the observational type. The observational studies fall into three broad categories: cohort, case-control, and cross-sectional study designs.

The cross-sectional study or survey is one in which a population, for instance all currently surviving Vietnam veterans, is examined for an assessment of current health status and status with regard to some exposure variable or variables. This type of study has several serious drawbacks, the major ones being the difficulty in estimating prior exposure, in establishing a time relationship between exposure and subsequent onset of disease and the problem of losses to the population from the relationship in question. As an example, since the cross-sectional study involves by definition only those individuals who are currently alive, if Agent Orange were the cause of a fatal outcome occurring within five to ten years of exposure, such an outcome would be totally missed by a current cross-sectional study.

A case-control study, also known as a retrospective study, is one in which subjects (cases) are selected for having a particular disease, such as cancer or the occur-

rence of birth defects, and control subjects are selected on the basis of absence of the disease. Thus a known or strongly suspected disease outcome is required for the case-control design to be applied. The two groups are then compared for past experience in relation to the exposure variable. For example, in the case of an Agent Orange study, veterans having children with birth defects and veterans with normal children could be selected and their Vietnam experience compared for probability of exposure to the agent. The case-control study offers several advantages. It is relatively low-cost for an epidemiologic study. For a small sample size, it is much more powerful than other types of epidemiologic study designs. The case-control study is also usually very much faster and easier to carry out than other types of epidemiologic studies. One of the major difficulties usually encountered is the problem of accurately defining the prior exposure in an unbiased manner since the outcome status (disease or no disease) is already determined.

The cohort study design, also known as the prospective study, is the type of epidemiologic study most closely approximating that of the true experiment. In this type of study design the study population is selected on the basis of known exposure and known non-exposure or upon some gradient of known exposure and this population is then followed into the future to observe for the occurrence of disease.

The characteristic which distinguishes this study from the true laboratory experiment is that the exposure and non-exposure or level of exposure is not under the control of the investigator. A variant of the cohort study is called the historical cohort. In this type of study the exposure has taken place at some point in the past and the study population or cohort is assembled from past records at the time of their original exposure. This cohort is then followed to some subsequent point in time to observe for disease outcome. This requires historical records on both the exposed and non-exposed study groups. The cohort study design is generally regarded by epidemiologists as the best for establishing a cause-effect relationship and for directly estimating risk from exposure. However, this study design is also the most expensive and difficult to conduct of all epidemiologic studies. The cohort study generally requires very large samples sizes and for disease outcomes which are rare in the population, may be impractical to conduct.

D. Measurement of Independent and Dependent Variables

Regardless of the type of study design utilized, the epidemiologic study is only as good as the measurements of the independent and dependent variables, or in the case of a study of an agent as herbicide orange, the measurement of exposure and disease outcome.

Measurement of exposure, particularly when the exposure has taken place many years in the past, can be an exceedingly difficult task. One of the common methods of estimating exposure is the use of a questionnaire which allows the individual to define his own exposure. Such a mechanism may be quite useful in many circumstances but is obviously subject to serious problems of bias. Another mechanism for measurement of past exposure is the utilization of existing records which place an individual in a circumstance of some exposure or indicate the fact of non-exposure. This type of exposure estimation is quite common in epidemiologic studies and will, of necessity, be used in the current study. The quality of the exposure estimation is, of course, dependent upon the quality of the records, which are seldom developed or maintained for the purpose of estimating an individual exposure. Thus, the use of existing records for an exposure determination is subject to error. However, since the records were developed and maintained during a time in which no such study was contemplated, the error which is created is unlikely to be due to human bias. The error that will result will be an error termed misclassification in which an individual is classified in one category such as that of exposed when in fact that individual belongs in another category such as non-exposed. The effects of such misclassification errors are discussed in section F below. The most ideal method of

estimating exposure would be a biologic measurement which estimates the actual absorption of material into the body. Unfortunately, while laboratory work has been done on the measurement of stored TCDD in fat, the method is not reliable enough to be employed in an epidemiologic study at this time.

Measurement of the outcome variable is frequently better in epidemiologic studies because of the availability of objective diagnostic measures. Many potential variables such as symptoms can only be elicited by a questionnaire. Such outcome measurement can be constructed with reliability and sometimes with validity checks to estimate the accuracy of the determination. However, questionnaire responses are always subjective and subject to considerable reporting error. The design and administration of the questionnaire in the current study will be a particularly serious problem because of the publicity and the inflammatory nature of the issue.

Even the so-called objective tests are not without difficulty. There is no such thing in medicine as a completely accurate and valid test which in all circumstances will correctly classify an individual in disease or non-disease status. Besides the problem of incorrect classification, many of the test procedures have an inherent lack of reliability, or variability, due to either the variable human biology or due to the circumstances of the la-

boratory procedure itself. The greater the variability, the less useful the test becomes because with increasing variability one can only detect larger differences between groups or one is forced to utilize a considerably larger sample size.

E. Bias in Epidemiologic Study Designs

One of the difficulties with epidemiologic studies in general is the concept of bias. Bias is defined as a systematic error which leads to a distortion in the true relationship between two variables in an epidemiologic study. Bias can arise in epidemiologic studies in a variety of ways. The anticipation and control of these biases is part of the science. An example of such a bias which could be encountered in a study of Agent Orange is that different types of individuals may have been assigned to different types of units within the military operation. For instance, soldiers who were better educated were more likely to be placed in headquarters, non-combat companies, than lesser educated soldiers. Because educational level is known to be related to health status, health differences would be expected in a comparison of headquarters and rifle companies because of the differences in educational level. The most serious potential bias facing any study of Agent Orange may result from the highly emotional nature of the issue. Because of the publicity which this substance has received, many veterans believe that they know the effects of the

agent on humans. Therefore, if the veterans taking part in a study are aware at the outset of their exposed or unexposed status, there is a strong probability of bias due to selective reporting of symptoms or diseases by those who are in the exposed category. Such selective reporting is a well known epidemiologic bias and can be extremely difficult or impossible to control unless subjects can be kept unaware of their true status until completion of data collection.

F. Effects of Misclassification in Epidemiologic Studies

One of the major problems in any scientific research is the problem of errors of measurement. In epidemiologic studies, in which population exposure and event experience are typically assigned to two or three classes, each covering some range of measures, errors in measurement may be compounded by placing an individual in an exposure or event category, or both, mistakenly. For example, if smoking is categorized as one pack per day or less and more than one pack, an individual who reports use at one pack per day may be underreporting by only one or two cigarettes per day, but would be misclassified as a light instead of a heavy smoker. Such misclassification would affect an apparent association of some disease outcome with heavy as opposed to light smoking. If there is also a possibility of misclassification in the outcome variable, then the effect on the apparent association is even more complicated.

Misclassification, then, in epidemiologic studies occurs when an individual is assigned an incorrect value for a study parameter. In this study for instance, a soldier who was exposed to Agent Orange but who is classified by us as non-exposed would be misclassified for exposure status. The effect of such misclassification has traditionally been assumed to reduce the degree of observed association between independent and dependent variables (e.g., Agent Orange exposure and disease) but not to create spurious association. However, recent development of the algebra of misclassification for the situation where subjects are classified as diseased or not diseased and exposed or not exposed has shown that the traditional assumption is not always correct.

Extreme misclassification errors can result in a change in the magnitude and even in the direction of an association. For this reason, given the potential for misclassification in this project in either exposure or outcome, the effect of misclassification must be addressed in the next planning phase and throughout the study. The literature on misclassification is not extensive, but careful consideration has been given by a number of authors, including Fleiss (1981) and Keys and Kihlberg (1963). Fleiss presents an excellent summary of the problems and has developed and referenced an algebra for the interpretation of misclassification errors.

In the proposed study, we hope that the misclassifi-

;ation of exposure will be relatively small and will not differ between the diseased and not diseased individuals, as it will be derived from both individual-independent Army records of troop assignment and unit locations, and records of spraying operations recorded before the selection of study participants and examination for disease. Exposure here is defined as being in an area at a time when likelihood of exposure was high. It does not mean actual physical exposure, since we have found no means for determining this. The potential misclassification of outcome (disease status) will be minor with respect to specific disease diagnoses, laboratory test results, etc., but will be larger if the outcome is defined in more general terms, such as "affected in some way" versus "unaffected".

G. Possible Research Questions

A primary consideration in the planning, development and execution of an epidemiologic study is the question (or questions) to be addressed and, it is hoped, answered by the study. The delineation of the question is not always a straightforward process, and in the current study, both scientific and political considerations make this delineation difficult.

There are a number of questions which could be addressed concerning the current perception of health and other problems by veterans of Vietnam service and of service during the Vietnam era. The one most discussed is, of

course, the question of the impact of exposure to Agent Orange on the subsequent health and well-being of the exposed veteran. The Interagency Work Group and some veteran's groups suggest that this is too narrow a question, that exposure may not realistically be definable, and that other Vietnam exposures may be equally or even more important. Their recommendation is to define the exposure as the experience "Vietnam". Political and social pressures impacting on service men of the Vietnam era might suggest an even wider view of exposure.

Listed here are a number of possible questions of increasing generality with some suggestions of the consequences of posing the question in that manner and groups which might represent "exposed" and "unexposed" populations in addressing the particular question.

In all of the questions, the term "disease status" should be construed to incorporate mortality as well as morbidity findings in the cohorts which would be studied.

1. Agent Orange exposure

Is there a difference in disease status among Vietnam veterans exposed to Agent Orange and similar veterans who also served in Vietnam but were not exposed to Agent Orange?

This is the question on which the present proposal is primarily based. The consequences of asking the question in this way are that there may be other exposures responsi-

ble for the health effects that will go unrecognized if the question is defined this narrowly. Some suggestion of these other exposures may derive from the Agent Orange study; certainly the narrower study should answer the narrower question and perhaps offer better definitions of exposure outcome for questions of other exposures.

The unexposed group would be defined from groups of individuals as similar as possible in personal and military characteristics to the exposed group (age, race, background, military status, period of service, Vietnam service, combat, etc.).

2. Other exposure

Is there a difference in disease status among Vietnam veterans exposed to other agents (physical, chemical, biological) and similar Vietnam veterans who were not exposed?

This question is more general than the first and would require the identification of all possible exposures and the estimation of those exposures for individuals. The study would quickly become even more massive than that necessary for the Agent Orange exposure. In the general sense of all exposures, it is probably unanswerably broad. In the sense of specific exposures which may be definable (e.g., cacodylic acid) some idea of importance may be derived from the first question, as described above, depending on the relationship of the alternative exposure to Agent

Orange exposure. This relationship may be a positive or negative correlation (occurring together frequently or rarely), independent, synergistic or antagonistic. With the exception of independence, all of these relationships have the potential for confounding the Agent Orange exposure-outcome relationship and must be, to the extent possible, identified.

The unexposed group for this question, especially in its general sense, is difficult to define. A group unexposed to any of the exposures is a possibility, as is an approach through multiple groups with different patterns of exposed/unexposed status.

3. Is there a difference in disease status - other than that due to or stemming from direct combat injury - among Vietnam veterans exposed to combat and similar Vietnam veterans never in combat?

This question is narrower than that of the general exposure but may not be of great interest, as it appears generally agreed that there are direct and indirect health problems that are more common among combat veterans. If the question is to relate to the special problems of Vietnam combat veterans compared to WWII or Korean veterans, then the comparison should be to other wars and should involve the peculiar circumstances of Vietnam, which is perhaps better answered by some of the other questions posed.

The comparision, unexposed group would comprise sim-

ilar Vietnam veterans without combat experience, or, if Vietnam combat is specified, the "unexposed" might comprise combat veterans of other periods. Definitions of similarity would be very complex in the latter case.

4. Vietnam experience

Is there a difference in disease status in veterans who served in Vietnam and similar veterans of the same era who served in other places?

In this question, the whole Vietnam experience is considered as a single exposure. Assuming that there was no selection for service in Vietnam which is probably an invalid assumption, this would utilize as the unexposed comparison group those who did not serve in Vietnam. The question (if the assumption were valid) is probably answerable, but the answer would not be particularly useful as it would allow no discrimination of effect among the nearly 3,000,000 men who served in Vietnam, nor the identification of factors associated with the diseases concerned.

5. Vietnam era

Is there a difference in disease status in veterans who served in the Vietnam era and veterans who served during periods of other or different military involvement?

This question serves to isolate the political and social problems of the Vietnam era and their impact on those in military service at the time. The question is global in scope; its answer is likely to be equally global and to be

of little benefit to anyone.

The "unexposed" group would comprise similar veterans of other eras, assuming that "similarity" can be defined appropriately. Any secular trends in health status or standards would complicate addressing this question.

Examining these questions, those most addressable and with the most useful answers seem to be the earlier more specific ones. The original Agent Orange question, addressed with suitable safeguards for confounding by other exposures and factors, would seem to be the most appropriate for this study.

APPENDIX C

REVIEW OF ENVIRONMENTAL BEHAVIOR OF AGENT ORANGE

Environmental Fate of Agent Orange

I. Introduction

Between 1962 and 1971, approximately 107 million pounds of herbicide were applied by aerial application over Vietnam (Table 1). While several herbicide formulations were employed (including picloram and cacodylic acid,) major use was made of the phenoxy herbicides: 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). During the approximate 10 year defoliation period, an estimated 56 million pounds of 2,4-D and 44 million pounds of 2,4,5-T were applied (Young et al. 1978; National Academy of Science 1974).

In particular, a combination of these two phenoxy compounds was used and code named Agent Orange or Herbicide Orange. Agent Orange was an approximate 50:50 mixture of the n-butyl ester of 2,4-D and the n-butyl ester of 2,4,5-T with a more accurate breakdown as follows:

n-butyl ester of	2,4-D	49.49%
free acid	2,4-D	0.13%
n-butyl ester	2,4,5-T	48.75%
free acid	2,4,5-T	1.00%
inert ingredients		0.62%

One gallon of Agent Orange contained an estimated acid equivalent of 4.14 pounds of 2,4,5-T. Application rate of the mixture was 1.5-3 gallons per acre (Young et al. 1978). The higher rate was apparently used during the later years; estimated poundage rate per acre based on National Academy of Science figures (1974) are presented in Table 2.

C

APPENDIX C

REVIEW OF ENVIRONMENTAL BEHAVIOR OF AGENT ORANGE

Environmental Fate of Agent Orange

I. Introduction

Between 1962 and 1971, approximately 107 million pounds of herbicide were applied by aerial application over Vietnam (Table 1). While several herbicide formulations were employed (including picloram and cacodylic acid,) major use was made of the phenoxy herbicides: 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). During the approximate 10 year defoliation period, an estimated 56 million pounds of 2,4-D and 44 million pounds of 2,4,5-T were applied (Young et al. 1978; National Academy of Science 1974).

In particular, a combination of these two phenoxy compounds was used and code named Agent Orange or Herbicide Orange. Agent Orange was an approximate 50:50 mixture of the n-butyl ester of 2,4-D and the n-butyl ester of 2,4,5-T with a more accurate breakdown as follows:

n-butyl ester of	2,4-D	49.49%
free acid	2,4-D	0.13%
n-butyl ester	2,4,5-T	48.75%
free acid	2,4,5-T	1.00%
inert ingredients		0.62%

One gallon of Agent Orange contained an estimated acid equivalent of 4.14 pounds of 2,4,5-T. Application rate of the mixture was 1.5-3 gallons per acre (Young et al. 1978). The higher rate was apparently used during the later years; estimated poundage rate per acre based on National Academy of Science figures (1974) are presented in Table 2.

Table 1. Estimated quantities of herbicides and TCDD disseminated in South Vietnam from January 1962 - February 1971. (Reproduced from: Young, et al., 1978.)

Chemical	Pounds
2,4,5-D[a]	55,940,150
2,4,5-T[b]	44,232,600
TCDD[c]	368
Picloram[d]	3,041,800
Cacodylic Acid[e]	3,548,710
Total of Herbicides	106,763,260

[a]2,4-D was an active ingredient in Herbicides Orange, Purple and White. From data in Table 7, the acid equivalents for 2,4-D in Herbicide Orange and White were calculated to be 4.14 lb/gal and 2.00 lb/gal, respectively. The acid equivalent for 2,4-D in Herbicde Purple was assumed to be 4.14 lb/gal.

[b]2,4,5-T was an active ingredient in Green, Pink, Purple and Orange. Approximately 276,000 gal of Green, Pink and Purple were sprayed in South Vietnam prior to 1965, when it was replaced by Herbicide Orange. Herbicides Green and Pink contained 8.16 lb/gal 2,4,5-T. Herbicides Purple and Orange contained 4.00 lb/gal 2,4,5-T (Table 7).

[c]The mean TCDD concentration in Herbicde Purple was estimated at 32.8 ppm. The mean TCDD concentration in Herbicides Pink and Green was estimated at 65.6 ppm. The mean TCDD concentration in Herbicide Orange was estimated at 1.98 ppm.

[d]Picloram was an active ingredient of Herbicide White.

[e]Cacodylic acid was the active ingredient of Herbicide Blue. The Herbicide Blue formulation contained 15.4 percent arsenic in the pentavalent organic form. The value includes 10,000 lb cacodylic acid disseminated in South Vietnam from 1962-1964.

Table 2. Herbicides Used in Vietnam 1965-1971. (Reproduced from: National Academy of Science, 1974.)

Agent	Active Chemical Components	Military Application Rate (lb/acre)	Millions of gallons used, Aug. 1965-1971
Orange	2,4-D	12.00	
	2,4,5-T	13.80	11.22
White	2,4-D	6.00	
	Picloram	1.62	5.24
Blue	Cacodylic acid	9.30	1.12
Total			17.58

The use of Agent Orange was discontinued in Vietnan by the U.S. Military when the toxicity of the formulation became apparent in 1970. At this time, parts per million (ppm) quantities of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were reported as a manufacturing contaminant in 2,4,5-T; none was found in any 2,4-D product.

Young et al. (1978) reported the mean TCDD concentration of some 492 Agent Orange samples (some of these sample sources dated back to at least 1964) as 1.98 ppm (0.0247 ppm). Based on these calculations the authors estimated 368 pounds of 2,3,7,8-TCDD were released over Vietnam (The National Academy of Science 1974) estimated 220-360 pounds of 2,3,7,8-TCDD were released).

The chlorinated dibenzo-p-dioxins are a family of compounds consisting of some 75 theoretical members, each with different physical and chemical characteristics. Of the 75 possible structural configurations some 40 have been identified (Esposito et al. 1980). Several of these have been reported in the 2,4,5-trichlorophenol precursor for manufacture of 2,4,5-T herbicide formulations (Woolson et al. 1972; Firestone et al. 1972). Of these only the 2,3,7,8-TCDD isomer is known to be extremely toxic at this time (Esposito et al. 1980). Chlorinated dioxins have also been found in 2,4-D, but not the 2,3,7,8-TCDD isomer (Woolson et al. 1972; Cochrane et al. 1980).

This report reviews and examines the environmental fate of the major constituents of Agent Orange, namely 2,4-D, 2,4,5-T and 2,3,7,8-TCDD and includes summary statements on picloram and cacodylic acid which were also used as herbicides in Operation Ranch Hand.

II. Environmental Fate

Any chemical released into the environment is subject to attack by both chemical and physical forces. Chemical attack (both biotic and abiotic) can proceed by reactions such as oxidation, reduction and hydrolysis while sunlight, water and temperature simultaneously play their physical part. The extent and rate of modification of the chemical molecule is in turn dependent on the structure of that compound - the factor that predicts its chemical behavior.

Soil

2,4-D, 2,4,5-T — These compounds have been used extensively over the past 30 years, and there is a large body of information regarding their behavior in soil. They undergo typical reactions of carboxylic acids, ethers, esters and of aromatic compounds in general (Melnikov 1971; Loos 1975; Crosby and Tutass 1966; Crosby and Wong 1973).

In early field studies, Klingman et al. (1966) reported that the n-butyl ester of 2,4-D was hydrolyzed to the 2,4-D acid within 30 minutes of application to pasture grasses; Smith (1972, 1976) also reported rapid hydrolysis of the n-butyl ester of 2,4-D in tests with clay, sandy loam and loam soils and noted that increasing the water content of these soils greatly increased the hydrolysis rate. After 24 hours no n-butyl ester of 2,4-D was present in the moist soil and no 2,4,5-T ester after 72 hours. In later work, Smith (1979) reported that in the laboratory loss rate of both 2,4-D and 2,4,5-T conformed to first order kinetics and that application of herbicide mixtures had little effect on loss rate. In these soil studies half lives were reported as follows:

Compound	Heavy Clay	Sandy Loam
2,4-D	12 days	<7 days
2,4,5-T	20 Days	14 days

Bovey and Baur (1972) applied an ester of 2,4,5-T to grassland in Texas at a rate of 0.56 and 1.12 Kg/ha and found that most of the 2,4,5-T disappeared from the soil within six weeks. Most of the initial concentration was confined to the upper 6 inches of soil (sampled to a depth of 1 meter). In addition, there was no indication of persistence or build up from year to year application of 2,4,5-T in this area. Soil studies in Oklahoma (Alton and Stritzke 1973) indicated a half life of 4 days for 2,4-D and 20 days for 2,4,5-T; in temperature controlled studies, the half life of 2,4,5-T was 4 days at 35°C and 60 days at 10°C under the same conditions (Walker and Smith 1979).

Other field and laboratory research also indicates a relatively short half life for these compounds as well as little penetration into soil. Ninety percent loss of 2,4-D and 2,4,5-T was reported in Canadian soil within 70 days of application and no residue was detected below 20 cm. (Stewart 1977). Newman et al. (1952) followed 2,4-D and 2,4,5-T under field conditions and detected no 2,4-D residue 6 weeks after application while 2,4,5-T persisted for over 19 weeks. In a water shed area, 90% of the applied 2,4,5-T disappeared in 15 days, and almost all was detected within the top 0-7.5 cm. soil layer (Lutz et al. 1973).

Radosevich and Winterlin (1977) followed the degradation of 2,4-D and 2,4,5-T esters applied at 4-5 Kg/ha to chaparral country. Over 50%

of the 2,4-D and 2,4,5-T recovered was found on soil surface litter (0-5 cm.) and 18-30% on vegetation. Up to 360 days after application, minimal residue was detected on surface litter (0.01-0.03%) and soil (0.01%). In a similar chaparral study, residues declined to 0.04 ppm 2,4-D and 0.05 ppm 2,4,5-T (all within the top 10 cm.) 12 months after application of approximately 95 ppm 2,4-D and 2,4,5-T to soil plots (Plumb et al. 1977). Forest studies show a similar degradation pattern with 2,4,5-T more persistent than 2,4-D (Norris 1966; Tarrant and Norris 1967). Following application of 2.24 Kg/ha of 2,4,5-T ester, forest floor levels declined 90% in 6 months, and after 1 year less than 0.02 Kg/ha remained (Norris et al. 1977).

Degradation studies in tropical soils also indicate rapid breakdown of both 2,4-D and 2,4,5-T. Yoshida et al. (1975) reported rapid degradation of 2,4-D in approximately 2 weeks and 2,4,5-T in 2 to 3 months in two Philippine soil types; in Hawaiian soil 2,4-D disappeared after 14 weeks, but after repeated application, disappearance took only 4 weeks (Akamine 1951).

In a study of tropical soils directly related to Agent Orange application in Vietnam, Blackman et al. (1974) came up with several conclusions on the behavior of 2,4-D and 2,4,5-T:

1. Herbicide behavior in Vietnam soils is similar to that reported for soils elsewhere.
2. Only when applied in massive amounts (1000 lb/acre) are they likely to produce phytotoxic symptoms to subsequent growth.

3. Areas where 100 lb/acre were applied may present mangrove problems but evidence of new growth was observed in heavily sprayed areas.
4. No residue was detected in areas sprayed 1.5 years before residue sampling began.
5. After one application, Agent Orange sensitive crops can be grown within 4-6 months.

Adsorption plays a critical role in the behavior of chemicals in soil, the immediate environment may occur in the anionic or undissociated molecular state. A number of investigators have reported that the presence of organic matter in soil enhances adsorption (O'Conner and Anderson 1974; Wershaw et al. 1969). However, because phenoxy compounds are weak acids, the adsorptive forces with soil particles are minimal, and the compounds are readily desorbed by water (Harris and Warren 1964; Scott and Lutz 1971). Norris (1970) reported that these compounds rapidly adsorbed to forest floor material, and that desorption was equally rapid.

Physical and chemical parameters of soil adsorption have been reported (Audus 1964; Miller and Faust 1972a,b; Grover and Smith 1974; Grover 1973; Haque 1974; Khan 1973; Koskinen et al. 1979 and O'Conner et al. 1980). All essentially agree that humic and moiety (i.e., organic matter) are important aspects in phenoxy herbicide soil adsorption, as is pH, and that adsorption data follow the Freundlich type isotherm.

TCDD - Kearney et al. (1972) studied the persistence of TCDD in sandy and silty clay loam soils in the laboratory. One year after

application of 1 to 100 ppm, 56% and 63% of the applied TCDD was recovered from the sandy and silty clay loam soils respectively. The authors emphasize that these application rates were, at minimum, one million times greater than levels that would be encountered in a 2,4,5-T application containing 1 ppm TCDD. Woolson and Ensor (1973) analyzed soil at Eglin Air Force Base, Florida, where 1060 Kg/ha 2,4,5-T was applied between 1962 and 1964. TCDD was not detected within the 1-meter deep soil profile. Harrison et al. (1979) monitored storage and loading sites at Eglin and found TCDD residue as high as 275 parts per billion (ppb), but contamination was confined to a small area.

Field plots were set up in Utah and Florida, and Herbicide Orange was injected 4-5 inches below the surface at a rate of 4000 lb/acre. Initial TCDD residue was 148 ppb in Utah and 0.375 ppb in Florida. Calculated half life for TCDD in these studies was 320 days in Utah and 230 days in Florida (Young et al. 1976). In another Eglin AFB study, Young et al. (1975) analyzed soil where 1894 lb/acre of Agent Purple (4 lb/gal 2,4,5-T) was applied between 1962 and 1964. These samples were analyzed 10 years after the last application. No TCDD was detected 6 inches below the soil surface, but residue was present throughout the 0-6 inch profile:

Depth below surface	TCDD (ppt)*
1 inch	150
1-2 inch	160
2-4 inch	700
4-6 inch	44
6-36 inch	None detected

* Parts per trillion

The National Academy of Science study (1974) also reported finding TCDD residue ranging from <1.2 to 23.3 ppb in soil from Pran Buri, Thailand, a former calibration site for Operation Ranch Hand in Vietnam.

There is little doubt from these data that TCDD is persistent in soil and that predictions on degradation are difficult to make on the basis of soil type and climate. However, persistence does appear to be confined to soils receiving massive treatment of 2,4,5-T (or TCDD). For example, rangelands and forests receiving repeated applications of 2,4,5-T at about 2 lb/acre do not appear to accumulate TCDD in the soil. This appears to be reflected in milk from cows grazing on treated pastureland where TCDD is either below detectable levels or when present at the low part per trillion (ppt) level. The same is true of tissue residue in grazing cattle and forest wildlife (Esposito et al. 1980; National Research Council of Canada 1978; Bovey and Young 1980).

Leaching and Runoff

2,4-D, 2,4,5-T - Movement of chemicals in the aqueous soil phase is fairly common and can occur in either vertical or horizontal directions. Studies with 2,4-D and 2,4,5-T indicate that only limited leaching and runoff occur except where heavy rainfall is involved (Bovey et al. 1974; Sheets and Lutz 1973).

Edward and Glass (1971) reported about 0.05% runoff of 2,4,5-T amine and only minimal percolation down through soil after applications of 11.2 Kg/ha. In a greenhouse study (pH 7.9) no 2,4,5-T was found below 35 cm. in a 150 cm. lysimeter column (O'Conner and Wierenga 1973). In plots treated with 2,4-D and receiving simulated rainfall,

White et al (1976) reported surface loss of 95% of the applied 2,4-D in 7 days, but no accumulation of 2,4-D was evident at a depth of 90 cm.

In forest studies, concentrations of 2,4-D and 2,4,5-T never exceeded 0.1 ppm in water for more than one day after application. Moreover, heavy rainfall up to 6 months later did not introduce detectable residue into streams; it was estimated that a 150 pound man would have to drink 179 gallons of this water (0.1 ppm) to ingest 1/100 of the LD_{50} for these compounds (Norris 1968; Norris and Moore 1970). Similarly, in another forest area treated with the isooctyl ester of 2,4,5-T, some residue was detected in runoff but only at levels reported to be well below the toxic level for man and fish (Lawson 1976).

Where the n-butyl esters of 2,4-D and 2,4,5-T were mixed in soils to a depth of 15 cm. (4400 Kg/ha), residues of both compounds were detected after 282 days. Even at this massive application level, 90% of the residue was detected in the top 30 cm of the soil profile. This study also indicated that downward movement was greater for 2,4-D than for 2,4,5-T (Young et al 1974). Other studies conducted in the field at normal application show that 2,4-D and 2,4,5-T remain well within the top 20 inches of soil (Bovey and Baur 1972; Smith 1975; Lutz et al 1973; Young et al 1974).

TCDD - Helling (1970) evaluated the movement of DCDD and TCDD by a soil thin-layer chromatographic technique employing five soil types and found both dioxins to be immobile. Kearney et al. (1973) observed that mobility of both of these dioxins decreased with increasing organic content of soil, concluding that both compounds were immobile in the

soil tested and probably no threat to groundwater contamination by either rainfall or irrigation.

Studies by the Air Force indicate that even with massive application and time TCDD essentially remains in the upper 6 inches of soil (Young et al. 1975). At an Eglin AFB loading site, TCDD was detected down to 1-meter; however, other sites in the same study were relatively free of TCDD contamination (Harrison et al. 1979).

Runoff and leaching do occur to some extent in areas where massive application have been made. Young et al. (1976) reported movement of TCDD to ponds at Eglin but, again, only low ppt levels were reported. Recently there have been reports of TCDD migration from chemical dump sites and landfills (Esposito et al. 1980).

Photodegradation

2,4-D, 2,4,5-T - Both 2,4-D and 2,4,5-T have been shown to undergo photochemical degradation in artificial light and in sunlight. The photochemistry of pesticides, including phenoxy compounds, has recently been reviewed by Crosby (1976).

Crosby and Tutass (1966) reported the photolytic decomposition of the sodium salt of 2,4-D in aqueous solution following irradiation in the laboratory (mercury lamp 254 nm) and in sunlight. Following mercury lamp irradiation, 2,4-D underwent rapid decomposition with 50% breakdown within 50 minutes of exposure. Analysis of the reaction mixture revealed 2,4-dichlorophenol along with 6 other degradation products, including a large amount of humic acid polymer material. Exposure to sunlight for

several days produced some of the same components including the humic acid polymer. From these data, the authors proposed a series of pathways for the photolytic decomposition of 2,4-D in aqueous solution.

Irradiation of 2,4,5-T in solution also showed that photolytic breakdown occurred but at a rate approximately one-third that of 2,4-D under similar conditions. Under artificial light, 2,4,5-T breakdown was slow with only 10% decomposition after 8 days of exposure. Isolated products included the chlorinated phenol along with intermediates and the dark polymeric humic material observed with 2,4-D. Decomposition of 2,4,5-T in sunlight was extremely slow but increased significantly when sensitizers (acetone, riboflavin) were added to the reaction mixture (80% in 2 days). Photolysis of the salts of 2,4-D and 2,4,5-T in solution appeared to produce analogous products. Photolysis of these dealkylated photoproducts was rapid (Crosby and Wong 1973; Crosby 1976).

Based on the work of Crosby and Tutass (1966) and Crosby and Wong (1973), a typical pathway for photolytic degradation begins with dealkylation to yield the phenol followed by reductive dechlorination and hydroxylation, ultimately ending in the formation of a polymeric humic material. Generation of chlorinated dibenzo-p-dioxins has not been observed in either study.

TCDD - In an early study, Crosby et al. (1971) reported rapid degradation of 2,3,7,8-TCDD and 2,7-TCDD (dichlorodibenzo-p-dioxin) isomers when these compounds were dissolved in methanol and irradiated with both artificial light and sunlight. TCDD and 2,7-DCDD were degraded by decreasing chlorine content, and 2,3,7-trichlorodibenzo-p-

dioxin was isolated and identified as a breakdown product of TCDD. However, TCDD applied to glass plates and soil did not undergo photolytic decomposition after 14 days of irradiation.

In subsequent studies (Crosby and Wong 1977), Herbicide Orange containing 15 ppm TCDD was applied to glass plates and exposed to summer sunlight. After 6 hours approximately 60% TCDD loss was observed. When applied to soil, about 85% of the TCDD remained in the soil as compared with 95% in the dark control. TCDD applied to rubber plant leaf at a rate of 6.7 mg Herbicide Orange/cm^2 of leaf surface was not detected after 6 hours exposure to summer sunlight, but at a lower application (1.3 mg/cm^2) 30% remained after 6 hours of sunlight exposure. Based on these results, the authors established three requirements for dioxin photolysis: dissolution in a light transmitting film; presence of an organic hydrogen donor; and ultraviolet light, all of which are met during the normal application of 2,4,5-T.

Aquatic Environment

The water environment includes irrigation supplies, groundwater systems, freshwater lakes and streams, drinking water reservoirs and coastal marine environments. There is abundant evidence that under normal application rates the phenoxy herbicides are short lived and do not bioaccumulate in water environments.

Bartley et al. (1970), in an extensive irrigation water study, monitored the dimethylamine salt of 2,4-D following application of 1.6 to 2.8 Kg/ha to ditch banks. Maximum 2,4-D concentration in water was 213 ppb but was below 50 ppb in over half of the sampling monitored.

Where MCPA (4-chloro-2-methyl phenoxyacetic acid) was applied to California rice pond water (1.0 kg/ha), no residue was detected in water or bottom mud 14 days after application (Soderquist and Crosby 1975).

Following treatment of a Tennessee reservoir with 22.4 Kg/ha and 44.8 Kg/ha of 2,4-D, only two water samples had detectable residues of 2,4-D (2 and 11 ppb) and no residue was detected in fish. However, 8 months after application, filter feeding mussels had levels ranging from 0.05-0.26 ppm (Wojtalik et al. 1971). Norris (1967) noted that streams traversing forested areas sprayed with 2,4-D and 2,4,5-T contained detectable residue (0.001-0.84 ppm), but levels diminished downstream. In one instance, however, 2,4,5-T residue persisted in a stream 16 weeks after application; in a marshy area ppm levels persisted for 10 days. No residues in these areas were detected 9 months later; however, the author cautioned against marsh spraying because of continual runoff into streams draining the area.

In laboratory studies designed to examine the dynamics of 2,4-D ester formulations in fresh water, Zepp et al. (1975) reported on three competing processes: chemical hydrolysis, photolysis, and volatilization and came up with the following conclusions:

1. In basic waters hydrolysis is the most important process for the methyl, 1-butyl, 1-octyl and 2-butoxyethyl esters.
2. In acidic waters the importance of the degradative process depends on the ester structure. Photolysis is the most important process for the butoxyethyl ester, vaporization for the butyl and octyl esters and both vaporization and photolysis for the methyl ester.

3. The loss rate is more rapid in basic than in acidic water.

4. The hydrolysis product of 2,4-D is resistant to chemical degradation and is nonvolatile. Therefore, photolysis is probably an important degradative pathway.

The authors calculated the half life of 2,4-D in 1-meter deep water as 20 days.

Groundwater contamination is of special concern, and a number of studies have been conducted to assess the possibility of chemical seepage into ground water supplies. Examination of Canadian farm ponds and wells revealed that 48% of the ponds were contaminated. 2,4-D was detected in 81% of the contaminated wells and 2,4,5-T in 32% of the wells. Pond residues of 6 and 11 ppb 2,4-D, and 6 and 14 ppb 2,4,5-T, were reported. All of this contamination, however, was associated with loading and dumping practices (National Research Council of Canada 1978).

Bovey et al. (1975) monitored an area treated at 2.2 Kg/ha 2,4,5-T every six months for approximately 3 years. Seepage and well water had 1 ppb 2,4,5-T residue, but no 2,4,5-T was detected in 122 drainage samples from a field lysimeter study where irrigation and natural rainfall were used to force 2,4,5-T into subsoil. O'Conner and Wierenga (1973) conducted greenhouse teaching studies with high rates of 2,4,5-T and concluded there was no danger of seepage into groundwater, particularly at lower levels.

(0.2 ppb) TCDD - TCDD is not very water soluble and therefore will behave differently in water than the more polar phenoxy herbicides.

In an aquatic model ecosystem soil was treated with ^{14}C-TCDD and residues monitored for about 4 weeks. Results suggested no degradation of TCDD and bioconcentration in exposed species ranging from 10^3 to 10^4 times the water concentration (Isensee and Jones 1975). Ward and Matsumura (1978) studied the fate of TCDD in lake water and sediment under laboratory conditions and came up with the following conclusions: TCDD is bound to sediment where it is stable and not readily available to microbial attack; very limited metabolism of TCDD occurs in the aqueous phase and metabolic products appear to be degraded more rapidly than the parent TCDD; water mediated evaporation of TCDD occurs.

Yockim et al. (1978) noted in another aquatic ecosystem study that water concentration of TCDD was dependent on the rate of soil desorption and, of course, water solubility of TCDD. Radioactivity in water from the TCDD treated soil reached equilibrium in 1 day (2-4 ppt), and bioaccumulation was noted in the organisms exposed in the system.

Young et al. (1976) examined an aquatic ecosystem draining the Eglin AFB test area in Florida where 73,000 Kg 2,4,5-T and 77,000 Kg 2,4-D were applied between 1962 and 1970. Samples collected and analyzed in 1973 had 10-710 ppt TCDD in the top 15 cm. of soil and 10-35 ppt in eroded silt that drained into an adjacent pond. The area supported a diverse fauna, and only low ppt TCDD residue levels were detected in aquatic species inhabiting the contaminated pond.

Monitoring studies have been conducted to assess the potential for bioaccumulation of TCDD in aquatic species. Baughman and Meselson (1973) reported TCDD residues in fish and crustacea from Vietnamese

waters; however, residue studies did not show TCDD contamination in a wide variety of aquatic species in Canada (Zitko 1972) or in a rice growing region of the U.S. where 2,4,5-T had been applied annually for 20 years (Shadoff et al. 1977). In addition, Bowes et al. (1973) did not detect TCDD in marine birds, mammals and fish species considered to be at the top of their respective food chain, suggesting that bioaccumulation of TCDD occurs but not biomagnification to the top tropic level as seen with DDT.

Studies on the behavior of TCDD in aquatic environments suggest that degradation occurs, but where high amounts have been introduced, persistence in sediment and water (by desorption) may be a problem. Bioaccumulation occurs but apparently not biomagnification to the top tropic level. Based on its nonpolar nature, one would expect TCDD to adsorb to particulates or sediment and partition into organic substrate. While available information tends to support this behavior pattern, more information is needed on the dynamics of TCDD (industrial effluents, drinking water supplies) in the aquatic environment.

Microbial Degradation

2,4-D, 2,4,5-T - Microbial degradation is certainly of major importance regarding the fate of phenoxy compounds in the environment, and numerous studies have reported on this degradation and detoxification. Early work by Newman et al. (1952) and Audus (1964) indicated that 2,4-D disappeared in 2 to 3 weeks while 2,4,5-T persisted anywhere from about 6 to 40 weeks in soil. Hammett and Faust (1969) noted that

biodegradation of 2,4-D followed zero-order kinetics and that the oxidation rate was independent of the substrate concentration.

Audus (1960) reported that it took 20 days for 80% breakdown of 2,4-D in soil treated at a rate of 100 ppm, but after retreatment 80% breakdown occurred in only 3 days. Torstenson et al. (1975) studied the effects of repeated applications of 2,4-D and noted a reduction in degradation time from 10 weeks to 4 weeks after 19 years of annual application (20 weeks to 7 weeks for MCPA).

Under generally similar conditions, 2,4,5-T appears to persist about 3 times longer than 2,4-D. McCall et al. (1981), for example, reported an average 50% degradation time (in six soil types) of 4 days for 2,4-D and 14 days for 2,4,5-T while 90% degradation of 2,4-D took 11 days and 2,4,5-T, 42 days. The half life of 2,4,5-T in forest soil was estimated to be 7 weeks (Newton 1971). In tropical soils Blackman et al. (1974) reported that phytotoxic residues of the n-butyl esters of 2,4-D and 2,4,5-T were not evident after 4 weeks. Rosenberg and Alexander (1980), however, reported little loss of 2,4,5-T in four tropical soils after 2 months. Of 52 bacterial groups isolated from soil and sewage, the authors found 41 that degraded 2,4-D and 2,4,5-T but only through cometabolism.

Microbial resiliency was exemplified by Young (1980) who reported that areas of Eglin AFB receiving 76,000 Kg/ha 2,4-D and 75,000 kg/ha 2,4,5-T from 1962 through 1970 had microbial populations similar to those from adjacent control areas. Moreover, studies in Utah where soil levels reached 10,000 ppm, a half life of 150 and 210 days was

reported for 2,4-D and 2,4,5-T. Stojanovic et al. (1972), as well as others, have observed that a mixture of the two compounds degrades faster than when the compounds are used alone.

Degradation pathways for phenoxy herbicides by microorganisms have been reviewed by Loos (1975). The major pathway for degradation of 2,4-D and MCPA by an Arthrobacter sp. and pseudomonads is by removal of the acetic acid side chain to yield the corresponding phenol. This is followed by ortho hydroxylation to form the catechol with conversion to the muconic acid and subsequent cleavage of the aromatic ring. Elimination of the 4-chlorine with replacement of hydrogen has also been postulated. There is also evidence that a pseudomonad hydroxylates the 6 position on the aromatic ring forming 2,4-dichloro-6-hydroxyphenoxyacetic acid.

Rosenberg and Alexander (1980) in labelled studies reported that cometabolism of 2,4,5-T led to chloride release and formation of phenolic products as well as cleavage of the ring. A pseudomonad soil isolate in this study degraded approximately 70% of the 2,4,5-T in 80 hours and approximately 60% was recovered as phenol.

2,4,5-trichlorophenol was converted in soil suspensions to 3,5-dichlorocatachol, 4-chlorocatechol, succinate and several tentatively identified products. The 3,5-dichlorocatechol product was also postulated by Horvath (1971) working with Brevibacterium sp. McCall et al. (1981) reported two major metabolites formed from microbial breakdown of 2,4.5-T. These included formation of the 2,4,5-trichlorophenol followed by microbial methylation to produce 2,4,5-trichloroanisole, but analogous metabolites were not observed for 2,4-D. The anisole was quite volatile with a 50% loss from

soil in 1 to 3 days. Degradation of 2,4-D was reported to be so rapid in this incubated system that intermediate products were difficult to isolate and identify.

Microbial degradation of TCDD in soils does not appear to be a rapid process. Matsumura and Benezet (1973) screened 100 microbial strains known to degrade chlorinated pesticides and found only five strains capable of degrading TCDD. Kearney et al. (1972) also reported that TCDD was not readily metabolized by soil organisms since the half life approximated 1 year. Helling et al. (1973) concluded from these studies that TCDD persistence would be expected since it is an insoluble, nonpolar, chlorinated molecule without biologically labile functional groups.

Pocchiari (1978) in tests with Seveso soil attempted to induce degradation by inoculation with microorganisms showing some ability to degrade TCDD; very minimal success was achieved. The absence of TCDD residue in the Lakeland soil of one study (Woolson 1973) where massive application occurred does suggest, however, that microbial degradation does occur. For the most part, however, it appears that microbes are not capable of rapid and complete elimination of soil or sediment bound TCDD residues.

Plants

Persistence and disappearance of 2,4-D and 2,4,5-T from plant surfaces has been monitored in a number of field studies. Klingman et al. (1966) applied high and low volatile esters of 2,4-D to pasture land at a rate of 2.24 Kg/ha and noted that forage residues declined

rapidly from 58 ppm to 5 ppm in 7 days. The authors also noted that 75% of the butyl ester was hydrolized to the acid 30 minutes after application. Bovey et al. (1974; 1975) reported no accumulation of 2,4,5-T in vegetation following approximately 3 years of semiannual application within the same area. Initial residues after treatment were high (28-113 ppm) but disappeared before the following application. Morten et al. (1967) also reported no build up of either 2,4-D or 2,4,5-T on vegetation after repeated application. Green tissue had a half life of about 2 to 3 weeks for both compounds with grasses averaging a little longer at 3 to 4 weeks.

In a semi-arid area considered poor for rapid breakdown, maximum concentrations of 2,4-D (95.2 ppm) and 2,4,5-T (92.4 ppm) were detected on chaparral vegetation 15 minutes after application but dropped rapidly and then remained at about 4 ppm 2,4-D and 3 ppm 2,4,5-T after 12 months (Plumb et al. 1977). Radosevich and Winterlin (1977), in a similar chaparral study, sampled up to 360 days after application of 4.5 Kg/ha of esters of 2,4-D and 2,4,5-T. They noted that 90% of the initial foliage residue disappeared within 30 days after application and then remained constant until winter rainfall. At 360 days approximately 0.01-0.02% of the initial foliage residue was detected.

In addition to photodegradation, volatilization, microbial attack, and wash off, 2,4-D and 2,4,5-T are also subject to uptake and metabolism by plants. With few exception, there appears to be little persistence in plants, but in some woody species, low level residues have lasted for more than 5 months. For most plants, however, 1-3 weeks

appears to approximate the half life of these compounds (National Research Council of Canada).

TCDD - Oats and soybeans grown in TCDD treated soil accumulated less than 0.15% of the TCDD soil concentration, when leaves were treated, no translocation beyond the leaf was detected (Isensee and Jones 1971). In addition, 94% of the TCDD applied to the leaf surface of soybeans remained there for 21 days, while residue on oat leaves continually decreased. In a similar study using sorghum, TCDD uptake from soil was reported to be one millionth of one percent of the TCDD in the soil (Bovey and Young 1980). Residue data for TCDD and plants is especially incomplete. However, the study of Crosby and Wong (1977) indicates rapid photolytic degradation of TCDD in Herbicide Orange on rubber plant leaves by sunlight with a half life of 1-2 hours (6.7 mg herbicide mixture/cm^2).

Volatization and Atmospheric Residue

2,4-D, 2,4,5-T - All ester formulations of 2,4-D and 2,4,5-T are volatile but vary in rate of volatility; amine and sodium salt formulations have little or no volatility problem. Baur et al. (1973) found 55% loss of applied 2,4,5-T at 60°C but no loss after 7 days at 30°C. Baur and Bovey reported dry preparations of 2,4-D subjected to 60°C resulted in over 50% loss of the compound in one day. Grover et al. (1972; 1973) reported vapor losses of 30% and 13% for butyl and isooctyl esters of 2,4-D in field studies.

Que Hee and Southerland (1974) reported volatility of the butyl esters of 2,4-D when applied as a thin film or drop on glass or leaf

surfaces increased directly with the available surface area to applied mass ratio and inversely with the adsorptive capacity of the surface. Grover (1976) conducted volatility studies in a closed flow system and reported the following rates of volatilization for esters relative to the nonvolatile 2,4-D amine salts (assigning the nonvolatile amine salts a value of 1):

Classification	Ester/salt	Relative rating
High volatile (HV)	mixed butyl	440
Low volatile (LV)	propylene glycol butyl ether	33
	butoxy ethanol iso-octyl	
Non-volatile (NV)	mixed aminex dimethyl amine diethanol amine	1

Grover et al. (1972) reported that 20 to 30% of the butyl ester of 2,4-D was collected as vapor drift after field application whereas little or no 2,4-D amine used in the same study was detected.

Phenoxy herbicide residues have been detected in air in areas where these compounds are used fairly extensively (Vernette and Freed 1962; Grover et al. 1976; Que Hee et al. 1975); Elias (1975) reported detecting residue of the butyl ester of 2,4-D at an altitude of 3000 feet. Data on volatilization and drift during defoliation use in Vietnam are not available, however, data available in this country and in Canada indicate volatilization and drift did occur. This is supported by Young et al. (1978) in their summary of the environmental fate of phenoxy herbicides in air during project Ranch Hand in Vietnam.

TCDD - Matsumura and Ward (1978) reported that water-mediated evaporation of TCDD may take place based on laboratory study. Esposito et al. (1980) cite a ^{14}C TCDD study conducted in a microagrosystem which indicates TCDD has a very low vapor pressure and that loss due to volatilization is very low. This is borne out in studies by Crosby (1971) and Crosby and Wong (1977) where TCDD was found to be relatively stable and persistent (at least up to 14 days) in soil and on glass plates unless requirements for photolytic degradation were supplied.

Currently, the generation of dioxins in fly ash from incineration of municipal wastes as well as from dispersal of particulates from dump sites is being investigated (Esposito et al. 1980).

Picloram and Cacodylic Acid

Approximately 3×10^6 pounds of Picloram (4-amino-3,4,6-trichloropicolinic acid) were released in Vietnam between 1962 to 1971 as the active ingredient in Herbicide White (Young et al. 1978). Picloram appears to be a relatively safe compound having low toxicity for man and other mammals, birds and fish. It is very sensitive to volatilization and can be easily leached from soil by rainfall. Soil losses ranging from 56 to 96% over one year's time are reported. It is only slightly photolabile and undergoes microbial breakdown only at a slow rate (Foy 1975).

Cacodylic acid (hydroxydimethylarsine oxide) was the active ingredient in Herbicide Blue, and some 3.5×10^6 pounds were used in Vietnam between 1962 and 1971. The degradation of cacodylic acid in soil is not well researched even though this compound has been used extensively over the years. It apparently degrades aerobically in soil to a volatile

organoarsenical and to a second compound by cleavage of the C-As bond(s); anaerobically, only the volatile compound is formed. Degradation in soil is apparently slow and cacodylic acid forms insoluble compounds in soil. This compound is considered to be moderately toxic (Woolson, 1975).

References

Akamine, E. K. Persistence of 2,4-D toxicity in Hawaii soils. Bot Gaz. 112, 312 (1951).

Alton, J. D. and J. F. Strilzke. Degradation of dicamba, picloram and four phenoxy herbicides in soils. Weed Science 21(6), 556 (1973).

Audus, L. J. Microbiological breakdown of herbicides in soil. In Herbicides and the soil. Blackwell Scientific Publishers, Oxford, 1-19 (1960).

Audus, L. J. Herbicide behavior in the soil. Chapter 5. In the Physiology and biochemistry of herbicides. L. J. Audus, ed. Academic Press, New York (1964).

Bartley, T. R. and R. R. Hattrup. 2,4-D persistence in irrigation water. Proc West Weed Sci Soc 23, 10 (1970).

Baughman, R. W. and M. S. Meselson. An analytical method for detecting TCDD (dioxin): Levels of TCDD in samples from Vietnam. Environ Health Perspect 5, 27 (1973).

Baur, J. R. and R. W. Bovey. Ultraviolet and volatility loss of herbicides. Arch Environ Contam Toxicol 2, 275 (1974).

Baur, J. R., R. W. Bovey and H. G. McCall. Thermal and ultraviolet loss of herbicides. Arch Environ Contam Toxicol 1, 289 (1973).

Binkley, R. W. and T. R. Oakes. Photochemical reactions of alkyl 2,4-dichlorophenoxyacetates. Chemosphere 1, 3 (1974).

Blackman, G. E., J. D. Fryer, A. Lang and M. Newton. The effects of herbicides in South Vietnam. Part B. Working Papers - Persistence and disappearance of herbicides in tropical soils. Nat Acad Sci, Washington, D.C. (1974).

Bovey, R. W. and J. R. Baur. Persistence of 2,4,5-T in Grasslands of Texas. Bull Environ Contamin Toxicology 8(4), 229 (1972).

Bovey, R. W., E. Burnett, C. Richardson, J. R. Baur, M. G. Merkle and D. E. Kissel. Occurrence of 2,4,5-T and picloram in subsurface water in the Blacklands of Texas. J Environ Qual 4, 103 (1975).

Bowes, G. W., B. R. Simonett, A. L. Burlingame, B. W. DeLappe and R. W. Risebrough. The search for chlorinated dibenzopurans and chlorinated dibenzodioxins in wildlife populations showing elevated levels of embryonic death. Environ Health Perspect 5, 191 (1973).

Colmer, A. R. The action of 2,4-D upon Azotobactu of some sugarcane soils. Appl Microbiol 1, 184 (1953).

Cochrane, W. P., J. Singh, W. Miles, B. Wakeford and J. Scott. Analysis of technical and formulated products of 2,4-dichlorophenoxyacetic acid for the presence of chlorinated dibenzo-p-dioxins. Presentation at the workshop on the "Impact of Chlorinated Dioxins and Related Compounds on the Environment," Rome, Italy, Oct. 1980.

Colmer, A. R. The action of 2,4-D upon Azotobactu of some sugarcane soils. Appl Microbiol 1, 184 (1953).

Crosby, D. G. and J. O. Tutass. Photodecomposition of 2,4-dichlorophenoxyacetic acid. J Agric Food Chem 14, 596 (1966).

Crosby, D. G., A. S. Wong, J. R. Plimmer and E. A. Woolson. Photochemical decomposition of chlorinated dibenzo-p-dioxins. Science 173, 748 (1971).

Crosby, D. G. The fate of pesticides in the environment. Annual Review of Plant Physiology 24, 467 (1973).

Crosby, D. G. and A. S. Wong. Photodecomposition of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in water. Agric and Food Chem 21(6), 1052 (1973).

Crosby, D. E. Herbicides photodecomposition. In: Chemistry, degradation and mode of action of herbicides, Vol. 2, 2nd ed., P. C. Kearney and D. D. Kaufman, eds. Marcel Dekker, N.Y. (1976).

Crosby, D. E. and A. S. Wong. Environmental degradations of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Science 195 (1977).

Edwards, W. M. and B. L. Glass. Methoxychlor and 2,4,5-T in lysimeter percolation and runoff water. Bull Environ Contamin Toxicology 6(1), 81-84 (1971).

Elias, L. Airborne GC analyzer for study of pesticide vapor drift. J Chromotogr Sci 13, 178 (1975).

Esposito, M. P., T. O. Tiernan and F. E. Dryden. Dioxins., U.S. EPA, Cincinatti, Ohio, EPA-6001 2-80-197, November, 1980.

Firestone, D., J. Ress, N. L. Brown, R. P. Barron and J. N. Damico. Determination of polychlorodibenzo-p-dioxins and related compounds in commercial chlorophenols. J.A.O.A.C., 55(1) 85-92 (1972).

Foy, C. L. Picloram and related products. In Herbicides: chemistry, degradation and mode of action, 2nd ed., P. C. Kearney and D. D. Kaufman, eds. Marcel Dekker, N.Y., 777 (1975).

Grover, R., J. Maybank and K. Yoshida. Droplet and vapor drift from butylester and dimethylamine salt of 2,4-D. Weed Sci 20, 320 (1972).

Grover, R. The adsorptive behavior of acid and ester forms of 2,4-D on soils. Weed Res 13, 51-58 (1973).

Grover, R., J. Maybank, K. Yoshida and J. R. Plimmer. Droplet and volatility drift hazards from pesticide application. Air Pollut Control Assoc, 66 Annual Meeting (1973).

Grover, R. and A. E. Smith. Adsorption studies with the acid and dimethylamine forms of 2,4-D and dicamba. Can J Soil Sci 54, 179 (1974).

Grover, R. Relative volatilities of ester and amine forms of 2,4-D. Weed Sci 24, 26 (1976).

Grover, R., L. A. Kerr, K. Yoshida, K. Wallace and J. Maybank. Residues of 2,4-D esters in air samples from Saskatchewan: 1966-1975. J Environ Sci Health B11(4), 331 (1976).

Haque, R. and R. Sexton. Kinetic and equilibrium study of the adsorption of 2,4-dichlorophenoxyacetic acid on some surfaces. J Colloid Interface Sci 27, 818 (1968).

Haque, R. Role of adsorption in studying the dynamics of pesticides in a soil environment. In: Environmental dynamics of pesticides, Environmental science research, V6. R. Haque and V. H. Freed, eds. Plenium Press, N.Y. (1975).

Harris, C. I. and G. F. Warren. Adsorption and desorption of herbicides by soil. Weeds 12, 120 (1964).

Harrison, D. D., C. I. Miller and R. C. Crews. Residue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) near herbicide storage and loading areas at Eglin AFB, Florida. AFATL-TR-79-20, Air Force Armament Laboratory, Eglin AFB, Florida (1979).

Helling, C. S. Pesticide mobility in soils. II. Applications of soil thin layer chromotography. Proc Soil Sci Soc Am 35, 737 (1971).

Helling, C. S., A. R. Isensee, E. A. Woolson, P. D. J. Ensor, G. E. Jones, J. R. Plimmer and P. C. Kearney. Chlorodioxins in pesticides, soils & plants. J Environ Qual 2(2), 171-178 (1973).

Hemmett, Roland B. Jr. and Samuel D. Faust. Biodegradation kinetics of 2,4-dichlorophenoxyacetic acid by aquatic microorganisms. Residue Reviews 29, 191-207 (1969).

Horvath, R. S. Microbial cometabolism of 2,4,5-trichlorophenoxyacetic Acid. Bull Environ Contam & Toxic 5(6), 537-541 (1971).

Isensee, A. R. and G. E. Jones. Absorption and translocation of root and foliage applied 2,4-dichlorophenol, 2,7-dichlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Agri Food Chem 19(6), 1210 (1971).

Isensee, A. R. and G. E. Jones. Distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in aquatic model ecosystem. Environ Sci Technol 9, 668 (1975).

Kaufmann, D. D. Pesticides and their effects on soils and water. Am Soc Agron, Spec. Pub. No. 8 (1966).

Kearney, P. C. Metabolism of herbicides in soils. Adv Chem Ser 60: 250 (1966).

Kearney, P. C., E. A. Woolson and C. P. Ellington Jr. Persistence and metabolism of chlorodioxins in soils. Environ Sci Technol 6(12), 1017 (1972).

Kearney, P. C., A. R. Isensee, C. S. Helling, E. A. Woolson and J. R. Plimmer. Environmental significance of chlorodioxins. In Chlorodioxins - origin and fate, E. H. Blair, ed. American Chemical Society, Washington D.C., 105-111 (1973).

Khan, S. U. Equilibrium and kinetic studies of the adsorption of 2,4-D and piclorams on humic acid. Can J Soil Sci 53, 429-434 (1973).

Klingman, D. L., C. H. Gordon, G. Yip and H. P. Burchfield. Residues in the forage and in the milk from cows grazing on forage treated with esters of 2,4-D. Weed 14, 164 (1966).

Koskinen, W. C., G. A. O'Conner and H. H. Cheng. Characterization of hysteresis in the desorption of 2,4,5-T from soils. Soil Sci Soc Am Proc 43(5), 871 (1979).

Lawson, E. R. 2,4,5-T residues in storm runoff from small watersheds. J of Soil & Water Conservation 31(5), 217-219 (1976).

Loos, M. A. Phenoxyalkanoic acids. Chapter 1. In Herbicides: Chemistry, degradation and mode of action, 2nd Edition, Vol 1. P. C. Kearney and D. D. Kaufman, eds. Marcel Dekker, New York (1975).

Lutz, J. F., G. E. Byers and T. J. Sheets. The persistence and movement of picloram and 2,4,5-T in soils. J Environ Quality 2(4), 485 (1973).

Matsumura, F. and H. J. Benezet. Studies on the bioaccumulation and microbial degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Health Perspect 5, 253 (1973).

McCall, P. J., S. A. Vrona, S. S. Kelley. Fate of uniformly carbon-14 ring labeled 2,4,5-trichlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid. J Agri Food Chem 29(1), 100 (1981).

Melnikov, N. N. Aryloxalkycarboxylic acids and their derivatives. Residue Rev 36, (1971).

Miller, R. W. and S. D. Faust. Sorption from aqueuous solutions by organic clays. I. 2,4-D by bentone 24. Adv Chem Ser III, 121 (1972a)

Miller, R. W. and S. D. Faust. Sorption from aqueuous solutions by organo-clays. II. Thermodynamics of 2,4-D sorption by various organo clays. Environ Lett 2, 183 (1972b).

Morton, H. L., E. D. Robinson, R. E. Meyer. Persistence of 2,4-D, 2,4,5-T and dicamba in range forage grasses. Weeds 15, 268 (1967).

National Academy of Science. The effects of herbicides in South Vietnam. Part A, Summary and Conclusions, Washington, D.C. (1974).

National Research Council of Canada. Phenoxy herbicides - their effects on environmental quality with accompanying scientific criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Publ No. NRCC 16075 (1978).

Nesbitt, H. J. and J. R. Watson. Degradation of the herbicides 2,4-D in river water. II. The role of suspended sediment, nutrients and water temperature. Water Res 14(12), 1689 (1980).

Newman, A. S., J. R. Thomas and R. L. Walker. Disappearance of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid from soil. Proc Soil Sci Soc Am 6, 21 (1952).

Newton, M. Disappearance of 2,4,5-T from forest ecosystems. Weed Sci Am Meeting Abstr. 57, pp30 (1971).

Norris, L. A. Degradation of 2,4-D and 2,4,5-T in forest litter. J For 64, 475 (1966).

Norris, L. A. Chemical brush control and herbicide residues in the forest environment. In Symposium proceedings on herbicides and vegetation management in forests, ranges and noncrop lands. Oregon State Univ., Corvallis, OR, 103-123 (1967).

Norris, L. A. Stream contamination by herbicides after fall rains on forest lands. Western Society Weed Sci Res Progr Rep, pp 33-34 (1968).

Norris, L. A. and D. G. Moore. The entry and fate of forest chemicals in streams. In Proceedings, Symposium, Forest land uses and stream environment. Oregon State University, Corvallis OR (1970).

Norris, L. A. Degradation of herbicides in the forest floor. In Tree growth and forest soils, C. T. Youngberry and C. B. Davey, eds. Oregon State University Press, Corvallis, OR (1970).

Norris, L. A., M. L. Montgomery and E. R. Johnson. The persistence of 2,4,5-T in a pacific northwest forest. Weed Sci 25(5), 417-422 (1977).

O'Conner, G. A. and P. J. Wierenga. The persistence of 2,4,5-T in greenhouse lysimeter studies. Soil Sci Soc Amer Proc 37, 398-400 (1973).

O'Conner, G. A. and J. U. Anderson. Soil factors affecting the adsorption of 2,4,5-T. Soil Sci Society Amer Proc 38, 433-436 (1974).

O'Conner, G. A. , P. J. Wieranga, H. H. Cheng and K. G. Doxtader. Movement of 2,4,5-T through large soil columns. Soil Sci 130(3), 157 (1980).

Plimmer, J. R., U. I. Klingebiel, D. G. Crosby and A. S. Wong. Photochemistry of debenzo-p-dioxins. In: Chlorodioxins - Origin and fate, E. H. Blair, ed. Advances in Chemistry Series 120, ACS, Washington D.C. (1973).

Plumb, T. R., L. A. Norris and M. L. Montgomery. Persistence of 2,4-D and 2,4,5-T in chaparral soil and vegetation. Bull Environ Contam and Toxicol 17(1), 1 (1977).

Pocciari, F. 2,3,7,8-tetrachlorodibenzo-p-dioxin decontamination. In, Chloronated phenoxy acids and their dioxins, C. Ramel, ed. Ecol Bull Stockholm 27, 67 (1978).

Que Hee, S. S. and R. G. Southerland. Volatilization of various esters and salts of 2,4-D. Weed Sci 22, 313 (1974).

Que Hee, S. S., R. G. Southerland and M. Vetter. GLC analysis of 2,4-D concentrations in air samples from central Saskatchewan in 1972. Environ Sci Technol 9, 62 (1975).

Radosevich, S. R. and W. L. Winterlin. Persistence of 2,4-D and 2,4,5-T in chaparral vegetation and soil. Weed Sci 25, 423-425 (1977).

Rosenberg, A. and M. Alexander. 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) decomposition in tropical soil and its cometabolism by bacteria in vitro. J Agric Food Chem 23, 705-709 (1980).

Scott, H. D. and J. F. Lutz. Release of herbicides from clay minerals as a function of water content. I. Kaoliniti. Proc Soil Sci Soc Am 35, 374 (1971).

Shadoff, L. A., R. A. Hummel and L. Lamparski. A search for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in an environment exposed annually to 2,4,5-trichlorophenoxyacetic acid ester (2,4,5-T) herbicides. Bull Environ Contam Toxicol 18(4), 478 (1977).

Sheets, T. J. and J. F. Lutz. Movement of herbicides in runoff water. Presentation: Am Soc Agri Engineering, Chicago IL (1969).

Smith, A. E.. The hydrolysis of 2,4-dichlorophenoxyacetate esters to 2,4-dichlorophenoxyacetic acid in Saskatchewan soils. Weed Res 12, 364 (1972).

Smith, A. E.. Field persistence studies with herbicides in prairie soils. In Environmental Quality and Safety. Suppl. Vol. 3. IUPAC 3rd Int. Congress. F. Coulston and F. Korte, eds. (1975).

Smith, A. E. The hydrolysis of herbicidal phenoxyalkanoic esters to phenoxyalkinoic acids in Saskatchewan soils. Weed Res 16, 19 (1976).

Smith, A. E. Soil persistence experiments with (14C) 2,4-D in herbicidal mixtures, and field persistence studies with tri-allate and trifluralin both singly and combined. Weed Research, 19, 165 (1979).

Soderquist, C. J. and D. G. Crosby. Dissipation of 4-chloro-2-methylphenoxyacetic acid (MCPA) in a rice field. Pestic Sci 6, 17 (1975).

Stehl, R. H., R. R. Papenfuss, R. A. Bredewag and R. W. Roberts. The stability of pentachlorophenol and chlorinated dioxins to sunlight, heat, and combustion. In, Chlorodioxin - origin and fate, E. H. Blair, ed. American Chemical Society, Washington D. C. 119-125 (1973).

Stewart, D. K. R. Persistence of 2,4-D, 2,4,5-T and dicamba in a dykeland soil. Bull Environ Contam Toxicol 18(2), 210 (1977).

Stojanovic, B. J., M. V. Kennedy and F. L. Shuman. Edaphic aspects of the disposal of unused pesticides, pesticide wastes and pesticide containers. J Environ Qual 1(1), 54 (1972).

Tarrant, R. F. and L. A. Norris. Residues of herbicides and diesel oil carriers in forest waters: a review. In Herbicides and vegetation management symp, Oregon State University, Corvallis, pp 94-102 (1967).

Torstensson, N. T. L., J. Stark and B. Goransson. The effect of repeated applications of 2,4-D and MCPA on their breakdown in soil. Weed Research 15, 157 (1975).

Vernetti, J. and V. H. Freed. 2,4-D volatility studies, 1962. Prog Rep Dept Agric Chem, Oregon State University, Corvallis OR (1962).

Walker, A. and A. E. Smith. Persistence of 2,4,5-T in a heavy clay soil. Pestic Sci 10, 151-157 (1979).

Ward, C. T. and F. Matsumura. Fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in a model aquatic ecosystem. Arch Environ Contam Toxicol 7, 349 (1978).

Weber, J. B., T. J. Monaco and A. D. Worsham. What happens to herbicides in the environment? Weeds Today 4, 16 (1973).

Wershaw, R. L., P. J. Burcar and M. C. Goldberg. Interaction of pesticides with natural organic material. Environ Sci & Tech 3, 271-273 (1969).

White, A. W. Jr., L. E. Asmussen, E. W. Hauser and J. W. Turnbull. Loss of 2,4-D in runoff from plots receiving simulated rainfall and from a small agricultural watershed. J Environ Qual 5(4), 487-490 (1976).

Wojtalik, T. A., T. F. Hall and L. O. Hill. Monitoring ecological conditions associated with wide-scale applications of DMA 2,4-D to aquatic environments. Pestic Monit J 4, 184 (1971).

Woolson, E. A., R. F. Thomas and P. D. Ensor. Survey of polychlorodibenzo-p-dioxin content in selected pesticides. J Agric Food Chem 20(2), 351-354 (1972).

Woolson, E. A., P. D. J. Ensor, W. L. Reichel and A. L. Young. Dioxin residues in Lakeland sand and bald eagle samples. Adv Chem Ser, E. H.Blair, ed, 120, 112 (1973).

Woolson, E. A. Organoarsenical herbicides. In Herbicides: chemistry, degradation and mode of action, 2nd ed, P. C. Kearney and D. D. Kaufman eds. Marcel Dekker, N.Y., 741 (1975).

Yockim, R. S., A. R. Isensee and G. E. Jones. Distribution and xoxicity of TCDD and 2,4,5-T in an aquatic model ecosystem. Chemosphere No. 3, 215 (1978).

Yoshida, T. and T. F. Castro. Degradation of 2,4-D, 2,4,5-T picloram in two Phillipine soils. Soil Sci Plant Nutr 21(4), 397 (1975).

Young, A. L., E. L. Arnold and A. M. Field studies on the soil persistence and movement of 2,4-D, 2,4,5-T and TCDD. Abstr. No. 226, Weed Sci Soc Am, Las Vegas, Nevada (1974).

Young, A. L., C. E. Thalken and W. E. Ward. Studies of the ecological impact of repetitive aerial applications of herbicides on the ecosystem of test area C-52A, Eglin AFB, Florida. Technical Report AFATL-TR-74-12. Air Force Armament Laboratory, Eglin AFB, Florida, and Department of Chemistry and Biological Sciences. U.S. Air Force Academy, Colorado 80840. 127 p. (1975).

Young, A. L., P. J. Lehn and M. F. Mettee. Absence of TCDD toxicity in an aquatic ecosystem. Weed Sci Soc of Am, Abstr. No. 107, 46 (1976).

Young, A. L., C. E. Thalken, E. L. Arnold, J. M. Cupello and L. G. Cockerham. Fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the environment: summary and decontamination recommendations. USAFA-TR-76-18, U.S. Air Force Academy, Colo. (1976).

Young, A. L., J. A. Calcagni, C. E. Thalken and J. W. Tremblay. The toxicology, environmental fate and human risk of herbicide orange and its associated dioxin. USAF OEHL Technical Report, Brooks Air Force Base, Texas (1978).

Young, A. L. Phenoxy herbicides and microorganisms. In The science of 2,4,5-T and associated phenoxy herbicides, R. W. Bovey and A. L. Young, eds. John Wiley & Sons, New York, 207 (1980).

Zepp, R. G., N. L. Wolfe, J. A. Gordon and G. L. Baughman. Dynamics of 2,4-D esters in surface waters hydrolysis, photolysis and vaporization. Environmental Science and Technology 9(13), 1144-50 (1975).

Zitko, V. Absence of chlorinated dibenzodioxins and dibenzofurans from aquatic animals. Bull Environ Contam Toxic 7, 105 (1972).

D

APPENDIX D

REVIEW OF LITERATURE OF EFFECTS OF AGENT ORANGE IN ANIMALS

REVIEW OF LITERATURE OF EFFECTS OF AGENT ORANGE IN ANIMALS

Each of the components of Agent Orange, including its dioxin contaminant have been studied independently in animal experiments. The following section provides a selective overview of the health effects in animals which have been associated with the use of 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD. For more detailed information see the more extensive reviews by: Young et al. (1978); IARC (1977); Ramel (1978); U.S. EPA (1980); Huff et al, (1980); Bovey and Young (1980); Kimbrough (1980); or Milby et al. (1981).

I. 2,4-D

Based on available evidence, 2,4-D appears to be clearly the least toxic component of Agent Orange, although there has been considerable controversy surrounding several areas of investigation.

A. Acute Toxicity

The oral LD50 for rats has been reported to range from 375 to 2000mg/kg (Young et al. 1978). In dogs this value has been reported to be as low as 100mg/kg and has been accompanied by myotonia, ataxia, and spasm of the hind legs; degeneration of the renal tubules; and necrosis of the liver and intestinal mucosa. (Drill and Hiratzka, 1953).

Toxic symptoms generally noted in animals poisoned with acute doses of 2,4-D have included the following: loss of appetite, loss of weight, depression, roughness of coat, general tenseness, and muscular weakness particularly of the posterior quarters. Postmortem findings usually include irritation of the stomach of small animals, minor evidence of liver and kidney injury, and in some instances congestion of the lungs (Rowe and Hyman, 1954).

B. Subacute and Chronic Toxicity

Subacute and chronic studies in a wide variety of animal species have produced a spectrum of effects ranging from no noticeable effects to death, depending on the route of administration and dosage used in each study. For example, in one study no adverse effects were noted in a group of 25 male and 25 female rats fed a diet for 2 years which contained an average dosage of 1250 mg/kg of 2,4-D acid (Hansen et al. 1971). On the other hand, 3 out of 4 dogs treated with daily doses of 20 mg/kg died within 18 to 49 days, while the surviving animal exhibited severe symptoms of toxicity. Symptoms noted were stiffness of hind legs, ataxia, weakness, difficulty with chewing and swallowing, and occasional bleeding from gums. Weight loss occurred after 7 to 12 days in these animals, and they experienced a terminal drop in lymphocyte count before death (Drill and Hiratzka, 1953).

Many studies have reported no effects or only slight effects in animals under various conditions. Effects which have been reported most commonly are growth effects. Other effects which have been described less frequently include liver and gastrointestinal effects, locomotor difficulties, hematologic and biochemical changes, EEG changes, and, as previously mentioned, death in some cases.

C. Developmental Effects

The embryotoxic and teratogenic potentials of 2,4-D seem to be quite variable with noticeable effects dependent on purity and concentration of the substance, method of administration, species and even strain of animal. The EPA (1980) "2,4-D Fact Sheet" states:

> In almost all tests on rats, mice, and hamsters to evaluate possible reproductive effects of 2,4-D, a no observable effect level (NOEL) has been established below which fetotoxicity was not observed. Only at high levels are life-threatening birth defects such as skeletal malformations observed.

Teratogenic effects occur at doses which approach those necessary for maternal mortality. EPA estimated that the level of exposure necessary to produce fetotoxic effects would be 500 and 1000 times greater than the dosage which might be received in a "worst case" situation.

D. Mutagenic effects

Most tests of the mutagenic potential of 2,4-D have been conducted in bacterial culture, or in plant or animal tissue cultures. Results from most of these tests have been

negative. Shearer (1980), for example, reported that all mutagenic assays of this substance for both forward and reverse mutation in bacteria have been consistently negative, even when conducted in the presence of an activation system prepared from the liver of mice and rats.

Although Syles (1973) found no increase in mutation rate and no evidence of mutagenicity in in vivo testing of 2,4-D in rats, Pilinskaya (1974) found that toxic doses of 2,4-D (100-300mg/kg) administered as a single oral dose significantly increased the frequency of aberrant metaphases (2-4 fold), with single fragments being the primary aberration seen.

Pilinskaya (1974) also observed that treatment of cultured human lymphocytes with 0.02 mg/ml of 2,4-D increased the number of chromatid aberrations (single acentric fragments) and, to a lesser extent, chromosomal aberrations (paired acentric fragments).

Based on available data, the EPA (1980) "2,4-D Fact Sheet" concluded:

> The vast majority of the mutagenicity studies conducted on 2,4-D are negative. However, there are three positive studies. Taken as a group, the results of the studies can best be described as inconsistent and inconclusive.

E. Carcinogenic effects

Young et al. (1978) reviewed the literature on the carcinogenic potential of 2,4-D and concluded the following:

> A review of the summary of the literature on the carcinogenic and

> tumorigenic potentials of 2,4-D in animals revealed that 2,4-D acid, and the isopropyl, butyl and isooctyl esters of 2,4-D did not adversely affect nor increase the incidence of tumors in test animals when fed at levels of 46.4 to 100 mg/kg of diet to mice or 1,250 mg/kg of diet to rats for 18 to 24 months. Those tumors that did occur were not necessarily in target organs and were the type tumors normally seen in aging laboratory animals of the species and strain being studied. Single subcutaneous injections of 21.5 to 215 mg/kg of 2,4-D acid, isopropyl and butyl esters of 2,4-D in DMSO did not produce carcinogenic or tumorigenic responses in male or female mice. A single subcutaneous injection of 21.5 mg/kg of the isooctyl ester of 2,4-D in DMSO did produce an increased incidence of reticulum-cell sarcomas in treated female mice. It should be noted that DMSO itself is now considered to be a potential carcinogen. At 62 mg/kg, 2,4-D acid injected intraperitoneally in mice inhibited the development of Ehrlich ascites tumor being maintained in mice.

A study conducted by Hansen et al. (1971) reported a significant increase in malignancies in a group of rats administered a maximum dose of 1250 ppm 2,4-D for 2 years. The significant increase occurred for total malignant tumors in males, breast neoplasms in females, and lymphsarcomas in both sexes. However, there was also a high incidence of tumors in the control animals studied, and thus the authors concluded that a carcinogenic effect was not shown. Recently Reuber (unpublished, 1979, cited in Milby et al. 1981) has maintained that the initial results reported by the authors were faulty and that a carcinogenic effect of

2,4-D was, in fact, demonstrated by the study. The results of this study are currently undergoing reinvestigation.

EPA (1980) has questioned the adequacy of the research that has been done to explore the carcinogenic potential of 2,4-D. In their "2,4-D Fact Sheet" they state:

> Several rodent studies have been conducted to date but none of these studies produced data that showed 2,4-D was oncogenic in test animals. These tests were conducted a decade ago and are considered (by EPA) to be inadequate by today's scientific standards. New studies on rodents are needed.

II. 2,4,5-T

This second major component of Agent Orange has a moderate overall toxicity rating. Caution must be taken when assessing the animal literature on the health effects of this substance, since the 2,4,5-T tested in many studies has undoubtedly been contaminated by varying degrees of the highly toxic contaminant 2,3,7,8-TCDD.

A. Acute Toxicity

There are species differences in the acute toxicity of 2,4,5-T and its derivatives. For the acid compound acute oral LD50's range from 100mg/kg body weight for dogs to 500mg/kg for rats, while for mixed butyl esters of this compound the LD50 ranges as high as 940 mg/kg for mice (in Young et al. 1978) . In one study (Bjorklund and Erne, 1966), doses of 100mg/kg body weight 2,4,5-T were fed to pigs and resulted in anorexia, vomiting, diarrhea,and ataxia. Autopsy findings included hemorrhagic enteritis and congestion of the liver and kidney. Kimbrough (1980) suggests that this compound would have to be considered very toxic according to the toxicity rating of Gleason et al. (1969).

Pathological changes reported in a recent literature review (Dost, 1978, cited in Milby et al. 1981) included myocardial lesions, bone marrow aplasia and lymphocytic depletion in thymus, spleen and lymph nodes of mice given lethal doses of 2,4,5-T.

B. Subacute and Chronic Toxicity

Groups of rats were fed diets containing 3, 10, 30, or 100mg/kg bodyweight of 2,4,5-T for 90 days (containing less than 1mg/kg TCDD). Pathological changes were noted only in those animals on the 100mg/kg diet. Among these changes were: depression in body weight gain, slight decrease in food intake, and elevation of serum alkaline phosphatase levels. Male rats also had slightly increased serum glutanic-pyruvic transaminase levels (Dow, 1970, cited in WHO, 1971).

Dogs fed 2,4,5-T (98.9% pure) 5 times per week for 90 days at dosage levels of 2, 5, or 10mg/kg body weight exhibited no adverse effects. Daily doses of 20mg/kg body weight resulted in deaths 11-75 days after the beginning of dosing (Drill and Hiratzka, 1953, cited in IARC, 1977).

C. Developmental Effects

Doses of more than 20mg/kg body weight 2,4,5-T (containing less than 0.1mg/kg TCDD) can increase the frequency of cleft palates in some strains of mice. Fetal growth retardation may also be observed when such doses are administered on days 6-15 of pregnancy (NTIS, 1968, cited in IARC, 1977). No clear-cut teratogenic effects have been reported in rabbits, sheep or monkeys. Few data are available concerning possible postnatal changes after prenatal exposure (IARC, 1977).

Milby et al. (1981) summarized the findings of the EPA FIFRA Scientific Advisory Panel (1979). This group concluded that commercial 2,4,5-T produces fetotoxicity and is teratogenic in rats and mice. The no observable effect levels (NOEL) for embryotoxicity for commercial 2,4,5-T taken from the literature and presented to the panel were as follows: rat, 25mg/kg/day; mouse, 20mg/kg/day; hamster, 40mg/kg/day; and monkey, 40mg/kg/day. Another study presented before the panel noted effects suggestive of reproductive toxicity at a dosage of 3mg/kg/day in rats. The panel believed that this dosage schedule should be considered for practical purposes a no observable effect level and recommended that it be used for subsequent evaluation of risk.

D. Mutagenic Effects

Bovey and Young (1980) described a number of tests of the mutagenic potential of 2,4,5-T in mammals and other organisms. Efimenko found single oral doses of 0.01 to 1.0mg/kg of the butyl ester in rats had no effect on the activity of spermatozoa, but increased chromosome aberrations in bone marrow cells without changing their mitotic activity. In chronic experiments at 0.01 to 0.1mg/kg/day for 1 to 7 months, there were dystrophic changes in the kidney and significant gonadotropic action. An increase in frequency of chromosome aberrations in the bone marrow cells was also observed.

Davring and Sunner (1971) showed that small doses of 2,4,5-T could affect female sterility, cause ovary damage, and defective follicular development in young Drosophila melanogaster. Adult flies, however, were unaffected even at high dosages.

Milby et al. (1981) assert, in reviewing the literature, that since virtually all studies of mutagenicity using 2,4,5-T are negative or inconclusive, and since the significance of mutagenicity tests for evaluating human health risk is unclear, there appears to be little immediate concern regarding mutagenic activity from 2,4,5-T in humans.

E. Carcinogenic Effects

Innes et al. (1969) administered 21.5mg/kg/day of 2,4,5-T in the diet to two strains of mice over a lifetime, but found no increase in tumor incidence. Kociba et al. (1979) fed groups of 100 rats each doses of 3, 10, or 30mg/kg of 2,4,5-T for two years. No increase in tumor incidence was reported. Muranyi-Kovacs et al. (1976) found no increase in tumors in mice given 100mg/l 2,4,5-T in drinking water for 2 months, followed by administration of 2,4,5-T at a concentration of 80mg/kg in the diet for a lifespan. (Estimated chlorinated dibenzodioxin level of less than 0.05mg/kg).

The EPA FIFRA Scientific Advisory Panel (1979, cited in Milby et al. 1981), concluded that "it appears that 2,4,5-T which is essentially free of contaminating 2,3,7,8-TCDD is not oncogenic in rats."

III. 2,3,7,8-TCDD

This substance (2,3,7,8-tetrachlorodibenzo-p-dioxin) is by far the most toxic compound associated with Agent Orange. Although it is present in only minute quantities as a contaminant, it has received considerable attention due to its wide range of toxic properties.

A. Acute Toxicity

The dioxin 2,3,7,8-TCDD is possibly the most toxic man-made molecule known. LD50's in animals range from 0.0006mg/kg for the male guinea pig to 50-70mg/kg for monkeys exposed to a single oral dose (in Young et al. 1978). Time to death may be delayed as long as 40 days after a single dose - a very unusual situation, since with most other compounds, animals receiving a toxic dose will die within 2 weeks (Kimbrough, 1980).

Moore et al. (1976) studied mice, guinea pigs and female monkeys and found that all exhibited severe thymus involution, as well as testicular degeneration in the males. Other common effects were reduction in the white pulp of the spleen combined with bone-marrow hypoplasia (decreased cell number). A summary of these and other pertinent findings is included in the accompanying table.

Summary of Acute Toxicity Effects of 2,3,7,8-TCDD*

	Mice	Guinea pigs	Monkeys (female)
Thymus involution	+++	+++	+++
Spleen reduction (white pulp)	+	+	+
Bone-marrow hypoplasia	±	++	+
Liver, megalocytosis/degeneration	+++	-	-
Bile-duct hyperplasia	±	±	+++
Testicular degeneration	++	+++	N/A
Fenal-pelvis hyperplasia	-	++	+
Urinary-bladder hyperplasia	-	++	-
Adrenal-cortical atrophy (Zona Glomerulus)	-	++	-
Hemorrhage: Intestinal	+ -	+ ++	- -
Ascites	++	-	+
Cutaneous lesions	-	-	+++

* Source: Moore et al, 1976, Key as follows:

- \- no effects
- \+ mildly affected
- ++ moderately affected
- +++ severely affected

B. Subacute and Chronic Toxicity

1. Dermatologic effects

2,3,7,8-TCDD is an active skin irritant and induces acnOpeform lesions in the skin of rabbit ears. Chloracne is thought to be the hallmark of TCDD exposure in humans, and an analogous hyperkeratosis and modulation of sebaceous structures to keratin cysts have been noted in monkeys, rats and hairless mice (in Huff et al. 1980).

2,3,7,8-TCDD is known to be a very potent inducer of the enzyme which controls production of porphyrin in the liver. Thus, it is thought to be related to the condition porphyria cutanea tarda.

2. Hepatic effects

The degree of hepatic involvement appears to be dose-dependent,and the severity of the hepatotoxic changes varies across species. Hepatic necrosis caused by this substance is probably a contributing cause of death in rats and rabbits, whereas hepatic necrosis and liver insufficiency are less extensive in mice and are minimal relative to these disorders observed in guinea pigs and monkeys (U.S. NIEHS IARC, 1978).

3. Renal effects

2,3,7,8-TCDD has been shown to decrease the renal function of rats in several studies. Anaizi et al. (1978) inferred from their studies of phenosulfonphthalein secretion in rats that the glomerular structures of these

animals were highly susceptible to 2,3,7,8-TCDD. Likewise, Hooke et al. (1978) noted a decrease in the capacity of renal tissue to transport p-aminohippurate and N-methyl-nicotinamide 7 days after exposure of rats to 25ug/kg of 2,3,7,8-TCDD, as well as a general reduction of GFR and effective renal plasma flow.

4. Endocrine effects

Besides being thought to be related to hormonal imbalances which may lead to acne, hirsutism, and loss of libido in humans, 2,3,7,8-TCDD has also been demonstrated to affect reproductive hormones in animals. For example, Piper (1979) has shown that this compound exerts a suppressive effect upon testicular microsomal cytochrome P-450 content in guinea pigs; Gustafsson and Ingelman-Sundberg (1979) have indicated that serum levels of prolactin and follicle stimulating hormone are affected in treated rats.

Similarly, Barsotti et al. (1979) have studied hormonal alterations in female rhesus monkeys fed a diet containing 500 ppt of 2,3,7,8-TCDD per day for 9 months and noted significant progesterone and estradiol level decreases, as well as a high rate of abortions in the treated animals.

5. Immunologic effects

2,3,7,8-TCDD appears to have a significant influence on immune function in animals. Vos, Faith and

Luster (1980) have summarized findings from a number of relevant studies:

> TCDD induced thymic atrophy and immunosuppression has been reported to occur in most laboratory animals examined but not as yet in humans. Exposure during pre- and/or post-natal life results in more severe effects than if the chemical is administered during adult life and in some species may be a prerequisite for immunosuppression. The effects appear to be focused on T cell functions although T helper cell function, at least in neonatally exposed rats, are unaffected. Humoral immunity is also compromised in most species but requires higher dosage levels than that which effects cell-mediated immunity. Effects on classical macrophage functions have not been observed. Using conventional immunological procedures, the immunological alterations are usually accompanied by signs of clinical toxicity, particularly decreased body weight gains. Surprisingly, decreased resistance to bacterial infection may occur following low-level exposure without concomitant suppression of functional immune assays or clinical signs of toxicity at least in mice. Increased endotoxin sensitivity has been observed following exposure in mice and may play a role in the decreased resistance following infection with Salmonella.

6. Hematologic effects

One of the major target organs for TCDD toxicity is the hematopoietic system (EPA, 1980). Some of the abnormalities noted have been thrombocytopenia in treated rats (Weissberg and Zinkl, 1973); significantly lowered leukocyte and lymphocyte counts in mice treated with as little as 1.0mg/kg TCDD (Zinkl et al, 1973); and anemia

associated with widespread hemorrhage in rhesus monkeys (Allen, 1967).

7. Other effects

As noted in a review by Huff et al. (1980), 2,3,7,8-TCDD stimulates a number of enzyme activities, most notably in the liver. It is a potent inducer of hepatic and renal microsomal drug metabolizing enzymes. Further, TCDD can simultaneously activate and suppress certain microsome-associated foreign-compound and steroid-hormone-metabolizing enzyme systems (Hook et al. 1975), as well as increase the activity of both renal and hepatic glutathione-S transferase (Kirsch et al. 1975).

2,3,7,8-TCDD is the most potent of the chlorinated dibenzo-p-dioxins in inducing hepatic delta-aminolevulinic acid (ALA) synthetase and aryl hydrocarbon hydroxylase (AHH) in chick embryo liver preparations (Poland and Glover, 1973a, 1973b).

C. Developmental effects

Studies of the developmental effects of 2,3,7,8-TCDD in animals have been performed using both the purified dioxin compound and also substances (primarily 2,4,5-T) which are contaminated with the dioxin compound. A number of fetotoxic and teratogenic effects have been reported.

Courtney (1970) demonstrated that mice exposed to 2,4,5-T containing 2,3,7,8-TCDD showed an increased incidence of cystic kidneys, while rats showed an increase

in gastrointestinal hemorrhages and increased ratios of liver to body weight. Other fetotoxic effects of these compounds which have been demonstrated include: thymic atrophy, fatty infiltration of the liver, general edema, delayed head ossification, low birthweight, fetal resorptions, and embryolethality (US EPA, 1980).

Schantz et al. (1979) fed a diet containing 50 ppt 2,3,7,8-TCDD to eight female rhesus monkeys for a period of 20 months. After 7 months, attempts were made to breed the females. In the treated group, 2 animals were able to carry their infants to term, and 2 were not able to conceive. There were 4 abortions and 1 stillbirth noted in this group. In contrast to the dioxin-treated group, all 8 animals in the control group were able to successfully reproduce.

Teratogenic effects have also been tested in a number of experiments. Courtney (1970) reported that 2,4,5-T containing 2,3,7,8-TCDD increased the incidence of cleft palate in two species of mice tested. (Cleft palate is generally thought to be evidence of teratogenesis, while other outcomes such as cystic kidney - noted earlier - are thought to be evidence of fetotoxicity.) Smith et al. (1976) estimated a threshold teratogenic dose of 0.1ug/kg per day 2,3,7,8-TCDD in a study of mice exposed to this substance.

Bovey and Young (1980) noted that Sterling (1975), in reviewing data on TCDD, considered the substance a potent

teratogen and that the literature has frequently stated this same belief. Bovey and Young (1980) also report that Dow Chemical (Anon, 1975), in responding to Sterling's paper, noted that TCDD is a teratogen principally to mice, a species quite susceptible to cleft palate when the pregnant female is exposed to a variety of environmental chemicals or physical stresses. In summary, Bovey and Young (1980) state:

> Quantitatively (TCDD) is a very potent teratogen; however, qualitatively the nature of the teratogenic effect of TCDD is far less than many other compounds, such as thalidamide or Vitamin A. The one teratogenic response most commonly associated with TCDD is cleft palate. TCDD tends to cause death of the embryo or fetus rather than a wide range of abnormalities.

As noted, most studies investigating reproductive outcomes after exposure to 2,3,7,8-TCDD or the phenoxy herbicides have concentrated on these outcomes subsequent to treatment of the female animal. Recently, however, at least one study has investigated the reproductive outcomes resulting from exposure of the male animal. For example, Lamb et al. (1980) attempted to determine the effects of "simulated Agent Orange" on reproduction and fertility of treated male mice. Male mice were given feed containing varying concentrations of 2,4-D, 2,4,5-T, and TCDD such that daily doses ranged from mixtures of approximately 40mg/kg 2,4-D, 40mg/kg 2,4,5-T and 2.4ug/kg TCDD to 20mg/kg 2,4-D,

20mg/kg 2,4,5-T and 1.2ug/kg TCDD. In the treated animals, dose-related liver and thymus toxicity were found and body weight gain was significantly reduced. Liver and thymus toxicity showed significant or complete recovery when the mice were returned to a control diet. Sperm concentration, motility and percent sperm abnormalities were evaluated and no significant effects were noted during or after the dosing periods. At the conclusion of an eight week dosing period treated males were mated to untreated virgin females. Mating frequency, average fertility, percent implantation and resorption sites and percent fetal malformations were all measured in relation to the treatment. No significant decrement in fertility or reproduction was noted in the study. There was no evidence of germ cell toxicity. Survival of offspring and neonatal development were apparently unaffected by paternal exposure to the simulated mixtures of Agent Orange.

D. Mutagenic effects

Experiments investigating the mutagenic potential of 2,3,7,8-TCDD have provided somewhat ambiguous results. Wassom et al. (1977, 1978) have noted that some studies suggest that this dioxin is a mutagen, while other studies have suggested that this is not the case.

A number of in vitro studies have been performed. The US EPA (1980) summarized the studies of the mutagenic effects of dioxins in several Salmonella strains. None of

the strains capable of detecting base-pair substitutions was positive when tested with TCDD, although some investigators had noted positive results in a strain capable of detecting frameshift mutations. (McCann, 1975; Nebert, 1976; Hussain, 1972; Seiler, 1973). Hussain et al. (1972) also reported base-pair substitution mutation in E.coli.

Khera and Ruddick (1973) performed dominant lethal assays in rats which were orally administered doses of 4, 8, or 12ug/kg per day of TCDD. Although the dosages used were toxic to the dams, no evidence of dominant lethal mutations was found.

The American Farm Bureau Federation (1979) concluded that the mutagenic action of 2,3,7,8-TCDD might be involved with DNA repair processes. This would suggest that this substance is an initiator of carcinogenesis. Thus, its mutagenic activity is consistent with carcinogenesis by initiation (in Milby et al. 1981).

E. Carcinogenic effects

Several studies have indicated that 2,3,7,8-TCDD is carcinogenic in animals. Van Miller et al. (1977) studied rats which were orally given TCDD in varying concentrations. The highest doses administered (50, 500, and 1000 ppb) were toxic and killed all animals in this group within 4 weeks. Lower levels (5 or 1 ppb) caused increased mortality and liver toxicity as well as an increase in cancer incidence. Levels of 500, 50 or 5 ppt also caused various types of

cancer. In the 5 ppt group, for example, 5 out of 10 animals had 6 neoplasms (earduct carcinoma, lymphocytic leukemia, adenocarcinoma, malignant histocytoma with metastases, angiosarcoma, and Leydig-cell adenoma) (in Huff et al. 1980). No neoplasms were observed in either the 1 ppt experimental group or the control group.

Kociba et al. (1978) administered doses of 0.1, 0.01, and 0.001mg/kg per day 2,3,7,8-TCDD to rats for two years and noted an increased incidence of various cancers. In the group ingesting 0.1ug/kg per day of TCDD there was an increased incidence of hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates, or tongue and a reduced incidence of tumors of the pituitary, uterus, mammary glands, pancreas, and adrenal glands. Levels of 0.01ug/kg day caused an increase of hepatocellular hyperplastic nodules and of urinary excretion of porphyrins (in females) and also caused an increased incidence of focal alveolar hyperplasia in the lungs. Levels of 0.001ug/kg day did not cause any significant changes in tumor incidence or toxicity.

In commenting on the significance of these two reports, Huff et al. (1980) have noted:

> These two reports show that chronic administration of 2,3,7,8-tetra CDD causes an increased incidence of neoplasms, but not whether 2,3,7,8-tetra CDD acts as an initiator or promoter. This consideration is particularly important because unequivocal evidence is lacking that 2,3,7,8-tetra CDD is a

mutagen or is metabolized and no evidence is available that 2,3,7,8-tetra CDD and/or metabolite(s) bind covalently to macromolecules.

REFERENCES

Allen, J.R., and Carstens, L.A., Light and electron microscopic observations in Macca Mulatta monkeys fed toxic fat, Amer. J. Vet. Res. 28(126):1513-1526, 1967.

American Farm Bureau Federation, "Scientific Dispute Resolution Conference on 2,4,5-T", Sponsored by the American Farm Bureau Federation (AFBF), Park Ridge, Illinois, 1979

Anonymous, Comments by the Dow Chemical Company on the presentation made by Dr. Theodore D. Sterling, Royal Commission Hearings on Herbicides and Pesticides; Vancouver, British Columbia, Canada, July, 16, 1974. The Dow Chemical Co., Midland, MI

Anaizi, N.H., and Cohen, J., The effects of TCDD on the renal tubular secretion of phenolsulfonphthalein, J. Pharmacol, Exp. Ther., 207(3):748-755, 1979

Barsotti, D.A, Abrahamson, L.J., and Allen, J.R., Hormonal alterations in female rhesus monkeys fed a diet-containing 2,3,7,8-tetrachlorodibenzo-p-dioxin, Bull. Environ. Contam. Toxicol. 21(4-5):463-469, 1979

Bjorklund, N., and Erne, K., Toxicological studies of phenoxyacetic herbicides in animals, Acta. Vet. Scand. 7:364-390, 1966

Bleiberg, J., Wallen, M., Brodkin, R., and Applebaum, I.L., Industrially acquired porphyria. Arch. Dermatol. 89:793-797, 1964

Bovey, R.W., and Young, A.L., The Science of 2,4,5-T and Associate Herbicides, New York:John Wiley and Sons, 1980

Courtney, K.D., Teratogenic Evaluation of 2,4,5-T, Science 168:864-866, 1970

Davring, L. and Summer, M., Cytogenetic Effects of 2,4,5-Trichlorophenoxyacetic Acid on Oogenesis and Early Embryogenesis in Brosophila Melanogaster, Hereditas 68:115-122, 1971

Dost, Frank N., Toxicology of Phenoxy Herbicides and Hazard Assessment of Their Use in Reforestation, U.S. Department of Agriculture Forest Service, California-Pacific Region, 1978

Drill, V.A. and Hiratzka, T, Toxicity of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid, Arch. Ind. Hyg. Occ. Med. 7:61-67, 1953

EPA, "Fact Sheet on 2,4-D", (April 22, 1980) and "Press Release" by Barbara Blum, April 29, 1980

Efimenko, L.P., Materials for assessing the gonadotropic and mutagenic action of the herbicide, 2,4,5-T butyl ester, Gig. Tr. Prof. Zabol. 18:24-27, 1974

Esposito, M.P., Tiernan, T.O., Dryden, F.E., Dioxins, Industrial Environmental Research Laboratory, November 1980

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (1979). Review of Notices of Intent to Hold FIFRA Section 6(b) (2) Hearing on 2,4,5-T and Silvex, Report submitted September 27, 1979

Gleason, N.N., Gosselin, R.E., Hodge, H.C., Smith, R.P., Clinical Toxicology of commerical projects. The Williams and Wilkins Co., Baltimore, 1969

Gustafsson, J.A. and Ingelman-Sundberg, M., Changes in Steroid Hormone Metabolism in Rat Liver Microsomes Following Administration of TCDD. Biochemical Pharmacology 28:497-499, 1979

Hansen, W.H., Quaife, M.L., Haberman, R.T., and Fitzhugh, O.G., Chronic toxicity of 2,4-dichlorophenoxyacetic acid in rates and dogs. Tox. Appl. Pharm. 20:122-129, 1971

Hook, G.E.R., Haseman, J.K., and Lucier, G.W., Induction and suppression of hepatic and extrahepatic microsomal foreign-compound-metabolizing enzyme systems by 2,3,7,8-tetrachlorodibenzo-p-dioxin, Chem. Biol. Interact. 10:199, 1975

Hook. G.E.R., Orton, T.C., Moore, J.A., and Lucier, G.W., 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced changes in the hydrxylation of biphenyl by rat liver microsomes, Biochem. Pharmacol. 24:335, 1975

Huff, J.E., Moore, J.A., Saracci, R., Tomatis, L., Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans, Environmental Health Perspectives 36:221-240, 1980

Hussain, S., Ehrenberg, L., Lofroth, G., and Gejvall, T., Mutagenic efforts of XCDD on bacterial systems, Ambio 1:32-33, 1972

Innes, J.R., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I., and Peters, J., Bioassay of pesticides and industrial chemical for tumorigenicity in mice: a preliminary note., J. Nat. Cancer Inst. 42(6):1101-1114, 1969

International Agency for Research on Cancer, IARC monographs on the evaluation of the carcinogenic risk or chemicals to man: some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzo-sioxins and misc. industrial chemicals 14:42-299, 1977

Khera, K.S., and Ruddick, J.A., Polychlorodibenzo-p-dioxin: perinatal effects and the dominant lethal test in the Wistar rates, in E.H. Blair, ed., Chlorodioxins--Origin and Fate (Advances in Chemistry Series 120, American Chemical Society, Washington, D.C.), 1973

Kimbrough, R.D., 2,3,7,8-T - Toxocity in animals relevance to human health, with notes on 2,4,5-T, picloram, cacoldylic acid and 2,4-D, Proceedings from the 2nd Continuing Education Conference on Herbicide Orange, Veterans Administration, May 28-30, 1980

Kimbrough, R.D., Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products

Kimbrough, R.D., Immune alterations, Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products, Elsevier/ North-Holland Biomedical Press, New York, 1980

Kirsch, R., Fleischner, G., Kamisaka, K., and Arias, I.M., Structural and functional studies of ligandin, a major renal organic anion-binding protein, J. Clin. Invest. 55:1009, 1975

Kociba, R.J., Keyes, D.G., Beyer, J.E., Carreon, R.M., Wade, C.E., Cittenber, D.A., Kalnins, R.P., Frauson, L., Park, C.N., Barnard, S.D., Hummell, R.A., and Humiston, G.C., Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats, Toxicol. Appl. Pharmacol. 46:279-303, 1978

Kociba, R.J., Keyes, D.G., Lisowe, R.W., Kalnins, R.P., Dittenber, D.D., Wade, C.E., Gorzinski, S.J., Mahle, N.H., and Schwetz, B.A., Results of a two-year chronic toxicity and oncogenic study of rats ingesting diets containing 2,4,5-T, Rd. Cosmet. Toxicol. 17: 504-521, 1979

Kociba, R.J., Keyes, D.G., Beyer, J.E., Carreon, R.M., and Gehring, P.J., Long-term toxicologic studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in lbaroatory animals, Ann. N.Y. Acad. Sci. 320: 397-404, 1979

Lamb IV, J.C., Moore, J.A., Marks, T.A., Evaluation of 2,4-D, 2,4,5-T, and TCDD toxicity in C57BL/6 mice: reproduction and fertility in treated male mace and evaluation of congenital malformations in their offspring, National Toxicology Program, 1980

McCann, J., et al., Detection of Carcinogens as Mutagens in the Salmonella/ Microsome Test: Assay of 300 Chemicals. Proc. Nat. Acad. Sci. 73: 950-954, 1976

Milby, T.H., Hustings, E.L., Whorton, M.D., Larson, S., Potential Health Effects Associated with the Use of Phenoxy Herbicides, Environmental Health Associates, Inc., October 1, 1980, Revised January 26, 1981

Moore, J.A., Gupta, B.N., and Vos, J.G., Toxicity of 2,3,7,8-Tetrachlorodebenzofuran - Preliminary Results. In: National Conference on Polychlorinated Biphenyls, Chicago, 1975, EPA-560/6-75-004

Muranyi-Kovacs, I., Rudali, G., and Imbert, J., Bioassay of 2,4,5-trichlorophenoxyacetic acid for carcinogenicity in mice, Br. J. Cancer 33(6):626-633, 1976

Nebert, D.W., Thorgeirsson, S.S. and Felton, J.S., Genetic Differences in Mutagenesis, Carcinogenesis, and Drug Toxicity, In Vitro Metabolic Activiation in Mutagenesis Testing, F.J.deSerrers, et al., ed. Elsevier/North Holland Publishing Co., Amsterdam, 195-124, 1976

NTIS (National Technical Information Service) Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Vol. 1, Carcinogenic Study, Washington, D.C., U.S. Department of Commerce, 1968a

NTIS (National Technical Information Service) Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Vol. 2, Teratogenic Study in Mice and Rats, Washington, D.C., U.S. Department of Commerce, 1968b

Pilinskaya, M.H., Cytogenetic effect of the herbicide 2,4-D on human and animal chromosomes, Cytology and Genetics 8(3):6-10, 1974

Piper, W.N., Toxicant Deregulation of Endocrine Heme Biosynthesis, Toxicology Research Projects Directory, 04:06, 1979

Piper, W.N., Rose, J.Q., and Gehring, P.J., Excretion and Tissue Distribution of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin in the Rat, Environmental Health Perspectives 5:241-244, 1973

Poland, A., and Glover, E., Chlorinated dibenzo-p-dioxins: potent inducers ofaminolevulinic acid synthetase and aryl hydrocarbon hydroxylase. II. A study of the structure-activity relationship, Mol. Pharmacol. 9:736, 1973

Poland, A., and Glover, E., 2,3,7,8-Tetrachlorodibenzo-p-dioxin: a potent inducer of aminolevulinic acid sythetase, Science 179: 476, 1973

Reuber, Melvin D., Carcinogenicity of 2,4-dechlorophenoxyacetic acid, Manuscript, NCI Frederick Cancer Research Center, Frederick, Maryland, 1979

Rowe, V.K., and Hymas, T.A., Summary of toxicological information of 2,4-D and 2,4,5-T type herbicides and an evaluation of the hazards to livestock associated with their use, Amer. J. Vet. Res. 15: 622-629, 1954

Schantz, S.L., Barsotti, D.A., and Allen, J.R., Toxicological effects produced in nonhuman primates chronically exposed to fifty parts per trillion 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), Abstract. Toxicol. Appl. Pharmacol. 48(1):A180, 1979

Seiler, J.P., A survey on the mutagenicity of various pesticides, Experientia 29:622-623, 1973

Shearer, R.W., Public Health Effects of the Aquatic Use of Herbicides: 2,4-D, Dichlobenil, Endothall, and Diquat in Literature Reviews of Four Selected Herbicides: 2,4-D, Dichlobenil, Diquot, and Endothall, Municipality of Metropolitan Seattle, 1980

Smith, F.A., Schwetz, B.A., and Nitschke, K.D., Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in CF-1 mice, Toxicol. Appl. Pharmacol. 38:517-523, 1976

Sterling, T.D., Toxic and teratogenic effect of 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Summary of evidence presented by the Royal Commission Hearings of the Assembly Committee on National Resources of the State of Wisconsin, 24pp., 1975

Styles, J.A., Cytotoxic effects of various pesticides in vivo and in vitro, Mutat. Res. 21:50-51, 1973

U.S. National Institute of Environmental Health Sciences/International Agency for Research on Cancer, Long-Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans. Joint Working Group Report, IARC, Lyon, France, 1978

Van Miller, J.P., Lalich, J.J., and Allen, J.R., Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin, Chemosphere 6(9):527-544, 1977

Weissberg, J.B., and Zinkl, J.G., Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin upon hemostasis and hematologic function in the rat, Environ. Health Perspect. 5:119-123, 1973

WHO, 1970 Evaluations of some pesticide residues in food, The Monographs. WHO/Food Add./71.42, pp. 459-477, 1971

Young, A.L., et al., The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin, USAF, OEHL Technical Report TR-78-92, 1978

Zinkl, J.G., Vos, J.G., Moore, J.A., and Gupta, B.N., Hematologic and clinical chemistry effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals, Environ. Health Perspec. 5:111-118, 1973

E

APPENDIX E

REVIEW OF LITERATURE ON REPRODUCTION EFFECTS OF AGENT ORANGE

Appendix E

REVIEW OF LITERATURE ON REPRODUCTIVE EFFECTS OF AGENT ORANGE

The animal studies have been recently reviewed (Wilson, 1977; Grant, 1979). The totality of the animal studies have found the following embryonic and fetal effects resulting from subjecting pregnant females to large doses of one or both of the two herbicides or to dioxin: embryonic death, fetal death, reduced fetal body weight, various minor skeletal anomalies, cystic kidneys, delayed ossification, neonatal edema and hemorrhage, reduced postnatal survival, absent eyelids, cleft palate, neural tube defects and reduced fertility.

The teratogenicity of phenoxy herbicides in experimental animals has been variable, with respect to dosage, species and strain. Most of the work has been done with 2,4,5-T. The amount of dioxin present as a contaminant has been variable. Tests have been done in pregnant female animals, generally with dosages far exceeding those which humans would experience in any non-accidental contact.

In a rat experiment there was a dose response relationship where with increasing dosages of 2,4-D the percentage of skeletal malformations and fetal deaths increased and the number of viable offspring and average fetal weight decreased (Kheru and McKinley, 1972). Similar results were seen for 2,4,5-T. In some experiments postnatal growth retardation was also observed. No changes

in reproductive performance were noticed in animals exposed in utero to these herbicides. Another study of 2,4-D in rats also observed minor skeletal anomalies (wavy ribs, delayed ossification), fetotoxicity and reduced fetal weight, but found no effects on fertility, gestation, Opviability or lactation (Schwetz et al. 1971). Dioxin itself is teratogenic in some species (Courtney and Moore, 1971). Teratogenicity appears to increase with the amount of dioxin contaminating the 2,4,5-T sample (Collins and Williams, 1971).

The current controversy concerning reproductive effects of herbicides relates to the effect on male reproduction, including affects long after the exposure occurred. There is a sparsity of animal data which bears on this aspect. Van Miller and Allan (1977) found, among other toxic effects, decreased spermatogenesis in male Sprague-Dawley rats fed lethal doses of TCDD. There was a marked reduction in testicular DNA synthesis in rats given 0.4mgm/kg intraperitoneally (Seiter, 1977). Rhesus monkeys fed a mixture of dioxins (primarily TCDD), demonstrated a decreased number of primary and secondary spermatocytes and absent spermatids in most cases, but spermatogenia and Sertoli cells were abundant. Similar changes were seen in dioxin treated chickens. These experiments on male rats and chickens were done with lethal and sublethal doses of dioxin. Nevertheless, because of the controversy and

because of some additional animal evidence that paternal exposure to other chemicals is related to some problems of reproductive outcome (Soyko and Jaffe, 1980), a study of the possible role of herbicides in affecting human male reproductive performance is warranted.

The possibility of mutagenicity of herbicides has been raised and has been reviewed (Wasson et al. 1977/1978; Grant, 1979). In over 20 experiments in 15 different systems, 3 studies found 2,4,5-T to be mutagenic (Grant, 1979). Only a few forms of dioxin have been tested for mutagenicity, and the most active form appears to be TCDD (Wasson et al. 1977/1978). In a three generation study of female rats ingesting TCDD, fertility, litter size, survival and growth of neonates was reduced in the F2 and F3 but not the F0 generation at a dose of 0.01 micrograms/kg/day (Murray et al. 1977). No evidence of dominant lethal mutations were found in the offspring of male Wistar rats fed various dosages of TCDD for 7 days prior to mating (Khera and Ruddick, 1973).

As always, the relevance of the animal data are difficult to interpret with respect to the human condition (Emanuel, 1976). Further, in laboratory mice, which are rather susceptible to the herbicides teratogenically, strain differences occur (Gaines et al. 1975). Herbicides have not been teratogenic in some species, such as rabbits (Thompson et al. 1971) and sheep (Binns and Balls, 1971).

No malformations were seen in rhesus monkeys treated with 2,4,5-T, but reduced fetal size was observed (Wilson, 1971). Lastly, the work on teratogenicity which has been done has been almost exclusively in pregnant female animals, always with doses considered to be massive with respect to possible human exposures.

There are several human studies which should be noted. There is a dearth of data on chromosome breakage related to exposure to herbicides (Grant, 1979). The National Academy of Sciences summary (1974) reported a study of chromosome analysis of exposed American workers and controls and found no increased chromosomal abnormalities. Yoder et al.(1973), on the other hand, in the peak spraying season found an increased percentage of chromatid breaks and gaps in lymphocytes of agricultural workers who were exposed to herbicides, primarily 2,4-D, amitrole and atrazine, but also 2,4,5-T. During the off-season, chromated abnormalities were less frequent in the case group compared to the controls. The biologic significance of chromatid breaks and gaps is poorly understood. In New South Wales, Australia, Field and Kers (1979) found a correlation between the season of conception of babies with neural tube defects (NTD) and the season of maximum spraying of 2,4,5-T. They further found a significant correlation between the animal birth prevalence rate of NTD and the usage of 2,4,5-T in Australia in the previous year over a ten year period. In

New South Wales during this period, the birth prevalence rate of NTD increased, while in the U.S.A., the rate decreased (Center for Disease Control, 1980), which is the case for several countries.

In Western Australia, Brogan et al. (1980) found a recent change in the season of conception of babies with cleft lip and palate, with spring and summer conceptions significantly more common than those in autumn and winter. They suggested that "...an association with exposure to insecticides and herbicides seems possible." This study has been strongly criticized by Bower and Stanley (1980) on methodologic grounds: small numbers of cases, no controls, and no particulars of insecticide usage. The question of cleft lip and palate and herbicides was addressed in a different manner in a study from Arkansas (Nelson et al. 1979). In this state, the principal use of 2,4,5-T has been on rice acreage, and the state was divided into high, medium and low exposure counties on the basis of the ratio of rice acreage to total acreage. Years covered were 1943 to 1974. Cases of clefts were ascertained from birth certificates and the Crippled Childrens Service. No significant relationship was found between 2,4,5-T usage (as defined) and rates of facial clefts.

Two very recent studies from New Zealand bear further on the possible relationship between human birth defects and herbicide exposure. In one study (Hanify et al.

1981) a complex statistical analysis was used to test the relationship of 2,4,5-T usage (kg/mg/year) in Northland and birth prevalence rates of congenital malformations during the years 1972-1976. No significant relationships were seen for any birth defect except talipes. The other study (Smith et al. 1981) was a mail questionnaire survey of ground agricultural sprayers as the case group with other agricultural contractors as the control group. It was remarked that, because of summer heat and frequent spraying in rugged terrain, ground sprayers frequently work dressed only in shorts and boots. Further, wives often help their husbands in the field. It would seem that the degree of exposure in the sprayers and their wives is such that if adverse reproductive effects occur in exposure to these chemicals, they would be likely to occur in this group. These sprayers used various insecticides and pesticides and 2,4-D, but 2,4,5-T is the main chemical sprayed. There were 459 married sprayers who reported 1172 pregnancies, compared to 422 agricultural contractors who reported 1122 pregnancies. There were no significant differences in the occurrence of congenital malformations, stillbirths, miscarriages or ectopic pregnancies. The rate of malformations was slightly but not significantly higher in the sprayer group, 2.0% compared to 1.6% in the controls. On the other hand, the sprayers had slightly fewer stillbirths and miscarriages than the controls. Among the

malformations, specifically the sprayers had fewer NTDs (1) than the controls (3), the same number of facial clefts (1 vs 1) and talipes (3 vs 3). While this study of a high expoure group offers no evidence of harmful reproductive effects of herbicides and other chemicals, the number of births is too small to make definitive statements about an effect of small magnitude.

The study which purported to show a relationship between the spraying of 2,4,5-T in the area of Alsea, Oregon, and the subsequent occurrence of spontaneous abortions in humans has been strongly criticized on methodologic grounds (Mantel, 1979; Wagner et al. 1979).

In summary, the few human studies offer conflicting evidence for the relationship between herbicide exposure and reproductive problems, but there are deficiencies in most, if not all, of these studies. As is usually the case, the animal studies, done with generally massive dosages of the chemicals in question, result in a variety of problems depending on the dosages, species and strain. Future studies should use the animal and human studies as guidance for the kinds of problems which should be looked for. These include the following: infertility, spontaneous abortion, stillbirth, low birth weight/prematurity/intrauterine growth retardation, congenital malformations, and deleterious chromosomal and single gene mutations and postnatal survival. It is recognized that this is no small order.

Some of these problems can be studied with relatively small numbers. For instance, every baby has a birth weight and gestational duration. Thus, possible problems of low birth weight/prematurity/intrauterine growth retardation, if they exist, may reveal themselves in a relatively small sample. Problems such as spontaneous abortion, stillbirth and postnatal survival will require larger series. Because of the small birth prevalence rate of congenital malformations, both in general and for specific malformations, still larger series will be required. The largest series will be required to detect possible single gene mutations.

These problems of pregnancy outcome appear to be multicausal and have several confounding factors. For instance, low birth weight, stillbirths and NTDs are related to maternal age, birth order and socioeconomic status (Butler and Alberman, 1969). Most chromosomal aneuploides are related to maternal age. Of particular interest is the recent finding that either parent can contribute the extra chromosome in Downs Syndrome (Magenis et al. 1977). Thus if this chromosomal anomaly is found, the parental source of the extra chromosome should be determined.

With respect to congenital malformations, very specific diagnoses need to be determined because of the heterogenicity of many of the defects. For instance, facial clefts are found in about 150 different syndromes, many of them of known single gene or chromosomal etiology. It

should also be mentioned that almost without exception the known human teratogens each produce a specific syndrome, a specific combination of anomalies. It might be expected that if herbicides are teratogenic, this pattern would be followed. Ideally, it would also be worth while to verify other deleterious outcomes, such as spontaneous abortion.

Vietnam veterans are an aging population and there is a group of sporadic autosomal dominant mutations which are strongly related to paternal age (Friedman, 1981). These defects include achondroplasia, Aperts syndrome and several others. These sporadically occurring dominant mutations, by definition, do not exist in the parents, nor do they recur in subsequent offspring. If any of these sporadic dominant mutations occur in offspring of herbicide-exposed Vietnam veterans, they would be expected to occur shortly after exposure if they are caused by the exposure. If they do occur, it would be difficult to determine if they occur excessively among the veterans' children compared to the general population.

Deleterious autosomal recessive mutations are also theoretically possible. These would not be expressed in the F1 generation and a large series would be necessary to test their occurrence. Lethal X-linked mutations would also require a large series to detect changes in the sex ratio.

The problem of infertility is another difficult aspect to study, since either partner might be the reason

for the couple's infertility. Therefore documentation of which partner is the cause is necessary.

In summary, to test possible harmful reproductive effects of the herbicides used in Vietnam will be is a complex and difficult task. It will be essential to pay attention to confounding factors, the multicausal nature of most these problems, the heterogenecity of many of the congenital malformations, and the sample sizes needed to detect possible effects.

Bibliography

Binns, W., and Balls, L. Nonteratogenic effects of 2,4,5-trichlorophenoxy acetic acid and 2,4,5-T propylene glycol butal esters herbicides in sheep. Teratology, 4:245, 1971.

Bower, C. and Stanley, F.J. Herbicides and cleft lip and palate. The Lancet, 2:1247, 1980.

Brogan, W.F., Brogan, C.E., and Dadd, J.T. Herbicides and cleft lip and p The Lancet, 2:597, 1980.

Butler, N.R. and Alberman, E.D., Perinatal problems. The Second Report of the 1958 British Perinatal Mortality Survey. Edinburgh and London, E. and L. Livingston Ltd., 1969.

Center for Disease Control: Congenital malformation surveillance report, January - December, 1979. Issued December, 1980.

Collins, T.F.X., and Williams, C.H. Teratogenic studies with 2,4,5-T and 2,4-D in the hamster. Bulletin of Environ. Contam. and Toxicology, 6:559-569, 1971.

Courtney, K.D., et al. Teratogenic evaluation of 2,4,5-T. Science, 168:864-866, 1970.

Courtney, K.D. and Moore, J.A. Teratology studies with 2,4,5-trichlorophenoxy acetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. and Appl. Pharmac., 20:296-403, 1971.

Emanuel, I. Problems of outcome of pregnancy: Some clues from the epidemiologic similarities and differences. In Birth Defects: Risks and Consequences. Kelly, S., Hook, E.B., Janerich, D.T., and Porter, I.H., eds, pp. 119-134. New York: Academic Press, 1976.

Field, F and Kerr, C. Herbicide use and incidence of neural-tube defects. The Lancet, 1:1341-1342, 1979.

Friedman, J.M. Genetic disease in the offspring of older fathers. Obstet. & Gynecol., 57:745-749, 1981.

Gaines, T.B., et al. Analysis of strain differences in sensitivity and reproducibility of results in assessing 2,4,5-T teratogenicity in mice. Abstracts of papers for the 14th Annual Meeting of the Society of Toxicology, March 9-13, 1975. Toxic Appl. Pharmac., v. 33, 1975.

Grant, W.F. The genotoxic effects of 2,4,5-T. Mutation Research, 65:83-119, 1979.

Hanify, J.A., et al. Aerial spraying of 2,4,5-T and human birth malformations: An epidemiological investigation. Science, 212:349-351, 1981.

Khera, K.S. and Ruddick, J.A. Polychlorodibenzo-p-dioxins: perinatal effects and the cominant lethal test in Wistar rats in 2,4,5-T formulations. J. Cell Sci., 10:15-25, 1972.

Khera, K.S. and McKinley, W.P. Pre- and postnatal studies on 2,4,5-trichlorophenoxy acetic acid, 2,4-dichlorophenoxy acetic acid and their derivatives in rats. Toxicol. and Appl. Pharmacol., 22:14-28, 1972.

Magenis, R.E., Overton, K.M., Chamberton, J., Brady, T. and Lovrien, K. Parental origin of the extra chromosome in Down's syndrome. Hum. Genet., 37:7-16, 1977.

Mantel, N. An evaluation of the statistical methods used in EPA's "Report of assessment of a field investigation of six-year spontaneous abortion rates in three Oregon areas in relation to forest 2,4,5-T spray practices" (the ALSEA II Report). Unpublished. Bethesda, Maryland: Biostatistics Center, George Washington University, 1979.

Murray, F.J., Smith, F.A., Nitschke, K.D., Humiston, C.G., Kociba, R.J. and Schwetz, B.A.. Three-generation reproduction study of rats ingesting 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol., 41: 200-201, 1977.

National Academy of Science: Report of the Committee on the Effects of Herbicides in South Vietnam; Part A - Summary and Conclusions. Nat'l Acad. of Sciences, Washington, D.C., 1974.

Nelson, C.J., et al. Retrospective study of the relationship between agricultural use of 2,4,5-T and cleft palate occurence in Arkansas. Teratology, 19:377-384, 1979.

Norback, D.H. and Allen, J.R. Biological responses of the non-human primate, chicken, and rat to chlorinated dibenzo-p-dioxin ingestion. Environ. Health Perspect., 5:233-240, 1973.

Schwetz, B.A., Sparschu, G.L., and Gehring, P.J. The effect of 2,4-dichlorophenoxy acetic acid (2,4-D) and esters of 2,4-D on rat embryonal, foetal and neonatal growth and development. Food and Cosmet. Toxicol., 9:801-817, 1971.

Seiler, J.P. Inhibition of testicular CNA synthesis by chemical mutagens and carcinogens, preliminary results in the validation of a novel short term test. Mutation Res., 46:305-310, 1977.

Smith, A.H., et al. Prelimary report of reproductive outcomes among pesticide applicators using 2,4,5-T. The N. Z. Med. J., 93:177-179, 1981.

Soyka, L. and Joffe, J. Male mediated drug effects on offspring. In Schwarz, R. and Jaffe, S., eds., Drug and Chemical Risks to the Fetus and Newborn. New York: Alan Liss, 1980.

Thompson, D.J., Emerson, J.L., and Sparschu, G.L. The study of the effects of 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) on rat and rabbit fetal development. Teratology, 4:243, 1971.

Van Miller, J.P. and Allen, J.R. Chronic toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats, Fed. Am. Soc. Exp. Biol., 36:396, 1977.

Wagner, S.L., et al. A scientific critique of the EPA ALSEA II study and report. Environmental Health Sciences Center, Oregon State University, Corvallis, October 25, 1979.

Wassom, J.S., Huff, J.E., and Loprieno, N. A review of the genetic toxicology of chlorinated dibenzo-p dioxins. Mutation Research, 47:141-160, 1977-78.

Wilson, J.G. Abnormalities of intrauterine development in non-human primates. In Diczfalusy, E. and Standley, C.C., eds. The use of non-human primates in research on human reproduction. Acta Endocrin. (Suppl.) No. 166: 261-292, 1971.

Wilson, J.G. Environmental Chemicals. In Handbook of Teratology, v. 1, General principles and etiology. Wilson, J.G., and Fraser, F.C., eds. New York: Plenum Press, pp. 357-385, 1977.

Yoder, J, Watson, M., and Benson, W.W. Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. Mutation Research, 21:335-340, 1973.

F

APPENDIX F

REVIEW OF LITERATURE ON HUMAN HEALTH EFFECTS FROM AGENT ORANGE

Appendix F

REVIEW OF LITERATURE ON HUMAN HEALTH EFFECTS FROM AGENT ORANGE

As noted earlier, Agent Orange was a defoliant comprised of equal parts of the phenoxy herbicides 2,4-D and 2,4,5-T and was contaminated by varying amounts of 2,3,7,8-TCDD. Since this defoliant mixture has never been released for general use, but rather has been associated almost exclusively with military operations, information regarding human health effects from its use has been principally based on studies of the components. This information has been derived from a variety of studies of industrial accidents, poisonings, and occupational exposures, as well as from a limited number of studies describing exposure of the general population to these substances.

I. Major Health Outcomes Associated with 2,4-D Exposure

Relatively few studies examining the human health effects of 2,4-D have been conducted. However, based on available animal and human data, it appears that this substance is clearly the least hazardous of the phenoxy acid herbicides (Milby et al. 1980). Moreover, unlike 2,4,5-T, 2,4-D is not contaminated by the highly toxic dioxin, 2,3,7,8-TCDD. (It has generally been assumed that 2,4-D is

not contaminated by any form of chlorinated dibenzo-p-dioxin. Recent studies by Cochrane et al. (1980), however, have indicated a potential for contamination by much less toxic di-, tri-, and/or tetra-chlorodibenzo-p-dioxins, although the 2,3,7,8-TCDD isomer has not been found.

A number of cases of acute exposure to high doses of 2,4-D have been reported in the literature. Nielsen et al. (1965) reported on the suicide of a 23-year-old male who ingested an estimated 6 gm or greater of this substance (equivalent to a dose of about 80 mg/kg). At autopsy all organs showed marked acute congestion, and severe, degenerative changes were found in the ganglion cells of the central nervous system. Several other authors have reported on no-effect exposures to this herbicide at lower known dosages. Young et al. (1978) have summarized adverse effects associated with poisoning by large doses of 2,4-D (or by the herbicide MCPA-s-methyl-4-chlorophenoxyacetic acid) including: CNS disorders, abnormal enzyme levels, anemia, thrombocytopenia, skeletal myositis with myoglobinuria, myocardial irritability, loss of color vision, peripheral nervous system disorders, pulmonary edema, and renal disorders.

Young et al. (1978) have summarized the major findings in the literature describing the adverse effects following exposure of field workers and applicators to 2,4-D

by either percutaneous or inhalation exposure. Common findings in these seven studies (which are mostly individual case reports) were peripheral neuropathy, CNS depression or dysfunction, gastrointestinal irritation, nephropathy, and asthenia. Also noted were hematopoetic depression, myopathy, cardiopathy, and dermatitis. In two of the studies (Goldmann et al. 1959, Todd, 1962), the four patients examined had only incomplete recovery from peripheral neuropathy during observation periods exceeding one to three years.

Tsapko (1966) reported transient symptoms of field workers who entered an area immediately after it was sprayed with 2,4-D. These symptoms included headache, retrosternal pain, general weakness, vertigo, nausea, vomiting, and mild leukopenia.

Bashirov (1969) examined 292 workers including 44 women involved with the production of 2,4-D. (Both the amine salt, and butylester were produced - the latter being of particular interest in that it is the form found in Agent Orange.) Headaches, the asthenic syndrome (characterized by anxiety and depressive-like manifestations), and gastrointestinal problems were particularly noted. Percentages of these workers presenting with various symptoms were as follows (in Young et al. 1978): weakness, fatiguability, headaches in 63%; asthenic syndrome with vegetative dysfunction in 61%; anorexia, bitter taste in

mouth, dyspepsia, abdominal pains, constipation in 51.7%; vertigo in 33%; dyspnea on exertion in 26.7%; and tachycardia, and precordial pain in 17.8%.

Fifty of these individuals were selected for controlled studies involving the liver and stomach. Bashirov noted that there were significant differences between the case and control groups in amount of gastric secretion, and in the antitoxin and carbohydrate functions of the liver. Additionally, there appeared to be a correlation between length of service and the changes in the functional state of the stomach (in Young et al. 1978).

EPA (1980) has indicated that, since most of the scientific data relevant to the registration and use of 2,4-D products since the 1940's has been based is quite old, there are currently significant gaps in the information regarding the potential for 2,4-D to cause carcinogenic, reproductive, neurotoxic and other health effects.

II. Major Health Outcomes Associated with Exposure to Dioxin, 2,4,5-T, and Other Dioxin Contaminated Compounds

Since in human exposures, 2,4,5-T and other related substances have almost without exception been contaminated with the much more toxic compound 2,3,7,8-TCDD, the contribution of the latter contaminant to the health effects attributed to exposure to the underlying compound must be carefully weighed. Separation of the effects of the dioxin from those of the underlying compound has in general not been possible. Therefore, in the following consideration of health outcomes, the effects of dioxin, 2,4,5-T, TCP, and related products will be considered together unless specifically noted.

A. Dermatologic

1. Chloracne

Chloracne is the health outcome most frequently and consistently associated with dioxin exposure. It can be caused by 1) skin contact, 2) ingestion, or 3) respiration of any of a number of chlorinated organics including chlorinated dibenzodioxins and dibenzofurans. It is often confined to the face which seems to be very susceptible no matter what the route of exposure. However, it can start on the legs or elsewhere and spread to the entire body (Jirasek, 1973). Lesions from this disease may last for anywhere from several months to more that 15 years. Bleiberg et al. (1964) maintained that previous adolescent

acne seems to predispose to severe chloracne; however, Poland, (1974) did not find this to be true. Individuals seem to vary greatly in susceptibility and there may be a lack of correlation between duration of exposure and severity or presence of the disease. Halprin, (1980) asserts that the only feature that distinguishes chloracne from normal acne is the development of characteristic acneform eruptions within one to three months after exposure to certain halogenated compounds. Generally, he maintains, the condition clears within one to five years. In Vietnam the disease was not observed in either ground troops or Ranch Hand troops, many of whom had been periodically examined by specially trained medical personnel. Halprin further theorizes that acne from Agent Orange would have developed one to three months postexposure; that in 1980 10% of acne cases would still be active; and that in 90% of persons having contracted the condition there would remain only scars which would not be distinguishable from normal acne. Harman, (1971) observed that of new patients with skin problems in Vietnam, only 3.8% were diagnosed as having acne. This condition often worstened within 6 weeks of arrival in Vietnam. However, as mentioned above, there were no definitive diagnoses of chloracne noted in Vietnam. Further, individuals with significant pre-existing acne were largely kept out of Vietnam.

Crow (1978) has suggested that all chloracnegens seem to be systemic toxins, but the dose needed for chloracne is much lower than that needed for systemic poisoning. Others, however, have maintained that systemic toxicity can occur independent of chloracne in dioxin-exposed individuals. Thus, there appears to be some question as to whether the systemic toxicity of this compound parallels its acnegenicity. Hay, (1979) questions whether chloracne is a sensitive indicator of dioxin exposure.

The most significant mechanism of toxicity for dioxin seems to be its enzyme induction ability, which may contribute to chloracne as well as other conditions which will be discussed further.

2. Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is "a disorder of heme pigment metabolism characterized by skin sensitivity, accumulation of excess pigment in the liver, and the build-up of the various porphyrin pigments. Skin findings include skin fragility, bullous lesions, pigmentation, and photosensitivity. It may be either herditary or acquired. The latter is usually associated with hepatic disorders". (Young et al. 1978).

Bleiberg et al. (1964) found that 11 out of 29 workers with chloracne acquired during the manufacture of 2,4-D and 2,4,5-T had PCT as evidenced by increased uroporphyrins. The severity of PCT was not proportional to

the severity of chloracne, and neither was it correlated with presumed exposure to 2,4-D or 2,4,5-T. Rather, previous liver damage seemed to predispose individuals to this condition. Jirasek, et al, (1973, 1976) found that 11 of 76 patients with chloracne had PCT. Eleven of 50 patients in the associated follow-up study had consistently elevated uroporphyrin levels while 12 persons had intermittently elevated levels. Other porphyrin levels were not elevated. Of the patients with elevated uroporphyrin levels 10 also had hyperpigmentation or hypertrichosis. In a study of the same cohort Pazderova-Vejlupkova et al. (1980) found that of patients with increased elimination of uroporphyrins one-half had dermal PCT symptoms. Crow, (1978) hypothesized that enzyme induction is the likely basis for porphyria caused by TCDD since this substance is known to be the most potent inducer of the enzyme delta-aminolevulinic acid synthetase - which controls porphyrin production.

Poland et al. (1971) have hypothesized that PCT and chloracne are independent syndromes.

3. Hyperpigmentation/hirsutism

Bleiberg et al. (1964) noted that 17 out of 29 individuals with chloracne had hyperpigmentation. At the same time, 14 of the 29 had hirsutism, which was always located on the temples. These conditions paralleled the severity of chloracne. Likewise Poland et al. (1971) found

that with an increasing acne score both of these conditions as well as scarring and eye complaints increased. Jirasek et al. (1973) described a cohort of 76 chloracne cases in which 19 individuals had either hyperpigmentation or hypertrichosis of the face or both without evidence of a porphyrin metabolic disorder.

4. Mucous membrane irritation

Symptoms and signs of mucous membrane irritation are mentioned in a variety of studies. Typically, Poland et al. (1971) described a number of individuals exposed to 2,4-D and 2,4,5-T in a manufacturing process. Some of the symptoms noted were itching of eyes, frequent tearing, bloodshot eyes and styes. Eleven percent of the individuals studied experienced inflammation of the buccal mucosa, while another 31% experienced hyperemia of the nasal mucosa. The extent of exposure to organic solvents or other substances which might have contributed to these symptoms was not described.

B. Internal

1. Liver damage

Bleiberg et al. (1964) had observed some liver dysfunction in individuals manufacturing 2,4-D and 2,4,5-T, although Poland et al. (1971) in resurveying the population at later date, found hepatic function mostly normal. (TCDD concentrations in the trichlorophenol used at the plant dropped from 10-25 PPM down to C.1PPM at the time of the second survey.)

Goldmann, (1973) found that of a group of 42 individuals with chloracne 4 had hepatitis. Of the 14 most severe cases studied 6 had liver damage. Jirasek et al. (1976) noted abnormal liver function in 11 out of 50 cases which they studied. Pocchiari et al. (1979) noted that 8% of subjects from a general population living in an area moderately to highly contaminated with TCDD showed hepatomegaly with idiopathic etiology, while another 24% showed hepatomegaly with an etiology dependent on alcohol or viral hepatitis. The author noted that no information is available on the criteria by which the hepatomegaly was evaluated. Huff et al (1980) have reported that an analysis of mortality rates for 1975-77 for two towns in the Seveso, Italy, area has shown an apparent increase in deaths from liver cirrhosis, although overall mortality has not seemed to change. They suggested that the validity and significance of these observations should be carefully evaluated.

Seventeen veterans claiming exposure to Agent Orange were studied and found to have a particular type of autoimmune antibody which reacts with the smooth muscle and nuclear components "and is often associated with several chronic liver diseases" (in Anon, 1980).

2. Elevated serum hepatic enzymes

Bleiberg et al. (1964) found elevated serum hepatic enzymes in a group of workers which they studied.

Similarly May, (1973) noted abnormal liver function tests in workers involved in a TCP explosion. Most of these tests returned to normal within 10 days.

Jirasek et al. (1976) reported that elimination of delta-aminolevulinic acid (ALA) was twice as high for individuals exposed to dioxin-containing substances as for controls. 2,3,7,8-TCDD has been demonstrated in experiments to be a potent inducer of this enzyme (ALA) as well as aryl hydrocarbon hydroxylase (AHH). (Also see Appendix B - Animal Effects.)

Martin and Walker (1979) described raised gamma glutamyl transpeptidase levels in dioxin-exposed workers.

3. Disorders of fat metabolism

Jirasek et al. (1976) found lipid metabolism changes in half of a group of 55 patients who had been involved in the manufacture of 2,4,5-T. In a five year follow-up study of the same group Pazderova-Vejlupkova et al. (1980) detected hyperlipemia in 67%; hyperchloresterolema in 56%; and hyperphospholipemia in 42% of the individuals studied. Many of the changes in lipid metabolism improved over the course of ten years.

Walker and Martin, (1979) studied 8 men with chloracne due to occupational exposure to TCDD, and found elevated triglyceride levels in them. These 8 individuals, when compared with controls, were found to have high density

lipoprotein (HDL) levels below the mean, total cholesterols levels above the mean, and total/HDL cholesterol ratios consistent with higher than average risk of ischemic vascular disease.

4. Disorders of carbohydrate metabolism

May, (1973) noted glycosuria in workers involved in an explosion of a TCP plant. Goldmann et al. (1973) and Jirasek et al. (1974) also found evidence of disorders of carbohydrate metabolism. Pazderova-Vejlupkova, et al, (1981) found that after follow-up of 55 individuals hospitalized in 1968-69 for chronic TCDD intoxication, 20% had "pathological" glucose tolerance tests, and another 20% had "pathological diabetic" flat glucose tolerance tests at the end of a ten year period.

5. Cardiovascular disorders

Jirasek, (1976) hypothesized that lipid metabolic disturbances associated with TCDD may contribute to arteriosclerosis. In a later study the author described instances of hypertension in individuals exposed to dioxin. Pazderova-Vejlupkova et al. (1980) found no cardiovascular problems of significance after a ten year follow-up of individuals, some of whom had been exposed to dioxin more than a dozen years earlier, although the size of the cohort studied was relatively small (55 individuals).

In 1963 an industrial accident released TCDD into the workplace at the Philips Duphar plant in Amsterdam.

There appeared to be a higher than expected incidence of myocardial infarctions in the individuals exposed in this incident (in Hay, 1979).

6. Respiratory tract disorders

Goldmann, (1973) noted that 5 out of 42 individuals with chloracne had tracheobronchitis as well and that 6 out of the 14 most severe cases had bronchitis.

7. Urinary tract disorders

Pazderova-Vejlupkova (1980) in a ten year follow-up study of exposed workers found no associated renal problems.

Kimbrough et al. (1977) found a single case of hemorrhagic cystitis associated with inflammation of the bladder wall, and focal polynephritis in a six year old girl exposed to a TCDD contaminated horse arena, though this condition was not noted several years later in a re-examination.

8. Pancreatic disorders

In a review of studies for IARC/NIEHS Huff et al. (1980) noted that pancreatic disorders were reported in Goldmann, (1972 and 1973). Goldmann, (1973) described one visitor who developed fatal pancreatic necrosis with chloracne after a 1958 visit to a plant which had had an accident involving TCDD in 1953.

9. Gastrointestinal disorders

Poland et al. (1971) noted that 30% of workers surveyed in a 2,4-D and 2,4,5-T plant had one or

more of the following GI complaints on an intermittent basis: nausea, vomiting, diarrhea, abdominal pain, or blood in stool. Approximately 8% had a history of "ulcers". The authors noted that, although the prevalence of gastrointestinal complaints seemed high, lack of comparison information from other studies would have made judgment of the abnormality or normality of the prevalence of these findings only conjectural.

10. Other internal and physiologic disorders

Goldmann, (1972) noticed a general increased susceptibility to infections among workers he was studying. Pocchiari, (1979) described a notable increase of infections in children following TCDD contamination of the general environment but thought that this increase may have been due to better ascertainment of cases.

Jirasek et al. (1976) noted that mean total blood protein was higher than expected for a group of individuals exposed to dioxin.

Martin, (1979) reported hypocalcemia in dioxin exposed workers.

C. Neurological

1. Polyneuropathies (peripheral neuritis, etc.)

Goldmann, (1972) reported that of 7 individuals with CNS problems in a cohort of 42 individuals

with chloracne, 3 out of the 7 had polyneuritis. Pazderova-Vejlupkova (1980) at the end of a ten year study of 55 individuals noted polyneuropathies in 33%. They hypothesized that this condition was due to TCDD action on nerve tissue and may have been potentiated by its negative effects on fat and carbohydrate metabolism.

2. Lower extremities weakness

This condition has been noted in several studies (e.g., Pazderova-Vejlupkova, et al, 1981, Poland et al. 1971, Goldmann et al. 1972).

3. Sensory impairments

Several studies have reported various sensory impairments involving sight, hearing, smell, and taste after dioxin exposure. Poland et al. (1971) for example, found that in 14% of workers in one study, experienced decreased hearing acuity (defined as inability to hear a watch ticking 1 cm from the ear.) The study did not indicate whether other sources of noise were controlled.

4. Central nervous system/peripheral nervous system disorders

Goldmann et al. (1973) reported that in a cohort of 42 individuals who had developed chloracne, 7 also developed CNS disorders. Jirasek, (1976) noted mild to moderately severe neurologic disorders in 17 of 55 workers studied and noted that some type of CNS neurological

symptoms were present in all cases. Peripheral neuronal damage occurred in 13 cases and usually involved the legs. Twenty-seven percent of the patients had an abnormal EEG (one very abnormal) in a follow-up cohort of individuals manufacturing 2,4,5-T (Jirasek et al. 1974).

Pocchiari et al. (1979) noted pathology in the peripheral nervous system which was often subclinical, as evidenced for example by decreased nerve conduction velocities. There was an increase in the percentage of idiopathic clinical and subclinical damage noted between a 1977 and a 1978 screening. However, motor conduction velocity and slow fiber conduction velocity tests on 200 workers from the two factories in the most highly exposed zone at Seveso were not significantly different from known reference values.

5. Various symptoms

A number of other neurological and related symptoms were noted in several studies. Among the recurring complaints were headaches, pain in arm and legs, muscular pains, overall tiredness, neuromuscular weaknesses, and loss of appetite (Goldmann, 1972, 1973; Jirasek, 1973). Many of these conditions were described as being more severe in relation to the presence of chloracne.

D. Psychiatric

1. Neurasthenic/depressive syndromes and other outcomes

A wide variety of neurasthenic and depressive conditions have been noted in individuals exposed

symptoms of asthenia are common and need not be related to chemical exposure.

E. Reproductive outcomes

A number of reports have explored the relationship between the use of dioxin-contaminated compounds in the environment and reproductive effects such as miscarriages or birth defects in the general population. (See Appendix C for further details.)

EPA (1979) initiated a study of miscarriages among women residing in an area in which 2,4,5-T and other herbicides were sprayed regularly in the surrounding forests. In this "Alsea II" study EPA concluded that there was a significantly higher rate of spontaneous abortions in the study area than in rural or urban control areas; that there was a statistically significant seasonal cycle to the spontaneous abortion rate; and that this cycle seemed to be positively associated with the time and concentration of the sprayings. The findings of this study have been strongly criticized by a number of authors (Wagner et al. 1979; Cook, 1980; Oregon Environmental Health Sciences Center, 1979.) These individuals contend that, among other weaknesses, both numerator (number of hospitalized spontaneous abortions) and denominator (number of births) were erroneous; a seasonal trend was only noted for one year, and may have been due to random variation; there was no correlation between the amount of herbicide used and the

number of abortions; and spraying information was misleading.

An incident at Seveso, Italy in 1976, involved exposure of a general population to dioxin contamination of their environment after an explosion at a nearby TCP plant. Homberger et al. (no date, cited in JRB, 1981) noticed a constant decline in birth rate from 17.1 to 12.6 per 1,000 for the years 1973-1977 which they attributed, however, to psychological factors resulting in increased voluntary birth control rather than to the direct effects of the TCDD.

Pocchiari et al.(1979) indicated that "no adequate evaluation of effect of TCDD exposure on frequency of spontaneous abortions was possible" at the time their study was conducted at Seveso. They noted that there were problems with the limited reliability of their estimates and that there may have been confounding effects in the findings due to the large number of therapeutic abortions. They also reported on the morphologic analysis of fetuses from 30 therapeutic and 4 spontaneous abortions and indicated that "no fetal damage indicating a mutagenic, teratogenic, or embryotoxic effect of TCDD-exposure was detected". Again, they conceded that there were problems with methodology due to the difficulty of detecting minor malformations and particularly organ damage in young fetuses; and due to the difficulty of determining exposure of the women involved.

In similar analyses, Tenchini et al. (1977) found a higher number of structural aberrations in the fetal tissues than in the maternal blood samples of fibroblast cells from adult tissues, but the frequency of these aberrations did not appear to be greater than expected to occur spontaneously in cultures of comparable cell types. Tenchini et al. point out that these preliminary findings do not indicate whether the higher frequencies of chromosome aberrations in fetal tissues were due to chromosome damage caused by 2,3,7,8-TCDD exposure (in Huff et al. 1980).

Other studies examining the relationship of 2,4,5-T and other herbicides to reproductive outcomes include the following:

McQueen et al. (1977) examined the relationship between this compound and neural tube defects in New Zealand and concluded that "there is no evidence to implicate 2,4,5-T as a causal factor in human birth defects".

Aldred et al. (1978) studied 2,4-D and 2,4,5-T use in Yarram, Australia and concluded that there was no relationship of their use to birth defects in a group of babies born in the district for the two years investigated.

Nelson et al. (1979) noting that increased rates of cleft palate and cystic kidney as well as embryotoxicity and teratogenicity were attributed to 2,4,5-T exposure in animals explored the relationship of cleft palate rates to usage of the compound for agricultural purposes in Arkansas. No significant differences were found in the cleft palate

rates between supposedly high and low exposure counties. The authors suggested that the problem should be re-studied, and noted that differences may not have been detected due to the limitations of the ecological study design.

Hanify et al. (1981) compared birth malformations identified from hospital records with densities of monthly aerial 2,4,5-T spraying in certain areas of New Zealand, and found a significant association between talipes and spraying (no other malformations, including cleft lip, were associated with spraying.)

It should be noted that virtually all of the studies in the literature deal with the consequences of exposure of females to these substances to subsequent reproductive outcomes. Information regarding reproductive outcomes in female spouses after male exposure to these compounds is a necessary area of exploration for further studies.

F. Mortality

Cook et al. (1980) traced between 1964and 1978 a cohort of 61 persons thought to have been exposed to TCDD in 1964 during the manufacture of TCP (as evidenced by signs of chloracne in 1964). The authors subdivided the population by date of exposure, and high or low exposure jobs, for analysis but found no significant differences in the number or types of deaths observed. The authors noted that this was a small cohort and thus had low probability of detecting a real difference. However they felt that the 14 year

latency period which was used should have been sufficient to detect results from a potent carcinogen. They thus concluded that TCDD was not a potent carcinogen.

Zack and Suskind, (1980) studied all perons with chloracne attributable to a 1949 TCP accident. One hundred twenty-one white males were followed from 1949 to 1978 with 100% ascertainment. The SMR for all deaths was 0.69. SMRs for specific causes of death, including malignant neoplasms and diseases of the circulatory system were not significant. Again, the study cohort was small. Further, the authors assumed that all skin disorders identified from plant medical records were chloracne. Therefore, individuals with any skin disorder comprised the cohort under study and may have represented a misclassification of exposure and thus may have underestimated risk of TCDD exposures.

Ott et al. (1980) studied a cohort of 204 workers from process crews manufacturing 2,4,5-T from 1951 to 1971. Mortality by duration of exposure and by interval since first exposure showed higher observed than expected rates only for "external causes". From medical records no cases of chloracne or PCT had been found. 1969 estimates of 2,4,5-T levels ranged from less than 0.1 mg/cu.m. to 6.2 mg/cu.m. Again this cohort was relatively small. Furthermore, more than 75% of the defined cohort worked less than 12 months in the jobs involving presumed heavy exposure.

Thiess et al. (1977) found the overall mortality of a cohort of 75 persons followed for an average of 20 years after a TCP accident at a BASF plant to be less than or equal to several sets of external controls. However, they did find an excess of gastrointestinal cancer deaths with 4 observed vs. 1-2 expected deaths. The authors also noted an excess of stomach cancer in this group.

G. Cancer

1. Primary liver cancer

Tung, (1973) alleged that primary liver cancer occurred in excess in Vietnam as a result of Agent Orange exposure of the general population. Though many other authors have noted varying degrees of liver damage or malfunction related to dioxin, none have reported an excess of liver cancer. Liver cancer is, of course, a rare disease.

2. Stomach cancer

Thiess et al. (1977) reported an excess of malignant neoplasms in a cohort exposed to TCP after 20 years follow-up. Included were an excess of GI cancers (4 observed vs 1-2 expected) and a significant excess of stomach cancers (2 observed vs less than 0.2 expected for each of 3 control groups in the 65-75 years age group).

Axelson et al. (1979) observed an apparent excess of stomach cancer among a cohort of 348 railroad workers exposed to phenoxy acids and amitrol.

3. Soft tissue sarcoma

Honchar and Halperin (1981) combined information from 4 cohorts exposed to TCP or 2,4,5-T (their own data combined with previously released data from Zack and Suskind (1980); Cook et al. (1980); and Ott et al. (1980 describing Monsanto and Dow workers). Although each of the individual cohorts did not reveal a significant excess of deaths related to soft tissue sarcomas, the combined cohorts together revealed 2.9% of deaths due to this condition vs. 0.07% expected.

Several case-control and cohort studies involving phenoxy acids and soft tissue sarcoma have been conducted by a group of Swedish authors. Most of these studies have been very well designed and have made strong efforts to control for confounding factors which may have otherwise influenced study findings.

Hardell, (1977) in clinical observations noted that a significant portion of patients with malignant mesenchymal tumors (a relatively rare condition) had reported massive occupational exposures to phenoxy acids 10-20 years prior to their condition (a reasonable latency period for development of cancer). Hardell and Sandstrom, (1979) further investigated this association by studying workers exposed to phenoxy acetic acids. They found a significant excess of malignant mesenchymal tumors in these individuals (estimated relative risk of 5.3). Efforts were made to control for

to TCDD (Goldmann, 1972, etc.). Pazderova-Vejlupkova, (1981) found a wide variety of psychiatric problems in workers exposed to TCDD. At the time of initial observation of dioxin intoxication, 64% of the workers were described as having neurotic symptoms and signs with disorders of vegetative nervous system, as well as neurasthetic and depressive complications. Pazderova-Vejlupkova, (1980) attributed many of the psychological problems to fear of disfigurement, death and disability on the part of the workers. After follow-up and treatment the depressive and anxiety components were reported to have completely disappeared.

Young et al. (1978) noted that many asthenic and other vegetative symptoms have been described in 2,4,5-T, TCP, and TCDD intoxication. For purposes of their report, they described asthenia as including the following: headache, apathy, fatigue, anorexia, weight loss, sleep disturbances, decreased learning ability, decreased memory, dyspepsia, sweating, muscle pain, joint pain and sexual dysfunction. True pathology is closely interwoven with the depression which undoubtedly exists as a result of other disorders, particularly the disfigurement of chloracne, therefore causing difficulty in interpretation of these symptoms. The authors pointed out that the signs and

other confounding factors such as smoking, working with other chemicals, rural residence, etc.

Eriksson et al. (1981) found a signficant association between use of phenoxy acids and soft tissue sarcoma (estimated relative risk of 6.8). Individuals working with phenoxy acids without dioxins or dibenzofurans (such as MCPA; 2,4-D; mecoprop; dichloroprop) had an estimated relative risk of 4.2.

Norstrom et al. (1979) performed an analysis of dioxin content in phenoxy herbicides used in Sweden and the United States in the periods covering the studies mentioned above and found values of 0.4 to 1.1 ppm for Scandinavian formulations compared with up to 6 ppm for U.S. batches.

4. Malignant lymphomas

Hardell et al. (1980) found an estimated relative risk of malignant lymphoma (Hodgkins and non-Hodgkins) of from 4.3 to 7.0 for workers exposed to phenoxy acids (excluding chlorophenols).

5. Other cancers

Epstein (Congressional testimony, July, 1980, p.173) suggested that preliminary reports concerning veterans (as yet unanalyzed) may indicate a high incidence of testicular cancer, even when allowing for selection bias. In one group of about 5,000 plantiffs approximately 200 testicular cancers (mainly seminomas) had been reported.

III. Major Health Effects Attributed to Exposure to Agent Orange

Agent Orange has been alleged to have caused a wide variety of health effects in the two populations principally exposed to it: the general population of South Vietnam, and military personnel serving in that country during the war. Considering the former group first, one can briefly categorize the major health outcomes reported.

A. Reproductive effects

Cutting et al. (1970) in a study of stillbirths and hydatidiform moles in a sample of Saigon, provincial, and district hospitals for the years 1960-1969, reported a decline in stillbirth rate, and no increase in malformation rate during this period (which includes the years of heaviest herbicide use.)

Meselson et al. (1972) noted that an apparent increase in the number of patients with some particular birth defects (e.g., cleft palate without cleft lip) relative to other birth defects appeared tohave been associated with the periods of herbicide spraying. In reanalyzing the data, NAS (1974) noted that herbicide spraying did not appear to be related to the distribution of birth defects.

Tung et al. (1971) reported a substantial number of cases of Down's syndrome and other deformities (ocular lesions, valgus feet, exaggerated lumps on forehead, etc.)

in children conceived and born when the spraying had occurred. He also reported that the number of chromosome abnormalities in these refugees to the North was higher than in normal people. The NAS Herbicides Report (1974) could find no conclusive evidence of association between exposure to herbicides and birth defects in humans.

Tung (1977) also reported that in May, 1966, 22 out of 73 pregnant women who had suffered eye inflammation after heavy spraying, had spontaneous abortions.

B. Liver cancer

Tung (1973) reported an increase in the number of people with primary liver cancer in proportion to all cancer patients admitted to Hanoi hospitals (1962-1968). Ten percent of cancer cases during this period were liver cancer cases, as compared to 2.9% in the period 1955-1961. However, no spraying of North Vietnam occurred during the war. Therefore, those individuals allegedly exposed to Agent Orange would have had to have been exposed in South Vietnam. Further, The author cautioned that dioxin may not have been the only causal agent involved, and that other factors such as aflatoxins and viral hepatitis infections must be considered.

C. Other adverse effects

The NAS Herbicides Report (1974) also reports on five major groupings of symptoms reported by many individuals as being related to herbicide exposure. These are:

1. respiratory tract symptoms (coughing, shortness of breath, soreness of throat, inability to breathe, bleeding from the nose, coughing blood, etc.)

2. central nervous system symptoms (headaches and dizziness)

3. gastrointestinal tract symptoms (diarrhea, nausea, stomach ache)

4. skin and ocular symptoms (skin sores, rash, eye irritation)

5. generalized symptoms (pain, fever, fatigue, trembling, perspiring, palpitations and general soreness)

Tung (1970) has further categorized a wide variety of acute symptoms experienced during the spraying of herbicides, as well as three major "syndromes" which represent secondary effects. The major symptoms detailed in one group of 179 hospitalized patients include: sensation of heat in the nose, rhinorrhea, sneezing (91%); vomiting sometimes with diarrhea (73%); sensation of burns in the eyes, tear shedding, sometimes with edema of the eyelids (73%); headache, asthenia (70%); sensation of burns on the skin, sometimes with erythema and phlyctenules (41%); and tachycardia, sometimes with giddiness or fainting (38%). The three "syndromes" comprised of secondary effects have been divided into: 1) syndrome of prolonged asthenia; 2)

syndrome of the eyes (ocular syndrome); and 3) genetic syndrome, which he has described further in several articles. Likewise, Tung has mentioned the skin disease chloracne among Vietnamese inhabiting sprayed areas. (This condition was not reported in U.S. troops stationed in Vietnam.)

The U.S. military personnel serving in Vietnam comprised the second major population exposed to Agent Orange. The symptoms and diseases which have been claimed to be related to Agent Orange exposure - and which represent the focus of the present study - are wide-ranging. They include health effects in all systems, including neurologic, gastrointestinal, genitourinary, hepatic, cardiovascular, respiratory, and reproductive systems; and represent a broad spectrum of diseases including several cancers and major reproductive outcomes.

Discussion

Although a wide variety of animal and human studies have explored the potential health hazards of the components of Agent Orange, no consistent pattern of findings regarding the health effects of these substances has emerged.

Animal studies have provided much basic information on the two herbicides and the dioxin contaminant contained in Agent Orange. Unlike human studies, they have provided information on known dosages administered by known routes of exposure. The compounds have generally been administered in relatively pure form, isolated from contaminants and other confounding chemical substances, and have been administered under a strict schedule under highly controlled conditions.

2,3,7,8-TCDD is clearly the most toxic of the substances associated with Agent Orange. It is thought to be the most toxic synthetic chemical known, has an extremely low LD50 in many species, and affects many organ systems at acute and chronic doses. It is a very potent enzyme inducer. It has caused chloracne-like skin lesions and has been found to interfere with porphyrin metabolism. It has been shown to be hepatotoxic, and may result in adverse effects in the immune system. This dioxin has been carcinogenic in several species, although mutagenicity tests have produced unclear results. TCDD has been shown to be a

strong teratogen, although this teratogenicty may be more of a quantitative rather than qualitative nature.

2,4,5-T has been described as having a moderate to high acute toxicity. It does not appear to be carcinogenic or mutagenic based on current evidence, although it may be teratogenic at levels approaching the maternal lethal dose. In evaluating the effects of 2,4,5-T, it is necessary to consider whether contamination by the toxic TCDD may have influenced results observed in a given study.

2,4-D appears to be a compound of moderate acute and chronic toxicity. Carcinogenic and mutagenic testing have been inconclusive. This compound may be teratogenic at levels approaching the maternal lethal dose.

There is sufficient animal evidence to conclude that human studies of Agent Orange are warranted. On the other hand, much of the animal data must be tempered by several classic warnings:

1) Many of the animal experiments reviewed in the literature have used extremely high doses of these substances - much higher than the relative doses which might be encountered by humans. Compounds with a margin of safety, or a no effect level for humans, may appear to be more toxic than warranted in animal studies.

2) There is a great difference among species in their susceptibility to the effects of TCDD, 2,4,5-T and 2,4-D. These compounds may be metabolized, stored and

excreted differently by various species, and thus, what is teratogenic, carcinogenic, or highly toxic to one species, may be relatively innocuous to another species.

3) Many of these experiments used only a small number of animals either for the total experiment or at given dosage levels. Small numbers may erroneously result in or obscure apparent experimental outcomes.

With these considerations in mind it is evident that caution should be exercised in extrapolating the results of animal experiments to humans. The results from these studies can nonetheless serve as valuable indicators of possible human effects.

In contrast to animal studies of the components of Agent Orange, human studies have been characterized by unknown dosages often encountered through multiple routes; by exposure for periods of time which are often unknown; by exposure to other chemical substances and agents which may confuse the results; and by other factors which beset observational studies. With these limitations in mind, however, it is possible to roughly characterize some of the findings in the literature.

Generally, it has not been possible to separate the health effects of 2,4,5-T and other dioxin-containing compounds from those of the underlying contaminant, 2,3,7,8-TCDD in human studies. Therefore, health effects from these substances must be considered together. The only

consistent finding associated with these substances has been chloracne. Porphyria cutanea tarda has also been reported in a number of instances, and may suggest an adverse liver response. Both of these conditions may be related to the potent enzyme-inducing properties of TCDD. A wide range of symptoms and diseases in most organ systems has been suggested, although evidence for many of these is inconclusive. Although carcinogenic effects have been postulated in several studies, currently available data does not support teratogenic or reproductive effects.

Acute exposure to high doses of 2,4-D may result in a variety of transient symptoms of intoxication including gastrointestinal upset, headache, vertigo, and weakness. Peripheral neuropathy following exposure has been reported. In some persons the hematopoeitic system may be affected. Carcinogenic, teratogenic or adverse reproductive effects have not been supported in the literature.

Findings of these studies may have resulted from influences other than the study factor alone. In these, and other studies, one must think in terms of defining the exposure; defining the outcome; and accounting for other factors which may confuse the relationship if one is to attempt to discern a causal pattern.

Many of these studies are characterized by the following weaknesses:

Definition of exposure - Persons in these studies have been exposed to an unknown dosage of the supposed agent over an uncertain period of time. Exposure may have been by multiple routes, but is generally unknown. Exposure to the agent of interest is almost certainly accompanied by exposure to other, possibly harmful, substances as well (e.g., other herbicides, solvents, etc.).

Definition of outcome - Most seriously, many of these studies have not established a baseline of health with which to compare an individual pre- and post-exposure. Almost without exception, appropriate control groups with which to compare the experience of the exposed individuals have not been included, are not appropriate, or are not described; hence many of the reported diseases and symptoms may be the result of background health problems which have been erroneously attributed to the agent under study. Further, definition of outcomes are often incomplete or inadequate. Measurement criteria are not well described, or are otherwise unaccounted for. Hence, many of the positive findings in these studies may be the result of spurious or inaccurate reporting.

Confounding - Confounding occurs in an epidemiologic study when the true relationship between the study and outcome variables of interest are distorted by the influence of another variable (which is not under study). Thus, in the studies presented in this appendix confounding may occur when agents other those under study (i.e., 2,4-D; 2,4,5-T;

or 2,3,7,8-TCDD) have been responsible for the health outcomes attributed to the study substances. Such confounders in the studies investigated may include: other chemicals in the workplace or environment; smoking; alcohol consumption; or socioeconomic or age differences between groups. Any of these potential confounders may contribute to the broad spectrum of health outcomes reported in these studies. For example, organic solvents used in manufacturing can cause mucous membrane irritation and other symptoms. Smoking is a well-documented cause of many chronic respiratory and cardiovascular disorders, as well as a broad range of symptoms. Excess alcohol consumption may be associated with a number of types of hepatic problems as well as neuropsychiatric symptoms and diseases. Socioeconomic factors and age are known to be associated with a substanial number of health outcomes. In spite of this fact, very few of the studies attempted to control for these confounders, although many authors at least acknowledged the potential influence of these factors on their study results. Thus, a marked presence of these confounders in individuals studies in a case-series or survey, or their unequal distribution between study and control groups, could have seriously influenced the findings of these studies, and may have erroneously suggested an association between study and outcome factors.

It has been pointed out that serious design difficulties in many studies may serve to erroneously create or enhance an impression that exposure to a given agent results in the health outcomes observed in the study. It must, on the other hand, be noted that study design limitations can obscure true health outcomes as well as create them. Some of the typical weaknesses in these studies which may serve to mask true differences are the following. 1) Appropriate questions regarding outcomes may not have been asked. Generally, for example, meaningful assessment of reproductive outcomes in workers, spouses, and children has not been attempted. 2) The outcome variables studied may not be the most appropriate or sensitive indicators for assessment of pathology from these exposures (e.g., mortality); 3) The latency period may not be sufficiently long to detect outcomes of interest. For example, as noted by several authors, cancer would not as yet be an expected outcome from the study of the 1976 Seveso TCDD exposure of a general population; 4) A small number of subjects is characteristic of many of the studies. The result of a small sample size is to decrease the ability of the study to detect true differences.

While the human studies, because of their limitations, do not provide definitive evidence of health

effects from Agent Orange, or its constituents, they do provide clues for use in further studies.

Aldred, J. E. et al. (1978). Report of the consultative council on congenital abnormalities in the Yarram District. Presented to both houses of the Australian Parliament.

Anonymous. (1980). Letter to the editor, Science News 117, 55.

Axelson, O., Edling, C., Kling, H., Andersson, K., Hogstedt, C., and Sundell, L. (1979). Updating of the mortality among pesticide exposed railroad workers. Lakartidningen, 76, 3505-3506.

Bashirov, A. A. (1969) Health conditions of workers producing herbicides of amine salt and butyl ester of 2,4-D acid. Vrach. Delo 10, 92-95.

Bleiberg, J., Wallen, M., Brodkin, R., and Applebaum, I. L. (1964) Industrially acquired porphyria. Arch. Dermatol., 89, 793-797.

Bovey, R.., and Young, A.L., 1980 The Science of 2,4,5-T and Associated Herbicides. (New York: John Wiley and Sons).

Cochrane, W. P., Singh, J., Miles, W., Wakeford, B., and Scott, J. (1980) Analysis of technical and formulated products of 2,4-dichlorophenoxy acetic acid for the presence of chlorinated dibenzo-p-dioxins. Laboratory Services Division, Food Production and Inspection Branch, Canada Agriculture, Ottawa, Ontario, Canada K1A005.

Cook, Ralph R., Townsend, Jean C., Ott, M. Gerald and Silverstein, Lawrence G. (1980). Mortality experience of employees exposed to 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). Journ. Occup. Med., 22, 530-532.

Cook, Ralph R. (1980). Letter to the editor, JAMA, 243:14.

Crow, K. D. (1978). Chloracne - an up to date assessment. Ann. Occup. Hyg. 21, 297-298

Cutting, R. K., Phuoc, T. H., Ballo, J. M., Benenson, M. W., and Evans, C. H. (1970) Congenital malformations, hydatidiform moles and stillbirths in the Republic of Vietnam 1960-1969. U.S. (Washington, DC.: Department of Defense. U.S. Government Printing Office No. 903.233.) 29 pp.

EPA, (1979). Report of Assessment of a Field Investigation of Six-year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices. Opp, OTS. Environmental Protection Agency.

EPA, (1980). Respondents Prehearing Brief on the Risks Associated with the Registered Uses of 2,4,5-T and Silvex. U.S. Environmental Protection Agency. FIFRA Docket Nos. 415, et al. January 25, 1980.

Epstein, Agent Orange Update, Hearing before the Committee on Veterans Affairs, U.S. Senate, September 10, 1980, pp. 173.

Eriksson, M., Hardell, L., Berg, N. O., Moller T., Axelson, O. (1981). Soft-tissue sarcomas and exposure to chemical substances; a case-referrent study. Br J. Indus. Med., 38, 27-33.

Goldmann, P. J. (1973). Severe, acute chloracne, a mass intoxication due to 2,3,7,8-tetrachlorodibenzo-dioxin. Der Hausarzt, 24(4), 149-152.

Goldman, P. J.. (1972) Extremely severe acute chloracne due to trichlorophenol decomposition products. A contribution to the perna problem. Arbeitsmedizin Socialmedizin Arbeitshygiene 7(1), 12-18.

Halprin, K.M. (1980). Chloracne recognition and its significance. Presented at the 2d Continuing Education Conference on Herbicide Orange, Washington, DC, May 28-30.

Hanify, J. A., Metcalf, P., Nobbs, C. L., and Worsley, K. J. (1981). Aerial spraying of 2,4,5-T and human birth malformations: an epidemiological investigation. Science 212.

Hardell, L., Eriksson, M., Lenner, P, Malignant Lymphoma and Exposure to Chemical Substances, Especially Organic Solvents, Chlorophenols and Phenoxy Acids, Lakartidningan 77(4):208-210, 1980.

Hardell L: Malignant mesenchymal tumors and exposure to phenoxy acids; a clinical observation. Lakartidningen 74:542-46 (1977).

Hardell, L. (1977). Soft-tissue sarcomas and exposure to phenoxyacetic acids and cancer. Lakartidningen 74, 2753

Hardell, L., Sandström A. (1979). Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br. J. Cancer 39, 711-17.

Harman, L. E. (1971). Chapter 21: Skin Diseases in United States Military Personnel Serving in Vietman, in The Skin. (Amsterdam: International Academy of Pathology) pp. 423-434.

Hay, A. (1979). Accidents in trichlorophenol plants: A need for realistic surveys to ascertain risks to health. Ann. N.Y. Acad. Sci.. 320, 321-324.

Homberger, E., Reggiani, G., Sambeth, J., and Wipf, H. K. (no date) The Seveso accident: its nature, extent and consequences. Ann. Occup Hyg., 22, 327-366.

Honchar, P. A., and Halperin, W. E. (1981). 2,4,5,-T, trichlorophenol, and soft tissue sarcoma. Lancet, Jan. 31, 268-269.

Huff, J. E., Moore, J. A., Saracci, R., and Tomatis, L. (1980). Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Envir. Health Perspec., 36, 221-240.

International Agency for Research on Cancer. (1977).. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and misc. industrial chemicals. 15, 42-299.

Jirasek, L., Kalensky, J., and Kubec, K. (1973). Acne chlorina and porphyria cutanea tarda during the manufacture of herbicides. Part I. Cesk. Dermatol., 48(5), 306-315.

Jirasek, L., Kalensky, J., Kubec, K., Pazderova, J., and Lukas, E. (1974). Acne clorina, porphyra cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides, Part II Cesk. Dermatol., 49(3), 145-157.

Jirasek, L., et al. (1976). Chloracne, porphyria cutanea tarda and other intoxications by herbicide. Der Hautarzt., 27, 328-333.

JRB Associates, Draft Bibliography, Health Effects of Herbicides Used in Vietnam, May 5, 1981.

Kimbrough, R. D.. Carter, C. D., Liddle, J. A., Cline, R. E., and Phillips, P. E. (1977) Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Arch. Environ. Health, 32(2), 77-86.

Martin, J.V., 2,4,5-T, Letter, The Lancet, December 8, 1979, pp. 1243.

May G: Chloracne from the accidental production of tetrachlorodibenzo-dioxin. Br J Ind Med 30:276-83 (1973).

Meselson, M.S., Westing, A.H., Constable, J.D. and Cook. R.E. (1972) Preliminary report of herbicide assessment commission of the American Association for the Advancement of Science. U.S.A. Congressional Record. In: Proceedings and Debates of the 92nd Congress, Second Session 118, Part 6, March 2-9, pp. 6806-6813.

Milby, T.H., Hustings, E.L., Whorton, M.D., Larson, S., Potential Health Effects Associated with the Use of Phenoxy Herbicides, Environmental Health Associates, Inc., October 1, 1980, Revised January 26, 1981.

National Academy of Science: Report of the Committee on the Effects of Herbicides in South Vietnam: part A — Summary and Conclusions. National Academy of Sciences, Wash, D.C. (1974).

Nelson, C. J., Holson, J. F., Green, H. G., and Gaylor, D. W. (1979). Retrospective study of the relationship between agricultural use of 2,4,5,-T and cleft palate occurrence in Arkansas. Teratology, 19(3), 377-384.

Nielsen, K., Kaempe, B., and Jensen-Holm, J. (1965). Fatal poisoning in man by 2,4-dichlorophenoxyacetic acid (2,4-D): Determination of the agent in forensic materials. Acta Pharmacol. Toxicol., 22, 224-234.

Norstrom, A., Rappe, C., Lindahl, R., and Buser, H. R. (1979) Analysis of some older Scandinavian formulations of 2,4-dichlorophenoxy acetic acid and 2,4,5-trichlorophenoxy acetic acid for contents of chlorinated dibenzo-p dioxins and dibenxofurans. Scand.J. Work Environ & Health 5, 375-378.

Oliver, R. M. (1975). Toxic effects of 2,3,7,8- tetrachlorodibenzo 1,4-dioxin in laboratory workers. Br. J. Ind. Med., 32, 49-53.

Oregon Environmental Health Sciences Center: A Scientific Critique of the EPA Alsea II Study and Report. Oregon State University, Corvallis (1979).

Ott, M. G., Holder, B. B., and Olson, R. D. (1980) A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. J. Occup. Med., 22(1), 47-49.

Pazderova, J., Lukas, E., Nemcova, M., Pickova, J., Jirasek, L. (1981) The Development and Prognosis of Chronic Intoxication by Tetrachlorodibenzo-p-dioxin in Men. Arch. Env. Hlth., 36(1), 5-11.

Pazderova-Vejlupkova, J., Lukas, E., Nemcova, M., Pickova, J., and Jirasek, L. (1980). Chronic poisoning by 2,3,7,8-tetrachlordibenzo-p-dioxin. Pracov. Lek., 32, 204-209.

Pocchiari, F., Silano, V., Zampieri, A. (1979). Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. Ann. N.Y. Acad. Sci., 320, 311-320.

Poland, A. P., Smith, D., Metter, G., and Possick, P. (1971) A health survey of workers in a 2,4-D and 2,4,5-T plant. With special attention to chloracne, porphyria cutanea tarda, and psychologic parameters. Arch. Environ. Health, 22(3), 316-327.

Reggiani, G. 1979..Estimation of the TCDD Toxic Potential in the Light of the Seveso Accident. Arch. Toxicol. (Suppl.), 291-302.

Taylor, J. S. (1979). Environmental chloracne: Update and overview. Ann. N.Y. Acad. Sci., 320, 295-307.

Thiess, A. M., and Frentzel-Beyme, R. (1977) Mortality study of persons exposed to dioxin following an accident which occurred in the BASF on 13 November 1953. Presented at the Fifth International Conference of Medichem - Occupational Health in the Chemical Industry, 9 pp.

Todd, R. L. (1962). A case of 2-4D intoxication. J. Iow Med. Soc. 52, 663-664.

Tenchini, M.L., et al. 1977. Approaches to Examination of Genetic Damage after a Major Hazard in Chemical Industry: Preliminary Cytogenic Findings on TCDD-exposed Subjects after Seveso Accident. Presented at the Expert Conference on Genetic Damage Caused by Environmental Factors, Oslo, Norway, May 11-13.

Tung, T.T., Anh, T.K., Tuyen, B.Q., Tra, D.X., Proceedings of Reunion internationale de scientifiques sur la guerre chimique au Viet Nam, E. Lederer, 91-Orsay, 12 December 1970.

Tsapko, V.P. (1966). The herbicide 2,4-D as a health hazard in agriculture. Gig. Sanit., 31, 449-450.

Tung, T. T., An, T. T., Tam, N. D., et al. (1973). Le cancer primaire du foie au Vietnam. Chirurgie 99, 427-436.

Tung, T. T., Tugen BQTKA, Tra, D. X., et al. (1971). Clinical effects of massive and continuous utilization of defoliants on civilians. Vietnamese Studies, 29, 53-81.

Wagner, S. L., Witt, J. M., Norris, L. A., Higgins, J. E., Agresti, A., and Ortiz, M. (1979). A Scientific Critique of the EPA Alsea II Study and Report. Environmental Health Sciences Center, Oregon State University, Corvallis.

Walker, A. E., and Martin, J. V. (1979). Lipid profiles in dioxin-exposed workers. Lancet, 8113, 446-447.

Young, A. L., Calcagni, J. A., Thaiken, C. E., and Tremblay, J. W. (1978). The toxicology, environmental fate, and human risk of herbicide orange and its associated dioxin. USAF Occupational and Environmental Health Laboratory Report No. USAF OEHL - 78 - 92.

Zack, J. A., and Suskind, R. R. (1980). The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. Journal of Occupational Medicine, 22(1), 11-14.

Young, A.L., et al. 1978. The Toxicology, Environmental Fate and Human Race of Herbicide Orange and Its Associated Dioxin. USAF, OEHL Technical Report TR-78-92.

G

APPENDIX G

REVIEW OF POPULAR PRESS ARTICLES ON AGENT ORANGE

REVIEW OF POPULAR PRESS ARTICLES ON AGENT ORANGE

I. Why review the nonscientific literature?

An epidemiologic study of the health effects due to Agent Orange exposure must consider nonscientific as well as scientific issues. Since this study has been mandated to address a highly emotional and political situation, as well as to answer an epidemiologic question, an acceptable and appropriate study design cannot ignore the political and emotional issues involved. For this reason, a review of the nonscientific media (i.e., magazines, newspapers, brochures, books, films, congressional testimonies, etc.) is important - it is here that these important issues will be voiced.

The following is a summary of the Agent Orange/Vietnam story as presented by the nonscientific media. The purpose of this review is threefold: 1) to summarize the Agent Orange story as it has been interpreted and presented to veterans and the public by the nonscientific media, so as to understand the Agent Orange story as it is likely to be perceived by veterans and the general public; 2) to point out misinformation, misinterpretations and conflicting information in the nonscientific media, and consequently, to uncover possible areas of confusion and/or misinformation among veterans and the public; 3) to highlight the concerns and complaints of

veterans and the general public relating to Agent Orange and the study of its health effects (e.g. suspected health effects and other possible significant exposures). The understanding gained in this review is a necessary step in the design of an epidemiologic study which is acceptable to veterans and the public, a study which is not only scientifically sound, but which also addresses the emotional and political issues surrounding the basic scientific question. This is not a comprehensive, but rather a selective, review. (Note: The information presented in this section does not necessarily represent our opinions or the facts as we see them; this section attempts to summarize the Agent Orange story as interpreted and presented by the nonscientific media.)

II. The Agent Orange/Vietnam situation as presented by the nonscientific media

A. Vietnam and the use of Agent Orange

1. Vietnam era statistics

According to the Vietnam Veterans of America (1, 2), 2,800,000 Americans served in Vietnam during the 11 year Vietnam era, 1,600,000 saw combat duty, 300,000 were wounded, and 57,000 died; 80% were volunteers, not draftees; the average age in 1981 of the Vietnam vet is 34 years.

2. The spraying of Agent Orange

The details of Agent Orange spraying in Vietnam have been reported in numerous popular sources, some

of which present conflicting information. Thus, confusion is likely to exist on this subject. The reported time period that Agent Orange was used in Vietnam varies between sources - reported periods of spraying are 1961 to 1970 (3, 4, 5), 1962 to 1970 (6), August 1962 to February 1971 (7) and 1965 to 1970 (8, 5). According to the VA, 90% of the total herbicide used in Vietnam was sprayed from fixed-wing aircraft under Operation Ranch Hand; spraying was also accomplished via helicopter, truck, boat, and backpack (9). Reportedly, 90% of Agent Orange was used for forest defoliation to deprive the Viet Cong of cover and to uncover areas of Viet Cong activity, 8% was used for crop destruction, and 2% was used around base perimeters (5, 9). Herbicides were also reportedly used to clear supply lines and communication lines (9).

One magazine reports that by 1967, 5% of South Vietnam's land mass had been sprayed (10). Another reports that by the end of the war, 10% of Vietnam's main forests had been "poisoned" as well as 33% of its mangrove forests and 3% of its cultivated land (11). The Veterans Administration is informing veterans that 8-10% of the land mass of Vietnam was sprayed with herbicides, with the most heavily sprayed areas being Rung Sat, the A Shau Valley and the DMZ (9).

The total amount of all herbicides sprayed in Vietnam has been estimated to be 17 million gallons (11) and 107 million pounds (12). According to Max Cleland and the VA, 94% of all defoliant used from 1965 to 1971 was Agent Orange (2, 9). Estimates of the amount of Agent Orange sprayed in Vietnam range from 10.6 million gallons (4) to 12 million gallons (13), and from 20,000 tons of Agent Orange (8) to more than 40 million pounds of 2,4,5-T (3).

Dioxin concentration is reported to have averaged 1.8 ppm (14), yet, conflictingly, range from 3-50 ppm (15, 2) and from 0.05 ppm to 47 ppm (16). The estimated total amount of dioxin dropped over Vietnam as reported in the popular press varies from 350-360 pounds (3, 17) to 1,000 pounds (3).

3. Exposure to Agent Orange

An estimated 2-2.8 million Americans served in Vietnam during the time of herbicide spraying (15, 3, 2). Estimates of the number of G.I.'s possibly exposed to Agent Orange as reported in various magazine and newspaper articles range from 46,000 (18), to at least 50,000 (17), to 80,000 (19), to 2.4 million (8).

In their educational film being shown to veterans, "Agent Orange: A Search of Answers" (9), the Veterans Administration has informed veterans of three possible modes of Agent Orange exposure: direct contact, entering a recently sprayed area, and consumption of contaminated food or water. The VA reports that those veterans at highest

risk of exposure are those who may have had direct contact with Agent Orange: Ranch Handers; Ranch Hand ground support personnel such as those who drained residue out of the drums, those who operated the machinery for moving the drums around, and maintenance crews who worked on Ranch Hand aircraft; ground troops who loaded Agent Orange from a drum to a backpack sprayer; backpack sprayers; drum handlers; and door gunners for helicopters used to spray Agent Orange. The VA also states in this film that the A Shau Valley, the DMZ, and Rung Sat were areas of concentrated and repeated spraying, and a veteran stationed in these areas is likely to have come into contact with herbicides. Also, it is stated that only a small amount of Agent Orange and TCDD ever reached the jungle floor because of the thick triple-canopy jungle, and that TCDD photodegrades "within a short time." So if a veteran had entered an area where defoliation had occurred, "chances are the area had been treated a few weeks earlier and most of the TCDD was in the process of breaking down" (9).

Other groups who may have been exposed to Agent Orange, as reported in congressional testimonies, are service helicopter units who flew along with spray helicopters to provide protection (20) and combat engineers who operated heavy equipment to clear defoliated (20) and newly sprayed (2) areas and burned the debris.

4. Agent Orange test-spraying

In 1966 and 1967, reports a Canadian magazine (10), Agent Orange and 8 other defoliants were sprayed on a 6 km strip of the Canadian Forces Base Gagetown. The vegetation at Gagetown is similar to that found in Vietnam. Canadian soldiers were on the ground at the time of the spraying. No information about any subsequent health effects was presented.

5. Agent Orange storage

Two newspapers (21, 22) report that 840,000 gallons of Agent Orange were stored at the Naval Construction Battallion Center at Gulfport, Mississippi from 1968 to 1977. Following heavy rains in 1979, low levels of dioxin were found in drainage ditch sediment in and near the site and in some aquatic life. As of November 1979, barriers were being contructed around the 12 acres used for storage to halt further movement of dioxin.

6. Burned at sea

After the spraying of Agent Orange was stopped, the Air Force was reportedly left with 2.3 million unused gallons. This leftover stock was incinerated at sea by the Vulcanus, a special poison-burning vessel (23).

7. Maude de Victor

According to several reports (15, 7, 12), Maude de Victor, a counselor at the Chicago regional office of the VA, was one of the first to notice a possible relationship between reported symptoms and "those

chemicals." She collected information on Chicago area veterans exposed to Agent Orange and their wives. When the VA reportedly was not impressed with her information, she approached a local TV station and brought her information to the public. A popular magazine (7) reports that de Victor was subsequently reassigned to the VA loan department where her job involves paper, not people.

B. Possible complicating factors

Several factors and considerations which might possibly complicate a study of Agent Orange exposure and subsequent health effects among ground troops have been highlighted in the popular media. Those familiar with the nonscientific literature relating to Agent Orange are likely to be aware of and expect to see the following issues addressed in our study design.

1. Possible sources of dioxin and 2,4,5-T exposure other than Agent Orange spraying in Vietnam:

a) Dioxins contaminate many chemicals (23). For example, traces of dioxin are present in Silvex, a popularly used herbicide, in chemicals used in textile factories, the pulp and paper industry, and in machine tooling plants.

b) 2,4,5-T was widely used in the U.S. on national forests, cattle pastures, rice crops,and power line rights-of-way (23, 8, 24, 25).

c) Dow Chemical reports that dioxins are a natural product of combustion and are ubiquitous in parts-per-billion concentrations (26).

d) Occupational exposure to 2,4,5-T and dioxin is possible (25).

e) Dioxins may be found in herbicide waste sites. Exposure to toxic wastes may include exposure to dioxins (25).

2. Other exposures with related outcomes:

a) Other herbicides were used in Vietnam which may cause symptoms similar to those associated with Agent Orange (27).

b) The experience of combat has been associated with many different effects (1):

- readjustment problems
- alcohol and drug problems
- poor family relationships
- delayed stress syndrome

c) Insecticides were widely sprayed in Vietnam to control malaria (9).

d) Illicit drugs were widely used by U.S. troops in Vietnam.

e) Dapsone, an anti-malarial drug, was widely used in Vietnam. It, reportedly, may be carcinogenic (2).

3. Other considerations

a) Veterans' groups reportedly feel that any study done by the VA may be biased (28).

b) The concern has been raised (5, 2, 29) that using available records to document exposure of ground troops will be difficult. One article (29) reports that a panel of government scientists have concluded that a scientifically valid Agent Orange study of ground troops may not be possible because of this problem.

c) Dioxin may slowly accumulate in fat tissue. Upon weight loss dioxin may enter the blood stream in high enough concentrations to cause adverse effects ("time-bomb theory")(15, 3).

d) Dioxin has been reported to be one of the most toxic chemicals known to man (8, 3, 30). (See section III B.)

C. Veterans' Concerns

1. Health Effects

Numerous health effects have been associated with exposure to Agent Orange. The following is a list of symptoms and diseases reported in the nonscientific literature.

-birth defects (1,3,5,8,10, 11, 13, 15, 17, 23, 25, 28, 31, 32, 33, 34, 35)
-cancer (1,3,5,8 10, 15, 17, 23, 25, 28, 32, 34 ,35, 36, 37)
-anemia (23)
-increased susceptibility to infection (23)
-chloracne (3, 8, 9, 11, 17, 23, 25, 37)
-loss of ability to heal wounds (23)
-death of fetus (17, 35)
-"like premature aging" (23)
-subtle, chronic toxic effects in adults (23)
-general failure of many organs and tissue systems (23)
-persistent rash (3,8,15)
-numbness in fingers (15, 28)
-psychological problems (3, 5, 15, 28)

-reduced libido (3, 15, 25, 35)
-fatigue (3, 9, 15)
-spontaneous abortion (5, 8, 11, 13, 15, 19, 24, 25, 31, 38)
-headaches (8, 9, 37)
-nervousness (8, 36)
-chronic vomiting (8, 25)
-general malaise (8)
-liver disorders (3, 17, 25, 28, 33, 36, 37)
-CNS disorders (3)
-neurological problems (3, 25, 37)
-numbness in legs (3)
-pins and needles in hands and feet (3, 9)
-tumors (31, 35)
-changes in immune system (25)
-changes in respiratory system (25)
-pus-filled lumps under skin (17)
-festering sores (5)
-blackouts (36)
-inability to detoxify alcohol (33,35)
-weight loss (33)
-breathing problems (33)
-skin diseases (10, 33)
-abnormal sperm (11)
-changes in skin color (35)
-sensitivity to light (35)
-desire to be alone most of time (35)
-paranoia (35)
-outbursts of temper (9, 35)
-weakening and pain in ankles, knees, wrists, elbows, shoulders (35)
-temporary loss of hair (35)
-unexplained hyperactivity followed by extreme fatigue (35)
-aching in joints and muscles (9)
-nausea (9, 37)
-general weakness (9)
-loss of drive (9)
-irritability (9)
-blood disorders (37)

2. Problems associated with the "Vietnam experience"

Several reports in the nonscientific literature have asserted that the "Vietnam experience" has left many Vietnam veterans physically and emotionally scarred and ill-prepared to readjust to civilian life.

The Center for Policy Research in New York (1) reports that 41% of returning combat veterans have persisting psychological, drug, or related problems, compared to 13% of returning veterans as a whole. (Unfortunately, information on selection of respondents was not available.)

In a 3 year study of 400 Vietnam combat veterans, John P. Wilson (1) reports that 41% had alcohol problems, 45% had family relationship problems, and over 6% had drug problems. An estimated 250,000 to 500,000 veterans are thought to be suffering from delayed stress syndrome. (Again, selection information was not available.)

Robert Muller of Vietnam Veterans of America points out that the problems and frustrations of the Vietnam veteran must be viewed in the context of the war as a whole, its background and meaning. There was little popular support for the war. The enemy was indistinguishable from civilians. Most Army of the Republic of Vietnam troops in the field did not want to fight. Upon returning home the veteran was not treated as a hero, he was "a scapegoat for the fact that it [the war] had not been "won",...a victim of a national desire to blot it out of memory" (1).

The 1979 Louis Harris Survey, Advance Study of the General Public's Attitudes Toward Vietnam Era Veterans (39), reveals that the general public feels the Vietnam experience contributed heavily to such reported problems of Vietnam

veterans as emotional problems, drug abuse, and health problems (see Table 1). (Based on 1,200 telephone interviews selected by stratified random selection with random digit dialing.)

Table 1 - General Public's Attitudes Toward Military Service in Vietnam and Veterans' Problems

	Caused or contributed heavily	Had nothing to do with, not sure, no answer
Mental or emotional problems	59.1%	12.7%
Problems with drugs or drinking	48.8	18.3
Problems with health	42.8	20.9

3. Frustration with the Veterans Administration

The frustration of Vietnam veterans with VA policy and perceived inaction has been reported in the nonscientific literature. Robert Muller characterizes VA policy as a "source of almost interminable frustration" (2, pg. 15). Representatives of the VA reportedly have commented that everything that can be done on a cost effective basis is being done for veterans possibly exposed to Agent Orange; veterans counter that they don't care about cost effectiveness, they want help (3).

An herbicide clinic has been established at the VA hospital in Northport, L.I. A 5 page (11 min) questionnaire and a routine physical and tests are offered to veterans possibly exposed to Agent Orange (13). The general reaction to this clinic as reported in the New York Times (13) is that the clinic is "grossly inadequate," "a farce," and that the doctors are unfriendly and unkind.

Numerous articles present the view that the government has refused responsibility for the plight of the veterans (1, 17, 40). The underlying sentiment seems to be, "I was there when my country needed me. Where is my country now that I need help?" (17). Robert Muller, Executive Director of Vietnam Veterans of America, summarized the frustrations of the veterans: "When we were in Vietnam, there was no problem in acting aggressively in sending us

into battle....After the war was over, however, that same sense of urgency and aggressiveness was no longer apparent in dealing with the problems the soldiers were left with....One would naturally expect that the Veterans Administration...would have been the leader in investigating these problems....Unfortunately, the record has been different" (1).

4. Concerns for study bias

Veterans reportedly suspect that the Air Force and the VA are biased against finding Agent Orange related problems (2, 28). May 7, 1980, a national coalition of Vietnam veterans filed a lawsuit in Federal District Court in Washington trying to block the proposed VA study because they were concerned the VA could not do an unbiased study (28). John Furst, Chairman of the National Veterans Task Force on Agent Orange, has testified before Congress that "I see no avenue by which credibility can be established for the VA or the Air Force in the minds of veterans" (2, pg. 37). Mr. Furst has testified that even the peer review process would not improve the credibility of an Air Force or VA study (2).

5. Veterans Sue

As of February 1980, 3,000 veterans who believe they are suffering from health effects due to Agent Orange exposure were plaintiffs in a suit against 5 companies that manufactured Agent Orange. They are asking

that the companies pay a percentage of their future profits into a trust fund for the compensation and care of dioxin-exposed veterans and their children. Estimated claims could amount to 40 billion dollars (17, 33). However, if the defendants, Dow Chemical Co., Mansanto Co., Thompson-Haywood Chemical Co., Hercules, Inc., and Diamond Shamrock Corp., manufactured the herbicide according to government specifications, then they may be immune from liability (41).

III. Scientific evidence relating to Agent Orange as interpreted and presented by the nonscientific media

A. Introduction

Many of the Agent Orange films and publications have interpreted and presented scientific results and scientists' opinions relating to the health effects associated with Agent Orange exposure. The purpose of the following section is to briefly summarize the scientific evidence as it has been interpreted and presented to veterans and the public by nonscientists and the nonscientific media. To design a study which will be acceptable to veterans and the general public it is important to know how they are likely to perceive the scientific evidence. (For a review of the scientific evidence as presented in the scientific literature see Appendices A, B, C and D.)

B. Dioxin toxicology

The toxicity of dioxin has been frequently illustrated by the nonscientific media. Two magazines have

reported dioxin to be so toxic "that three ounces could kill the population of New York City if poured into the water supply (3, 8). Dr. Diane Courtney, head of EPA's National Environmental Research Center, has been quoted as saying that dioxin is "by far the most toxic chemical known to mankind" and that phenoxy herbicides "should not be used in any way at all" (3). Dioxin has also been characterized as being at least one million times more toxic than the cancer-causing polychlorinated biphenyls (30).

C. Animal research

Several animal studies and the opinions of scientists involved with animal research have been reported by the nonscientific media.

Dr. Matthew Meselson has been reported in several nonscientific articles (23, 30, 42) as stating that though definitive data on the health effects of dioxin is lacking, his research indicates monkeys fed dioxin in ppt doses develop tumors, birth defects and subtle, chronic toxic effects. Dr. Meselson has been quoted in the New York Times (30) as stating about dioxin: "it is now beginning to appear that it is the most powerful carcinogen known."

Several articles have presented the research results of Dr. James Allen (15, 30, 42). Dr. Allen reports that rhesus monkeys fed low doses of dioxin developed chloracne and growths on their extremities. He is reported as stating

that after 20 years of dioxin research with rats and monkeys he has not been able to determine a safe level of exposure (42). His statement that dioxin produces tumors in rats at exposures as low as 5 ppt is presented as evidence in one article (8) that dioxin and cancer seem to be linked, and in another (30), that dioxin is unquestionably carcinogenic.

The "time-bomb" theory has been proposed for the possible delayed effects of dioxin (3, 15). Dr. Barry Commoner (3) writes that, possibly upon weight loss, dioxin which may have been stored in fat is released into the blood stream. He reports that this type of delayed effect has been observed in fish in water contaminated with chlorinated hydrocarbons. However, the VA is informing veterans that the "time-bomb" theory has not been proven (9).

Health effects following accidental exposure to herbicides are frequently cited as evidence supporting Agent Orange toxicity. For example, in 1978, 7 years after a Wisconsin farm was accidently sprayed with 2,4,5-T, one toxicologist found that, in addition to health effects reported by the family members, 60-80% of the chickens had been born with birth defects (8).

The Vietnam Veterans of America (16) have highlighted the importance of the NIH study in which 2,4,5-T was found to possibly cause birth defects and stillbirths in mice. Reportedly, the results of this study prompted the Department of Defense to discontinue Agent Orange use.

In its 1979 decision to suspend most uses of 2,4,5-T in the U.S., the EPA essentially summarized the scientific animal literature for veterans and the public by stating that data from animal studies was one of the reasons which warranted the partial ban. This has been presented in several articles as an indictment against Agent Orange (16, 43).

Not all animal research has been presented as evidence against Agent Orange, however. One magazine (44) has presented as evidence for the "partial clearance" of Agent Orange a study of mice exposed to the components of Agent Orange in which no significant increase in birth defects was found. Also, several sources warn about the problems in extrapolating animal research data to humans (9, 11, 43).

D. Human reports

1. Vietnam evidence

Several articles have presented reports of Agent Orange related health effects being suffered by Vietnamese (3, 8, 11, 15, 16, 32). Dr. Val Woodward is reported as stating that the symptoms veterans claim are caused by Agent Orange are similar to those he observed among Agent Orange exposed Vietnamese people in 1971 in Bach Mai Hospital (15). The studies of Dr. Ton That Tung (described in one article as "the world's leading expert on dioxin" (3)) have been widely reported (3, 8, 11, 15, 32).

Dr. Tung has reportedly observed an increased incidence of liver cancer and birth defects among Vietnamese supposedly exposed to Agent Orange. One magazine article (11) presents case reports of birth defects among Vietnamese children (with photographs) and links them to Agent Orange exposure. This article also reports that 1/4 of all births are miscarriages in the main hospital in Tay Minh, a region which reportedly was heavily sprayed with Agent Orange. This statistic is presented as evidence that Agent Orange is linked to birth defects.

2. 2,4,5-T ban

The EPA's partial ban of 2,4,5-T (a component of Agent Orange) on February 28, 1979, has been followed with great interest in the nonscientific literature (3, 8, 16, 23, 24, 31, 43, 45, 46). The 2,4,5-T ban has frequently been presented as supporting evidence of Agent Orange's potential danger to humans (3, 8, 16, 24, 31, 43), and has even been called by veterans "a major victory for humanity" (43). The EPA decision was reportedly based on strong animal test data and a significantly increased frequency of miscarriage in women living in Alsea, Oregon, subsequent to the spraying of 2,4,5-T by the U.S. Forestry Service (16, 24, 43, 46). The EPA ban has been interpreted to mean that 2,4,5-T posed "an imminent hazard to humans" (24). The Vietnam Veterans of America write that in the course of these ban proceedings, the "EPA concluded that

there is no safe level of exposure to the dioxin in Agent Orange" (16). One article reports that a TV documentary has characterized the use of 2,4,5-T in the U.S. in this way: "If enemy planes sprayed our lands with chemicals regularly used by the U.S. Forestry Service, it would cause a grave international incident" (3). This article also makes the assertion that "half of the pregnant women in some localities either aborted or gave birth to malformed children following the helicopter spraying of 2,4,5-T by the Forest Service and the lumber companies" (3).

Dow Chemical, it is frequently reported, insists that 2,4,5-T is safe (8, 11, 23, 24, 26, 42, 43). They concede that dioxin is extremely toxic but argue that the concentration of dioxin in the 2,4,5-T used in this country is so low (0.2 ppm) that it is harmless (43). They, and others, reportedly consider the Alsea, Oregon, evidence to be seriously flawed (24, 43, 45). In addition, Dow has reported that dioxins are a natural product of combustion and are ubiquitous in ppb concentrations (26). According to the New York Times (45), Dow has stated that out of thousands of scientific studies of 2,4,5-T, not a single documented case of human injury has been produced. A Dow public affairs manager is quoted as stating, "we know more about 2,4,5-T than we know about aspirin. How long do you want the chemical industry to continue to prove that nothing has happened?" (42). A Dow attorney reportedly stated, "we

can't let the EPA simply ban a product in the face of science" (43).

Veterans, in response to Dow's claims that 2,4,5-T is safe, argue that, in general, the concentration of dioxin in Agent Orange was 20 times the dioxin concentration in the domestic 2,4,5-T banned by the EPA; an estimated 4 ounces of dioxin was sprayed in the U.S. before the EPA ban; if dioxin is so dangerous that 4 ounces constitutes an emergency, then the hundreds of pounds of dioxin sprayed over Vietnam is an even graver emergency (16).

3. Accidental exposure

The nonscientific media has reported several accidental exposures to the constituents of Agent Orange and their related health effects.

The contamination of Seveso, Italy, with dioxin is probably the best known Agent Orange related accident (8, 23, 43). In July, 1976, a factory explosion released a cloud of dioxin into the atmosphere. One article (23) reports that hundreds of people were evacuated, their furniture and clothing were destroyed, hundreds were disfigured with chloracne, thousands of animals died, and local officials urged pregnant women to have abortions. Barry Commoner has been reported as stating that the 38 cases of birth defects which have been documented in the Seveso area in the year following the accident "were due directly to dioxin" (8). One article (8) reports an

increased incidence of spontaneous abortion among Seveso women. Another (43) reports that no great increase in the number of birth defects has been noticed. Dow Chemical reportedly cites Seveso as proof that "dioxin...is not a doomsday chemical since no human deaths were reported" (8).

One magazine article (23) reports that a German factory was demolished and buried because of a high death rate among workers 5 years after an explosion contaminated the plant with dioxin.

Following a 1949 explosion at its West Virginia plant, which exposed a large number of workers to high concentrations of dioxin, a Monsanto study reportedly found no excess of cancer deaths or circulatory diseases (43). Another source (12), however, reports that following this accident exposed workers developed symptoms including chloracne, pain in skeletal muscle, shortness of breath, loss of sensation in the extremities, fatigue, irritability, vertigo, and loss of libido.

Recent European studies have been cited which reportedly link exposure to the constituents of Agent Orange with cancers (43, 47). Swedish studies reportedly have found an excess of soft-cell tissue and stomach cancer among 2,4,5-T workers (47). A German study also reportedly found a high incidence of stomach cancer among workers accidently exposed to 2,4,5-T (43).

H

APPENDIX H

PROPOSED AGENT ORANGE TROOP EXPOSURE AND NON-EXPOSURE COHORT SELECTION CONCEPT PAPER

Jerome G. Bricker, Ph.D.

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D.C. 20301

HEALTH AFFAIRS

4 DEC 1981

MEMORANDUM FOR THE CHAIRMAN, AOWG SCIENCE PANEL

SUBJECT: Proposed Agent Orange Troop Exposure and Non-Exposure Cohort Selection Concept Paper

For many months the Science Panel as well as the Agent Orange Working Group (AOWG) has researched many avenues to seek out a plausible means to establish reasonably exposed and non-exposed field troops in Vietnam with respect to herbicide orange spraying. Public Law 96-151 mandates an epidemiological study to endeavor to determine if exposure to Herbicide Orange (2,4-D, 2,4,5-T, 50/50 mix with the contaminant 2,3,7,8-TCDD) caused deleterious health effects among exposed military personnel.

The following concept paper presents a proposed methodology to identify research cohorts by using three large groups of military personnel. The first group of approximately 12,000 people would constitute a relatively heavily exposed ground troop population serving in Vietnam; the second group, also of 12,000, would serve as a non-exposed Vietnam troop population; and the third group of 12,000 would be personnel in the military service stationed in the southern part of the United States in the same time period. The second group of non-Herbicide Orange exposed Vietnam veterans is considered very important from the standpoint of determining whether other chemicals, diseases and toxins (e.g., aflatoxin B) present in Vietnam may be the source of illnesses and symptoms affecting those veterans who have filed claims. This paper (with its tabs) will sequentially discuss the factors which contribute to a typical herbicide exposure and how they might have affected the ground soldier operating in the tropical jungles of Vietnam. After establishing the necessary technical background information, we will proceed to address how an exposed population may be found and how we may in some measure determine a potential degree of exposure. Next a proposed method of locating an unexposed serving-in-Vietnam population will be presented. Pentultimately, we will provide a brief discussion of the technique to select a non-exposed, non-service in Vietnam control group having similar demographic characteristics. Finally, and perhaps most importantly, a technique will be advanced to secure (by means of the use of information already on file in the Veterans Administration Agent Orange claim file) a verification program to assure the concerned veterans organizations that truly highly exposed military units have been selected as the study population.

Exposure Considerations

Although a large quantity of herbicides were sprayed by Ranch Hand aircraft from 1965 through 1970 including a preponderance of Herbicide Orange, the question still remains as to actually how much of the herbicide reached the ground to 8 ft level of the dense forests. Studies have shown that about 13 percent of the herbicide released at 150 ft. altitude from a C-123 flying at 150 knots is vaporized into the air or drifts away as a cloud before the droplets hit the top layer of the forest. Hence, the original aircraft load of 1,000 gallons is immediately reduced to 870 gallons. The remaining 870 gallons are then disseminated over a distance of 14 kilometers or 8.96 miles. The swath width per aircraft has by testing been determined to be 260 $\pm$ 20 feet, hence the area covered per aircraft with these 870 gallons is 5,280 ft/mile X 260 ft X 8.96 miles = 12,300,288 square feet covered by one aircraft spraying 870 gallons of Orange. This would give a concentration of herbicide of .0000707 gals/sq ft on top of the jungle canopy. However, in a dense 3 layer jungle canopy such as the ones defoliated in Vietnam, the layers of foliage entrapped and absorbed 84 percent of the 350μ size droplets. The lowest level of foliage was anywhere from 15 to 25 feet above the floor of the jungle. Foliage impingement and absorption reduces the concentration of herbicide reaching the ground zone (0 to 8 ft) by 84 percent. This results in concentration of droplets entering the 0 to 8 ft above ground zone to .0000042 gal/sq ft. (100% - 84% X .0000707 gals/sq ft). Converting gallons/sq ft to ounces/sq ft we have (.0000042 X 128 oz/gal) giving a concentration of .0005376 oz/sq ft. Five ten-thousandths of an ounce per square foot is a very small amount if it contained 2 ppm of TCDD.

Other factors acting over time to reduce residual herbicide on the foliage include absorption of Orange into the plants within 30 minutes from these size droplets. An ultra-violet half life of TCDD in the presence of 2,4-D and 2,4,5-T (hydrogen donors) of about 6 hours with conversion to less toxic tri- and di-chlorodibenzo dioxins also would reduce the concentration of TCDD present on sun exposed leaves. Further, TCDD has been shown to have an extremely low vapor pressure and an even lower solubility in water (2.0×10^{-7}). Herbicide foliage coverage and absorption rates are confirmed by the profound leaf kill and leaf drop effects produced on the top cover foliage even when rain occurs within an hour after the spray mission (pre-1965 testing, Kontum). Comparing the concentration of penetrating herbicide at the 0 to 8 ft level by another means it comes to about .166 gallons/acre. Here in the United States it was customary to apply 2,4,5-T in agricultural use at the rate of 2 gallons per acre.

Because of the aforementioned experimental factors, it does not appear that even if an individual were directly under a triple level

jungle canopy during a Ranch Hand spray run that he would receive a total body dose on his uniform of more than .0000084 gal/head and shoulder area (.0010752 oz/man's area) especially if he remained still as the droplets would fall almost vertically. He might be able to increase his clothing dosage if he ran rapidly through the forest in the direction toward the aircraft flight path, however, that would be difficult in a dense jungle because of the underbrush.

We should note, however, that not all of the areas defoliated by Ranch Hand aircraft were dense tri-canopy level jungle forests. Also, Ranch Hand aircraft resprayed the same forests after the top canopy had been removed by earlier spray missions. Hence, in these situations the herbicide droplet penetration to ground level would be much greater. Likewise, the secondary cloud drift and evaporation would also increase as the droplet fall distance is considerably extended (3X). Unfortunately no test data has been located which will give us reliable experimentally determined vaporization and secondary cloud effects. Some reports by Dr. Minarik of Fort Detrick give an evaporation rate of 3 percent for Orange. Air Force presentations listed up to 13 percent loss from small droplet cloud generation and evaporation as the spray hits the turbulent airstream from the aircraft. From studies by Minarik, about 12 percent of the droplets are smaller than 200μ in diameter. Droplets less than 200μ are more subject to drift and can travel up to 1,584 feet from release line. Smaller than 100μ droplets can travel up to 1 km. laterally from the line source before impacting on plants or ground.

Therefore, troops under sparse canopy or relatively open forests could receive as high a concentration of Orange as .0000707 gals/sq foot. Converting .0000707 gals/ft^2 to ounces/ft^2, we find a concentration of .00905 oz/sq foot at the ground. Our individual soldier standing in an open area would thus receive a droplet dose of .0181 oz of herbicide in the form of very small ($< 300\mu$) droplets on his head and uniform. There does not appear to be any way to estimate what his inhaled dosage might be as so many variables come into play.

On the other hand, perimeter spraying of fire bases and camps was a much less rigidly controlled operation than Ranch Hand flights. Helicopter spraying movies prove that spraying was conducted over populated fixed positions, armored personnel carriers, and guard towers. Contrary to earlier beliefs Herbicide Orange was also utilized in considerable quantities around bases and along lines of communication. Helicopter spraying was at low altitudes over areas which had already been cleared of high trees, thus the surface contamination at ground level would likely be much heavier due to the rotor blade downwash, lack of tree foliage absorption, and close proximity to stationary troop locations. Add to this the employment of ground spraying apparatus such as by use of chemical agent

decontamination spray trucks (600 gallons at 800 lb/in^2 pressure), hand sprayer back-pack apparatus and Buffalo turbines (150 mph air blast at 10,000 ft^3/min volumes finely atomized) and we have several sources of unregulated droplet and aerosol spray devices. Military movie and other photo coverage indicates that it was common to spray fire base perimeters at about 5 week intervals. Since usually all sides of the perimeter would be sprayed regardless of the wind direction some spray drift over troop inhabited areas would be expected. Because of the need for clear fire zones to prevent infiltration of the firebases free spraying commonly was practiced. This in my opinion would be a much closer and far more concentrated exposure to herbicides than for troops under a dense jungle canopy being sprayed by C-123 aircraft. There also would probably be a greater respiratory and residual artifact contamination source for percutaneous and alimentary absorption of the herbicide. It was surprising to find that some units kept fairly accurate records of perimeter spraying dates, however, they frequently failed to note the gallons used and the type of herbicide. Times of application varied much more than the dawn or dusk regimen of the Ranch Hand operational spray missions. For the aforementioned reasons, any highly exposed sample of personnel would have to include repetitious ground spraying of the unit's base camp and fire bases to ensure additional exposure beyond that encountered from Ranch Hand mission proximity.

A third but extremely frequency limited source of exposure could result from low altitude jettison of herbicide cargoes from C-123 aircraft under dire emergency conditions. The C-123 10" dump valves were capable, when fully operable, of dumping 1,000 gallons within 30 seconds. This would empty the tank in a distance of 1.33 miles with no control of droplet size compared to the usual boom spray dissemination line of 8.96 miles. The concentration during a maximum jettison would therefore be about 6.74 times more concentrated for the shorter line source providing that all of the agent reached the ground. The ground dosage would vary with release altitude and meteorological conditions. However, here we encounter problems concerning how much liquid herbicide would pass through the atmosphere and reach the ground to contaminate ground troops. Possibly, if the herbicide dump took place at 3,000 feet or more (minimum altitude to avoid effective small arms fire hits) most if not all of the agent would evaporate before reaching the ground or drift for long distances as a diluting cloud. This opinion is based on the 13 percent evaporative loss and cloud drift experienced at very low altitude runs just above the jungle canopy. So far we have been unable to find any actual test data to confirm or deny whether herbicide released from high altitude would reach the ground. Early (before 1961) large area crop destruction testing showed an altitude of 1,000 to 1,500 ft to be the optimum altitude for maximum crop area coverage of very small size droplets ($\leq 100\mu$). But if the herbicide were released at 500 feet or less altitude in dense

concentrations (10" dump valve orifice) the per foot concentration would be .1424 gallons assuming uniform release distribution (not necessarily true because of hydrostatic pressure variance with time). Under this situation probably liquid herbicide would reach the ground surface. Wind velocity, aircraft speed, ambient temperature and humidity, and wind direction would further affect evaporation and dispersion of the herbicide before it reached the ground. It would, however, be possible if considered necessary to run actual dump testing at a remote location such as Dugway Proving Ground using still available Air Force Reserve C-123s and the A/A45Y-1 tanks and booms. I would recommend that the same Herbicide Orange formulation be used to ensure accurate results from altitude drops at varying heights. The matter of obtaining EPA clearance could be a problem for such a test.

When seeking a heavily herbicide exposed troop concentration, it would seem wise to include units which were under or in close proximity to low altitude orange jettisons. Any dumps over air bases or troop encampments should be especially considered as exposure sources. These dumps are the third criteria in establishing a high troop exposure index in the proposed methodology.

Possible Heavy Orange Exposure Cohort Selection

The large area spraying of herbicides, especially Herbicide Orange, by fixed wing aircraft seems to be of continuing urgent concern to most of the veterans' organizations. Most of the press coverage has also focused on this particular aspect of herbicide use even though the area covered in Vietnam was limited to 10 percent of the major land mass and the proportionate poundage was considerably less than the amounts of similar herbicides produced and sold in the United States during the same period (approximately 110 million pounds). Because of the worldwide constant use of 2,4,5-T since the end of the 1940s to the early 1970s, it may be impossible to find any group of persons who have not had some exposure to dioxin if they are older than 10 years. As other records obtained from GSA show there were 36 different combinations of phenoxy herbicide stock numbers available in various packaged quantities for Federal agency use. Therefore, as suggested in our Science Panel meetings, it may be a matter of total degree of exposure rather than being able to find a truly unexposed cohort. The recent EPA findings of dioxin presence in adipose tissue of six persons at autopsy in rural Ohio lends credence to this postulation as does the presence of dioxin in fish in the Great Lakes and dioxins in the stack gases from a municipal waste incinerator.

Even though these serious confounding factors exist within our whole environment we should still focus on choosing units which were in relatively close proximity to Herbicide Orange fixed wing spray tracks during a selected year. This, with some degree of precision,

was accomplished in the initial battalion studies in which company size units of the 1st of the 9th Air Cavalry were located as having been within one kilometer of a herbicide spray track within seven days of the date of spraying. With further alteration of the computer matching program we could perhaps narrow the time interval to one day for exposure proximity. The selected battalion already studied had a personnel turnover of 2,400 men in the one year studied, thus four more comparably sized units could provide a sample cohort of 12,000 exposed persons. These other battalion size units may be initially screened for herbicide exposure by picking only those organizations which were assigned to areas in which maximum spraying activities took place as shown by our fixed wing spray map overlays. Perhaps an additional 8 to 10 battalion studies would need to be undertaken to select the five most highly exposed battalion size units. Marine battalions should also be reviewed and unit locations compared to herbicide tracks.

Selection of 10 battalions with multiple close proximity locations to fixed wing spray tracks would complete step one criteria qualification of the highly exposed 12,000 member cohort out of a possible complement of 24,000 personnel from 10 battalions. See Tab A for a graphic representation of how these units might meet the step one criteria by dates of close Ranch Hand spray tracks as obtained by the computer matching program used in the earlier battalion studies.

Next these ten battalions would be examined under the step two criteria. Step two involves a detailed review of the records of each base camp and fire base occupied by each unit of each of the 10 battalions to determine how often, and when the base perimeters were sprayed with Herbicide Orange. This would be a particularly important step for reasons mentioned in the background section of the paper (potential high close exposure). Spray frequency dates for herbicide perimeter spraying would be recorded for each of the 10 battalions during this same one year period. The third column of Tab A presentation shows how this could possibly develop a series of spray date listings of exposures.

Battalion size units (10 battalions) meeting both step one criteria (heavy fixed wing spray proximity) and step two criteria (frequent perimeter sprayings of base camps) would then be examined for qualification in meeting step three criteria. Step three criteria would be that units of the battalion had to be encamped or operating within 2 kilometers of a Herbicide Orange low altitude emergency jettison. A two kilometer range was selected since an aerosol concentration to this distance from ground zero would be fairly likely from such a massive spill (see background section). It should be remembered that it would be a line source (1.3 miles) rather than a point source. The only exception would be from an aircraft crash without ensuing fire. No computer printouts of any

accuracy are available for determining either Criteria 2 or Criteria 3 qualification, hence manual checking from paper records and map plotting would be necessary. The probability of achieving Criteria 3 qualification because of low frequency of low altitude dumps would be slim resulting in the presentation shown in Column 4, Tab A.

Proposed Unexposed Vietnam Combat Cohort

As stated earlier, location and positive verification of unexposed units may be the most difficult aspect of the unit selection process. Non-qualification under Criteria 1 may not be as difficult as earlier thought. National Academy of Science Study computer map overlays drawn by calendar years for crop and defoliation missions show entire provinces which were never sprayed by fixed wing aircraft in a one year period. Therefore, units operating exclusively in these non-sprayed provinces would be initially selected. Again ten battalions (hopefully with a total troop complement of 24,000 persons) would be selected. After qualification of units by not meeting Criteria 1, the expected most difficult part of the selection process under Criteria 2 would be attempted. Our proposed approach for locating non-Criteria 2 qualified units (those not exposed to any local perimeter herbicide spraying) from the 10 battalions selected above would be to seek units far removed from major supply centers, really out in remote hamlets at the end of the logistics supply chain. Here the hope is that unit supply was so difficult that mainly ammunition, food and medical supplies took priority and hence there was no room to send along herbicides for use in perimeter spraying or the use of herbicides would not be needed for defensive purposes. We would also look for units who were both base camp support party and those operating out in the jungle such as Special Forces or Ranger units. The selected units must however be exposed to the indigenous diseases and other hazards of the jungle and be using protective measures such as insecticides, insect repellent, and preventive malarial medications. They also should be using the full spectrum of weapons including riot control chemical agents, etc. This selection for non-qualification under Criteria 2 may be quite laborious and require more than 10 battalion surveys, but consider it to be very critical in producing a valid study and solution to our vexing problem of exactly what is or are the sources of illnesses. Non-qualification of Criteria 3 of those units who non-qualified under Criteria 1 and 2 should be very easy as most of the herbicide jettisons from C-123s took place in the combat spray area or near their operating bases, hence they would be nowhere near these remotely located companies. As in the highly exposed cohort we would strive for a minimum cohort size of 12,000.

Proposed Non-Exposed, Non-Vietnam Control Cohort

One prime criteria with several secondary criteria would apply to this "Control" cohort. The prime criteria would be that no members of this group would have ever served in Vietnam or other areas of Southeast Asia including Thailand. Secondary selection criteria would include young males of the same age ranges as the test population and of the same general racial distributions. We believe a suitable 12,000 member cohort meeting these criteria could be located for the 1967-1969 period from either Fort Benning, Georgia or Fort Hood, Texas. Records of these posts could be checked to determine if the post engineers had utilized any 2,4,5-T in the troop areas during the sampling time frame (1967-69).

Proposed Validation of Selected Cohort Samples

Validation in the context of this proposal would be a form of assurance to the concerned veterans that a likely heavily exposed group of veterans had been selected for study. The information to accomplish this must come from the Veterans Administration (VA) which receives input for and maintains the Agent Orange Registry (AOR) consisting of names of veterans who have filed claims regarding personal effects from herbicides. From the available input forms and claims forms supplied by the VA, it appears that a necessary and valuable sequence of information pertaining to Vietnam service has not been obtained from these veterans claiming harmful effects. The information which is needed consists of the individual military assignments and the dates of same while the individual was serving in Vietnam. We understand that the entire AOR contains approximately 67,000 names, however, there is a secondary group of persons who have filed claims numbering about 12,000. This latter group would be used to validate the heavily exposed cohort and also the non-exposed service-in- Vietnam cohorts. The entire comparison would be based on knowing each individual's unit assignments and dates of assignment. Two possible ways appear feasible for obtaining the desired unit assignment information. These methods are described in the following paragraphs:

Method 1.--The VA would provide the 12,000 name listing, including the man's full name, social security number, service number, and date of birth, to the Department of Defense. The DoD would then send the list to the St. Louis Records Center for withdrawal of the records and shipment to Washington where the necessary information on unit assignments would be extracted and added to the computer list of names (12,000). This would complete the data base necessary for the validation steps following. Cost estimated to be at least $75,000 with good unit and time accuracy.

Method 2.--The VA would prepare a letter requesting unit assignments and dates of assignments with an enclosed return-stamped

envelope and dispatch these letters to all 12,000 veterans who have filed claims. As the information is returned it would be added to a computer listing tied to each person's name. The cost would probably be at least $20,000, however, the return rate could not be guaranteed although since these are all concerned veterans having claims it probably would be good. Nonresponders could then be checked out through use of the St. Louis Records Center to provide the missing information. The potential problem with this less expensive method would be that the veterans, in some cases working only from memory, could provide inaccurate unit assignment designations and incorrect dates. There would be no sure way, without using Method 1, to be confident of absolute accuracy.

The author would opt for Method 1 because of the assured accuracy of units and 100 percent reporting on all individuals in the sample.

Assuming one or another way has been used to secure unit assignments and time of assignments for these 12,000 veterans while in Vietnam, we would then undertake two comparisons:

First Comparison: A computer program would be developed to provide a military unit of assignment frequency distribution bar graph from these 12,000 claimants in the VA files. See Tab B for a hypothetical representation of such a bar graph. The Y axis would consist of a listing of all units of assignment as provided by the 12,000 veterans in descending order of frequency of reporting of the same military unit. The X axis would be a numerical scale of the number of claimants. Hopefully, some particular military units would be reflected as having multiple claimants from the same unit. Similarly we could also, on a much smaller scale, prepare unit/individual frequency distribution bar graphs for persons recorded in the: (1) VA Mortality Study, (2) AFIP Tissue Study, and (3) Vietnam veterans in the CDC Birth Defects Study.

The above series of frequency distribution graphs could be used for two possible purposes: First, as a lead pointer to units which might be investigated for unusual herbicide or other chemical/environmental exposures (detailed historical operational review). This might provide better insight into the real disease problems. Second, as a validation technique for the units selected as heavily exposed to herbicides. If our initial selections of units to make up the 12,000 member cohort were reasonably correct as the veterans believe to be the case of exposure, we should find names of claimants who were assigned to these more heavily exposed battalions.

Second Comparison: Similarly the units selected as unexposed to any herbicide spraying from either the ground or air should have no VA register claimants having been assigned. But, if VA claimants did report assignment to these unexposed units (and we are sure of the lack of exposure) this would lend credence to the hypothesis that other substances or environmental factors were responsible for the

reported illnesses. Then the investigatory problems would be much more numerous. Tab C provides a chart representation of the hoped-for positive validation of the sample selected exposed and non-exposed battalion cohorts. If we can achieve such a correlation (as depicted in Tab C) this should provide positive proof to the various veterans organizations that we have selected the proper exposed units for the full scale epidemiological follow-up study.

Standard in-depth epidemiological techniques would then be employed with the total 36,000 member sample to attempt to prove or disprove altered rates of incidence of suspected illnesses and conditions.

Units serving in Vietnam prior to 1965 were not considered as an adequate population sample for the following reasons:

(a) Insufficient military populations to choose from,

(b) Absence of large quantity orange spraying by fixed wing aircraft or helicopters,

(c) Use of many unstandardized herbicides in small quantities,

(d) Lack of precise data on herbicide spraying,

(e) Variance in combat roles, troop utilization, and weapons employment from those used after 1965, and

(f) Poorly documented Vietnamese unit spraying of herbicides from helicopters using insecticide spray equipment.

I wish to express my appreciation for the thoughts expressed in the letter of 30 October 1981 to the Chairman, AOWG Science Panel from Dr. Michael Gough and Helen Gelband of the Office of Technology which generated the final information necessary for the development of this proposal. Also, without the continuing information input provided by Mr. Richard Christian for the past many months, this proposal would not have been possible. I also appreciate very much the constructive review and critique by Captain Peter A. Flynn, MC, USN.

Respectfully submitted for your consideration.

Jerome G. Bricker

Jerome G. Bricker, Ph.D.
Member, AOWG Science Panel

Enclosures
Tabs A thru C

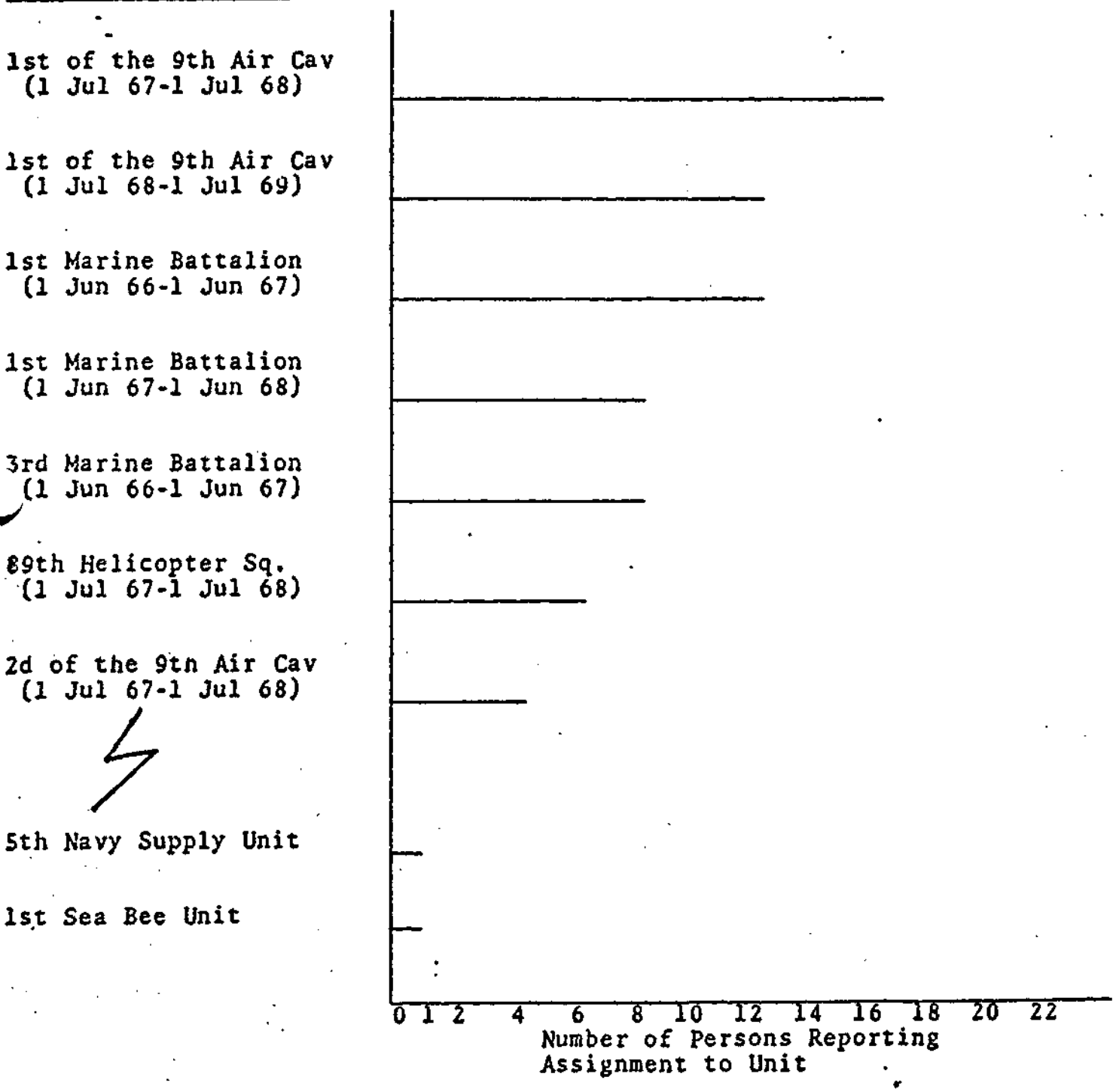
Representation of Highly Exposed Unit Selection Process

Unit Designation	Ranch Hand Exposure (Unit within 1 Km of Spray on following	Perimeter Spraying Done on Units Firebases on:	C-123 Jettisons (Unit within 2 Km of low altitude dump)
1st of the 9th Cav (1 Jan 68-30 Dec 68)	1/5/68 1/10/68 3/5/68 4/10/68 5/15/68 7/10/68	1/10/68 2/28/68 4/15/68 6/1/68 8/15/68	3/5/68
	6 exposures	5 exposures	1 exposure
1st Marine Battalion (1 Jul 67-30 Jun 68)	7/2/67 8/10/67 8/11/67 8/12/67 8/12/67 10/1/67 3/2/68	7/15/67 8/30/67 10/15/67 11/30/67 2/10/68 5/10/68	8/11/67
	7 exposures	6 exposures	1 exposure

Continuing thru the other 8 battalion size units to search a potential sample of 24,000. Then select the 5 most heavily exposed battalions as cohort

(NOTE: All dates above are fictious and are used for illustrative purposes only.)

Unit Assignment Frequency Distribution Chart From 12,000 Veterans Claims



(NOTE: Values are fictious and used for purposes of illustration.)

Validation Sample Technique

Selected High Exposure Units	Claimants found from	
1st of the 9th Cav (1 Jan 68-30 Dec 68)	AOR	12
	VA Mort. Study	2
	AFIP Study	1
	CDC Study	2
1st Marine Battalion (1 Jul 67-30 Jun 68)	AOR	8
	VA Mort. Study	1
	AFIP Study	2
	CDC Study	3
Selected Non-Exposed Vietnam Units		
1st Navy Sea Bee Unit	AOR	0
	VA Mort. Study	0
	AFIP Study	0
	CDC Study	1
10th Tac Recon Ranger Battalion	AOR	0
	VA Mort. Study	1
	AFIP Study	0
	CDC Study	0

(NOTE: Values and units are fictious and used for illustration purposes only)

APPENDIX I

POTENTIAL CONFOUNDERS

POTENTIAL CONFOUNDERS

Following is a list of the possible confounding factors we have thus far identified. Each is a potential confounder because it: 1) may have been unequally distributed among U.S. ground troops in Vietnam and may have been associated with likelihood of exposure to Agent Orange, and 2) is known to be associated with one or more adverse health outcomes. These potential confounders must be considered in the selection of cohorts and the analysis of collected data.

The possible confounders are:

1. Personal characteristics
    a. age
    b. race
    c. SES
    d. education
    e. drafted vs. enlisted
    f. genetic predisposition, e.g. Porphyria Cutanea Tarda
    g. health practices, e.g. frequency of bathing

h. geographic region of residence in U.S.

i. discharge status

j. combat vs. noncombat experience

k. military occupational specialty (MOS)

l. Vietnam area of service

m. occupation before/after Vietnam

2. Chemical, physical, biological and psycho-social exposures before, during and after service in Vietnam

a. biological exposures

1. malaria

2. cutaneous fungal diseases

b. other herbicides

c. source of water supply in Vietnam

d. Agent Orange dissolving vehicle

e. 2,4,5-T, 2,4-D, TCDD exposure other than through Agent Orange exposure in Vietnam

f. riot control agents

g. malathion and other insecticides

h. drugs: illicit

1. marijuana

2. barbituates

3. amphetamines

4. opiates

5. hallucinogens and miscellaneous illicit drugs

i. Drug use before and since service in Vietnam

j. drugs: licit

1. primiquine

2. chloroquine

3. dapsone

4. griseofulvin

k. alcohol

l. tobacco smoking

m. season

n. time period

We have begun investigation of these factors. However, a thorough investigation will require both a search of the Army records during the development of the exposure likelihood index and selection of cohorts, and the use of DTIC files. The Coordinating Center should be given DTIC clearance so that these potential confounders may be more thoroughly investigated.

REFERENCES

Akers, W.A., Prophylactic griseofulvin against Trichophytors mentogrophytes infection. Cited in the Dianosis and Treatment of Fungal Infections, Harry M. Robinson Jr., Ed., Springfield:Charles C. Thomas, Inc., 1974

Allen, A.M., Skin Diseases in Vietnam, 1965-1977. In Ogribens A.J. (ed.) Internal Medicine in Vietnam, Office of the Surgeon General and Center for Military History, U.S. Army, Washington, D.C., 1977.

Balayan, E.A., Lepakhin, V.K., Rudenko, G.M., Opioid analgesics and narcotic antagonists. In Duker M.N.G.: Meyler's Side Effects Drugs, Excerpta Medica, Amsterdam, pp. 102-122, 1980

Bleiberg, J., Wallen, M., Brodkin, R., and Appelbaum, I.L., Industrially Acquired porphyria. Archives of Dermatology, 89:793-797, 1964

Bourbe, A.T.C., Joy, R.J.T., Malaria as understood by soldiers. Military Medicine, 132(May):366-70, 1967

Bridger, R.J., A study of malaria rates in the Que Son Mountains of Vietnam. Military Medicine Journal, 138(7):413-417, 1973

Colbach, E., Marijuana use by G.I.'s in Vietnam. American Journal of Psychiatry, 128(2):204-207, 1971

de Verneuil, H., Aittren, G., Nordmann, Y., Familial and sporadic porphyria cutanea. Human Genetics, 44:145-51, 1978.

Doss, M., Chronic hepatic porphyria in Humans (endogenic factor). In Strik J.J.T.W.A. and Kolman, J.H. (eds.), Chemical Porphyria in Man, Elsevier/North Holland Biomedical Press, Amsterdam, pp. 11-26, 1979

Dunn, C.H., Vietnam Studies. Base Development in South Vietnam, 1965-1970, Washington, D.C., Department of the Army, 1974

Graham, W.R., Adverse effects of Dapronl. International Journal of Dermatology, 14(7):444-500, 1975

Grossman, M.E., Beikers, D.R., Poli-Fitzpatrick, M.B., Deleo, V.A., Harber, C.C., Porphyria cutanea trends. Clinical features and laboratory findings in forty patients. The American Journal of Medicine, 67:277-286, 1979

Harclerone, J., The effect of marijuana on reproduction and development. National Institute on Drug Abuse Research Monograph Series 31, pp. 137-166, 1980

Harvey, S.L., Hypnotics and sedatives. In Gilman, A.G., Goodman, L.S., Gilman, A.: The Pharmacological Basis of Theraputics, Gtw ed., MacMillan Publishing Comapny, New York, pp. 339-375, 1980

IARC, DAPSOME. IARC Mongraphics, 24:59-76, 1980

Jones, R.T., Human effects: An overview. In NIDA Research Monograph, Series 31: Marijuana Bias Research Findings, pp. 54-74, 1980

Muhlbauer, J.E., Pathar, M.A., Porphyria Cutanea Tarda. International Journal of Dermatology, 18(10):767-780, 1979

National Institute for Occupational Safety and Health, Occupational Exposure to malathion: criteria for a recommended standard. U.S. Department of Health, Education and Welfare, Public Health Service Center for Disease Control, National Institute for Occupational Safety and Health, DHEW publication; no..(WIDSH)76-205), 183 p., 1976

Nell, S., Medical Support of the U.S. Army in Vietnam. Department of the Army, Washington, D.C., 1973

Ognibene, A.J., Ayranulocytoner due to daprone. Annals of Internal Medicine, 72:521-24, 1970.

Poland A., Glover, E., 2,3,7,8 - Tetrochlorodibenyo - p dioxin: A potent inducer of g - aminolevulimi acid synthesis. Science, 1979:476-7, 1973.

Ramsey, J.C., Lavy, T.C., and Braun, W.H., Exposure of forest workers to 2,4,S-T: Calculated exposure levels. Project Completion Report to National Forest Producers Association, 1979

Ramsey, J.C., Smith, F.A., Lavy, T.C., Park, C.N., and Brown, W.H., Dose Levels of 2,4-D in Forest Workers. In Lavy, T.C.: Determination of 2,f-D Exposure received by Forest Applicators, Spring, 1980

Robins, L.N., Veterans drug use three years after Vietnam. National Institute on Drug Abuse, Rockville, Maryland, 1975

Robins, L.N., The Vietnam Drug User Return. Special Action Office for Drug Abuse Prevention. Series A, Number 1, Executive Office of the President, 1974

Robins, L.N., The Vietnam drug user returns. Special Action Office Monograph, Series A, no. 2, Washington, D.C., U.S. Government Printing Office, 1974

Rogers, B.W., Vietnam Studies. Cedar Falls - Junction City: A Turning Point. Department of the Army, Washington, D.C., 1974

Rollo, I.M., Drugs used in the chemotherapy of malaria. In Gilman A.G., Goodman L.S., Gilman, A.: The Pharacological Basis of Therapeutics, MacMillan Publishing Co., New York, pp. 1038-1060, 1980.

Schoof, H.F., Research and Control activity on vector-borne diseases in Southeast Asia. Technical Development Laboratories, National Communicable Disease Center, Savanah, Ga., 1969

Stanton, M.D., Drug use in Vietnam. Archive of General Psychiatry 26:279, 1972

Stanton, M.D., Drugs, Vietnam, and the Vietnam Veterans: an overview. Am.J Drug Alcohol Abuse, 3(4):577-70, 1976

Stimmel, B., Heroin Dependency. Stratton Intercontinental Medical Book Corporation, New York, p. 138, 1975.

Strick, J.J.T.W.A., The occurrence of chronic hepatic porphyria in man caused by halogenated hydrocarbons. In Strick, J.J.T.W.A. and Koeman, J.H. (Eds.), Chemical Porphyria in Man. Elsevier/North Holland Biomedical Press, Amsterdam, pp. 3-11, 1979

Taylor, J.S., Environmental Chloracne: Update and Overview. Ann, N.Y., ALAD, Science, 320:295-307.

Tester-Dalderup, C.B.M., Anteprotogoal drugs. In Dake, M.N.G.: Meyler's Side Effects of Drugs, Excerpta Medica, Amsterdam, Holland, pp. 493-491, 1980

Treanor, J.J., Skripol, J.N., Maryjuana in a tacical unit in Vietnam. U.S. Army Medical Bulletin, 22:29-37, 1970

U.S. Congress Senate Committee on the judiciary, Subcommittee to investigate juvenile delinquency, Drug Abuse in the military: report. December 1971, based on hearings and investigations, 1966-70, Burch Bagh, Chairman, 92nd congress, 1st session committee print

U.S. Congress Senate Committee on labor and public welfare, Subcommittee on alcholism and narcotics. Military Drug abuse 1971: hearings June 9 and 22, 1971: 92nd Congress, 1st session

U.S. Congress House Committee on armed services. Special subcommittee on alleged drug abuse in the armed services. Alleged drug abuse in the armed services: hearings, September 22 - December 15, 1970; Briefings and interviews: Southeast Asia inspection trip, January 2-19, 1971, 91st congress, 2nd session, 1971.

U.S. Congress, House Committee on armed services. Special subcommittee to investigate alleged drug abuse in the armed services. Inquiry into alleged drug abuse in the armed services, in the 91st Congress, 2nd session: report, April 23, 1971, 92nd Congress, 1st session, 1972.

Weiner, N., Norepinephrine, epinephrine and the sympathomemetric amines. In Gilman, A.G., Goodman, L.S., Gilman, A.: The Pharmacological Basis of Therapeutics, MacMillan Publishing Co., New York, pp. 138-175, 1980.

Zinberg, N.E., Heroin Use in Vietnam and the United States. Archives of General Psychiatry, 26:486-488, 1972

J

(J)

May, 1975

THE INSTITUTE FOR SOCIAL SCIENCE RESEARCH

SURVEY RESEARCH CENTER

U.C.L.A.

A MANUAL FOR INTERVIEWERS

Edited by Vi Dorfman

Appendix J

CONTENTS

STATEMENT OF PROFESSIONAL ETHICS

All interviewers for the Institute For Social Science Research-Survey Research Center are expected to understand that their professional activities are directed and regulated by the following statements of policy.

The Center undertakes a study only after it has been evaluated in terms of its importance to society and its contribution to scholarly knowledge. The Center does not conduct studies which are, in its opinion, trivial, of limited importance, or which would involve collecting information that could be more easily obtained by other means; nor does it undertake secret research or conduct studies for the sole benefit of one individual, company, or organization. The Center is a community of scholars whose findings are available to everyone. An effort is made to disseminate research results as widely as possible; this is done through books, journal and magazine articles, news releases, papers presented at professional meetings, and in the classroom.

The rights of human subjects is a matter of primary concern to the Center. All study procedures are reviewed to assure that the rights of individual respondents are protected at each stage of research. While it is the policy of the Center to make study findings public, the utmost care is taken to see that no data are released that would permit any respondent to be identified. All information that connects a particular interview with a specific respondent is removed as soon as the interview is received at the Center; this information is maintained in special confidential files. Interviews themselves are identified only by numbers.

The strict precautions taken by the Center to protect the anonymity of respondents would be undermined if the interviewer did not treat information concerning respondents with equal regard. Interviewers perform a professional function when they obtain information from individuals by means of the personal interview, and they are expected to maintain professional ethical standards of confidentiality regarding what they hear and observe in the respondent's home. All information about respondents gained during the conduct of research is privileged information, whether it concerns the interview itself or includes extraneous observations of the respondent's home, family, and activities.

I. INTERVIEWING PRINCIPLES AND PROCEDURES

A. BUILDING A GOOD INTERVIEWING RELATIONSHIP

Interviewing is one of the most important parts of any survey. Indeed, without interviews neither the coders, the programmers, nor the analysts could work. They would be missing the information which can only be obtained by asking people directly, and such data is the backbone of survey research. Study directors try hard to develop the best questionnaire possible, but even the best questionnaire is only as good as the interviewer's skill in using it. It is crucial that interviewers ask the questions properly, record the respondents' replies verbatim, and probe meaningfully.

Communication is not simple and communication in interviewing is complicated by the personalities of the people involved. It has been found that respondents usually react more to their relationships with the interviewer than to the content of the questions they are asked. In other words, respondents may remember more about the interviewer and about how the interview was conducted than they will about the topics covered in the interview. This emphasizes the importance of the interviewer's being an understanding person capable of accepting what the respondent says without apparent judgement or rejection of the respondent.

The intent of the interviews conducted by the ISSR Survey Research Center is to gather reliable information. They are not intended to change or influence the respondent; the Center simply wants to find out how things are and how people feel and think. In order to maintain an objective, information-gathering atmosphere, the respondent must find satisfaction in talking to a receptive person without fear of appearing inadequate.

By training and practice, the interviewer will acquire skills to help the respondent. He will become a professional person, skilled in setting the stage for the respondent so that he can gather frank, complete, and relevant answers to the questions.

The first step in the interviewing process involves establishing rapport with the respondent and getting him to cooperate in giving the needed information. It is at this time that you must do a job of selling yourself and the survey.

1. Increasing Respondent's Receptiveness

Experience in many surveys indicates that there are three factors which help bring about the respondent's receptiveness.

THE RESPONDENT NEEDS TO FEEL THAT HIS ACQUAINTANCE WITH THE INTERVIEWER WILL BE PLEASANT AND SATISFYING. The respondent's reaction to the interviewer as a person is very important. The respondent will react more favorably if he gets the feeling that the person at his door is sincerely interested in his opinion.

THE RESPONDENT NEEDS TO SEE THE SURVEY AS BEING IMPORTANT AND WORTHWHILE. The interviewer should try to interest the respondent in the study. Hopefully, you can get the respondent to see the interview as a real opportunity to express his views. He needs to understand what is expected of him during the interview, what the purpose of the interview is, and how the information he gives will be used. The full burden of the introduction is on the interviewer; few respondents know what is expected of them. All respondents, even those who are least interested, should feel that the survey is important and that their cooperation is meaningful to the survey results.

BARRIERS TO THE INTERVIEW IN THE RESPONDENT'S MIND NEED TO BE OVERCOME. The interviewer must be alert to doubts the respondent may feel, even if the respondent does not express them vocally. The respondent may feel that the interviewer is a salesperson of some sort. He may feel inadequate, that he doesn't know enough, or that he will be embarrassed by difficult questions or by giving the wrong answers. Any such perceptions on the part of the respondent must be neutralized by the interviewer's early statements. This can be done briefly by convincing statements from the interviewer on the purpose of the study, how the respondent was selected, the anonymous or confidential nature of the interview, the beneficial impersonal uses of the research findings, and by the personality of the interviewer. The interviewer must adapt himself to each individual respondent, giving sufficient information to motivate initial cooperation. Assure the respondent that their are no right or wrong answers. We are interested in his/her opinions only.

The interviewer's friendly manner, his introductory statements, and the success with which he answers the respondent's questions from the respondent's viewpoint are the things which will sell him and the survey to the respondent. However, over-friendliness and personal involvement may actually lead to your obtaining less information; it is important to maintain an objective attitude.

Your effectiveness in this early stage is increased by the knowledge that the job you are doing is legitimate and important, by knowing what you are doing and how it is done.

The first thing the respondent notices about the interviewer is his appearance. Aim for simplicity and comfort. Avoid identification with groups or orders (for instance, pins or rings of clubs or fraternal orders). Always carry your official University of California Survey Research Center identification card.

The next thing the respondent focuses on is what you say and the way in which you say it. Following are some pointers on this introduction.

TELL THE RESPONDENT WHO YOU ARE AND WHOM YOU REPRESENT. Introduce yourself by name, saying that you are an employee of the Institute for Social Science Research, the Survey Research Center at U.C.L.A., a research organization which does studies on topics of national importance. If necessary, show your identification card at this point to support your statements.

TELL THE RESPONDENT WHAT YOU ARE DOING. The instruction book for the survey will give you background information. Try to have this information clearly in mind on each study since it must be explained to the respondent in a way to stimulate his interest. Also mention that the respondent's answers are confidential; neither he nor his address will be identified in any way.

TELL HOW THE RESPONDENT WAS CHOSEN. It is important that the respondent understand he is part of a "cross section" survey, and that he was chosen quite impersonally only because he happens to be a particular person at a particular address. You may say something like this: "You see, in trying to find out what people think, we don't talk with everyone, but we try to talk to men and women of different ages in all walks of life. We start by selecting certain tracts from all over the County. In each of these tracts the Center selects blocks, and then specific addresses. Then when the interviews from all these addresses are combined, we have a cross section of the people."

USE RESPONDENT LETTERS AND CLIPPINGS. On most studies conducted by the Center you will get respondent letters. These letters to the respondents will have been sent out prior to your first calls at the addresses. These letters contain the basic facts of the survey and may help you, especially when they are timed to arrive just a day or so before your first visit.

You may want to also carry newspaper clippings about the Center's work, copies of past survey findings, and other materials to demonstrate to the respondent how our findings are used, the importance of our work, and the integrity of the Center's surveys on some occasions.

DOORSTEP INTRODUCTIONS SHOULD BE BRIEF. The doorstep is not a very convenient place to carry on a conversation and to establish a friendly relationship. For this reason, the doorstep introduction usually should be brief, just sufficient to get you inside the house.

At the doorstep the interviewer should not ask questions to gain permission for the interview but should suggest the course of action which he desires. For instance, instead of asking "May I come in?" --to which a respondent could easily say "No" --say, "I would like to come in and talk with you about this." Questions which permit negative responses can lead the respondent into refusing to be interviewed.

The interviewer should assume the respondent is not too busy and should approach his meeting with the respondent as though the interview were going to take place then, at the time of contact. By all means, make arrangements to return at a more convenient time if the respondent suggest this, but accept this situation at the respondent's instigation. Suggest it yourself only as a last resort when you want to leave the door open for another try at a time when the respondent might be more willing to be interviewed.

ADAPT YOUR APPROACH TO THE SITUATION. The most successful interviewer is one who is able to size up the situation quickly on the basis of what little information is available and to act accordingly. Approach each respondent (or person who answers the door) as though he is friendly and interested. Vary your approach according to your intuition about the person. With some respondents, you can get an interview with only a brief explanation of basic points, but with others you will need to go into some detail.

Remember not to get too specific about the interview in introducing yourself and the survey to the respondent. It is important that you avoid introducing a bias into the interview by predisposing the respondent to answer in any certain way. Very general statements can be made successfully: "We are getting information on how people feel about important issues in our country"; "We are interested in how people are getting along financially these days".

RAPPORT IS YOUR GOAL. Rapport is the personal relationship of confidence and understanding between the interviewer and the respondent; it provides the foundation for good interviewing. The respondent's impression of you during your introduction, and the manner in which you adapt yourself to the situation from the respondent's point of view determine considerably the rapport that will develop.

A requisite to good rapport is that the respondent knows where he stands in the interview. The interview is actually a new situation for most people, and when it begins the respondent doesn't know what is expected of him or how far he can safely go in expressing his opinions.

2. Characteristics of a Good Interviewing Relationship

The characteristics of a good interviewing relationship can be described in the following terms:

Warmth and responsiveness on the part of the interviewer: The respondent needs to feel the interviewer is genuinely interested in him, and accepts him as a person.

A permissive atmosphere in which the respondent feels completely free to express any feeling or viewpoint. By his attitude and behavior, the interviewer demonstrates that no answer is out of place.

Freedom from any kind of pressure or directive questioning: The interviewer in no way states his ideas, reactions, or preferences. Although he is permissive and understanding, the interviewer must remain objective.

In this kind of atmosphere, THE RESPONDENT NOT ONLY FEELS FREE TO TALK BUT IS ACTUALLY STIMULATED TO TALK.

3. Answering Respondent's Questions

Most people will go through an interview without asking you any questions; some will ask for information during the introduction, or after you've started the interview. However, you should always be ready with an answer. Listen to the respondent and answer only what he has asked.

Some of the questions respondents ask are:

"How did you happen to pick me?"
"Who gave you our name?"
"I don't know enough about this. Why don't you go next door?"
"What's all this about, anyway?"
"Why are you doing this survey?"

You should have ready and convincing answers to questions like these. The study instruction book, and your conferences with your supervisor all will provide the information to answer these questions.

4. If The Respondent Is Busy Or Away

Usually when the selected respondent is at home you will be able to interview him then. However, in some cases the respondent is actually too busy, is getting ready to go out, etc., so that an interview at that time is not feasible. If you are convinced that the respondent is actually busy, give a general introduction and try to stimulate his interest to the extent that he will be willing to see you at a later time. You may need to suggest several times before you and the respondent can agree on a convenient time.

If the selected respondent is not at home, introduce yourself and briefly explain your visit to someone in the dwelling who can tell you when the respondent will be at home. It is, of course, a good plan to establish friendly relations with this intermediary since his attitude can help or hinder you in making contact with the proper respondent. Sometimes it helps to explain briefly why you cannot interview someone other than the prescribed respondent. ("We scientifically choose addresses and also select the respondent. This enables us to talk to men and women of different ages and different walks of life.")

If other persons are present, suggest to the respondent before beginning the interview that he might prefer to talk to you in a more private place. Even though a respondent might refuse to be interviewed under these circumstances, the presence of outsiders might cause a reluctance to talk about certain things.

5. Leaving The Respondent

The respondent should feel that his time has been well spent and that the interview has been worthwhile. Any questions or doubts he might have about the interview should be cleared up before you leave. If the respondent has any questions, answer them; offer to have a report sent to him if one is available. Hand him a "Thank You Card" which you have signed; and then thank him for his cooperation and time. It is important to leave the respondent with a friendly feeling toward the Center, the interview and you.

B. USING THE QUESTIONNAIRE

Once the interviewer has introduced himself and started the rapport-building process, he is ready to begin the interview itself. The interviewer's goal is to collect accurate information by using the survey questionnaire according to sound interviewing practice. To fulfill this goal, the interviewer needs to know some basic facts about the questionnaire and how it is used.

1. The SRC Questionnaire

The questionnaire is the basic tool which the interviewer uses to collect survey information. The purpose of the questionnaire is to help the interviewer obtain accurate and complete information. It does this by meeting three criteria:

The questionnaire is based on the research objectives of the study. Every survey is designed to obtain certain information. The study staff decides what pieces of information they need in order to fulfill the purposes of the study, and they then decide what questions will get the needed information for them.

The questionnaire is designed to assist the interviewer in building rapport. The wording of the questions, the choice of words and language, logical question order, and friendly and conversational ways of phrasing the questionnaire flows easily from item to item and often leads the respondent to anticipate the next question because it seems to him the logical topic to discuss. When the questionnaire changes to a new topic, transition statements are included so the interviewer can help the respondent "shift gears" to a new area of discussion: thus, the questionnaire is respondent-centered and designed to provide a conversational rather than an interrogational atmosphere.

The questionnaire helps to standardize the interview. The researcher needs to combine and to treat statistically the data collected in all the interviews. This means that the data must be collected in a uniform manner for all respondents. Thus, all the people in a sample must be asked the same questions, in the same way.

Research has shown that people's answers are strongly influenced by the wording of a question. If a question is differently worded for different respondents, it will not yield comparable results among interviews. Experiments have been tried in which interviewers were given the objectives of a survey and asked to word their own questions. It was found that different interviewers worded the objectives in different ways; the interviews, thus, were not comparable.

Experience also indicates that question order must be the same from interview to interview because changes in question sequence affect respondents' answers. The use of a fixed questionnaire, then, helps standardize the many hundreds of interviews taken on a survey.

Finally, each SRC interviewer is a part of a large group of interviewers. It is only when each interviewer uses the questionnaire in the same fashion as all other interviewers that we can hope to collect information that is uniformly accurate and comparable.

The interviewer plays two roles in the interview: that of a "technician" who applies standard techniques and uses the same instrument (the questionnaire) for each interview; and that of a human being who builds up a relationship with each respondent.

2. Asking The Questions

The question now arises, what are the specific techniques the interviewer can use to carry out these two roles?

USE THE QUESTIONNAIRE, BUT USE IT INFORMALLY. The interview should be taken in an informal and relaxed atmosphere. The interviewer should avoid creating the impression that the interview is a quiz or cross-examination in any sense: he must be careful that nothing in his words or manner implies criticism, surprise, approval or disapproval of either the questions he asks or of the respondent's answers.

ASK THE QUESTIONS EXACTLY AS WORDED IN THE QUESTIONNAIRE. The wording and order of the questions have been tested previously and are designed to obtain the desired information. Do not reword any question. Read to the final question-mark and stop. Do not read material printed in capitals; these are instructions to you.

ASK THE QUESTIONS IN THE ORDER PRESENTED IN THE QUESTIONNAIRE. Question order needs to be standardized from respondent to respondent if the interviews are to be comparable.

ASK EVERY QUESTION SPECIFIED IN THE QUESTIONNAIRE. In answering one question, a respondent will sometimes also answer another question appearing later in the interview. Or, from time to time, when the interviewer needs to ask a series of apparently similar questions, the respondent may say, "Just put me down as 'Yes' to all of them". In this case, the interviewer may wonder whether she sould skip the questions which are apparently answered. The answer to this question is "no". In cases where asking the question will lower rapport dangerously, the interviewer must, of course, be satisfied with what he already has. However, it is the interviewer's responsibility to make certain that the respondent is fully exposed to each question specified on the questionnaire. Assuming the respondent has already answered a question is a dangerous practice. Every question should be asked, even when it has been previously answered. The interviewer can do this by letting the respondent know he is aware of the earlier response and by asking the respondent's cooperation in answering again.

LISTEN TO THE RESPONDENT until he finishes each statement. Failure to do so can result in your putting down incorrect or incomplete entries. The two most common errors of this type are:

(a) Failing to listen to the last half of the sentence because you are busy recording the first half.
(b) Interrupting the respondent before he has finished, especially if the respondent hesitates. A respondent often hesitates when trying to recollect some fact, and you should allow sufficient time for this to be done. Also, people will sometimes answer, "I don't know," when actually they are merely considering a question. When you think that this may be the situation, wait for the respondent to finish the statement before repeating the question or probing.

REPEAT AND CLARIFY QUESTIONS WHICH ARE MISUNDERSTOOD OR MISINTERPRETED. Questions are phrased to be understood by respondents all over the County, and you will find that most of the people you interview do indeed understand them. Occasionally, however, a respondent may misunderstand or misinterpret what is

asked. When this happens, you can only repeat the question just as it is written in the questionnaire; this should not prove to be embarrassing since what you said the first time was not heard or understood. Frequently the respondent is capable of understanding the question but has missed a word or two. If you think it is helpful, you can preface the repetition of the question by a phrase such as "I see" or "Oh, yes" and then repeat the actual question. A conversational tone will go far in making the question sound new, even though you are using exactly the same words.

(a) Maintaining Rapport

Occasionally rapport may be broken during the interview despite your efforts because the respondent finds a particular question "too personal" or for other reasons. If that happens, take time out to re-establish rapport and to reassure the respondent regarding the impersonal, anonymous nature of the survey. This may be done by restating the confidential nature of the questionnaire and the anonymity of each respondent.

(b) Gathering Personal Data Information

Questions about the respondent's age, sex, schooling, marital status, income, religious preference, etc., are usually at the end of the questionnaire. There is generally no resistance on the part of the respondent to this personal data. If, however, the respondent asks why you want his age, religion, income, or something else, you might say something like this:

> Well, as I was saying earlier, we are talking with people of different ages and various occupations in all parts of the County. We put all the interviews together to see whether men feel differently than women, whether young people feel differently than old people, and so on. To do this we need to know a few things about the people we talk to.

This gives the respondent a logical reason for our desiring the information and shows him why his cooperation will be of help. If there seems to be a need for further reassurance, you may add: "As I mentioned, the interview is completely confidential. The survey report is simply a summary of all the interviews, without, of course, identifying anyone."

If you are matter-of-fact in your approach, you probably will not encounter any problems. People are used to giving such information about themselves to various agencies, so that gathering such data represents much less difficulty than new interviewers often imagine.

C. STIMULATING DISCUSSION--PROBING

One of the most challenging and important aspects of the interviewer's work is "probing." The quality of the interview depends a great deal on the interviewer's ability to probe meaningfully and successfully.

1. What Is Probing?

Probing is the technique used by the interviewer to stimulate discussion and obtain more information. A question has been asked and an answer given; for any number of reasons, the answer may be inadequate and require the interviewer to seek more information to meet the survey objectives. Probes get this additional information by motivating the respondent to communicate more fully so that he

enlarges on what he has said, or clarifies what he has said, or explains the reasons behind what he has said.

Even the best questionnaire may occasionally bring first responses which are inadequate. An answer may be inadequate because it is only a partial answer and therefore incomplete; it may be irrelevant, about something besides the subject of the question; it may be unclear, meaning any one of several things; it may be inconsistent, in conflict with other information. In the following example, note how the inadequate replies fail to answer the question:

Question: "Do you think it will make a lot of difference to the country whether the Democrats or Republicans win the November elections, or that it won't make much difference which side wins?"

Answer: "Yes, I do." (Unclear answer)

Question: "Considering the country as a whole, do you think we'll have good times, or bad times, or what between now and a year from now?"

Answer 1: "Oh, maybe good times, maybe bad. It all depends." (Unclear answer)

Answer 2: "I hope we'll have good times." (Irrelevant answer)

Question: "We're interested in finding out how people consider government bond drives. How do you feel about them?"

Answer 1: "Well, I don't think they're..uh, I don't know." (The respondent obviously had something in mind, but didn't say it: incomplete answer)

Answer 2: "Oh, I'll tell you--I think the government better get busy and do something about the food prices before we all go broke." (Irrelevant answer)

These answers illustrate some of the problems interviewers face. The interveiwer cannot accept these replies because they don't fulfill the question objectives adequately. Obviously, some method of stimulating discussion on the topic of the question is needed so that clear, complete, and relevant answers are obtained.

2. Kinds of Probes

Several different neutral techniques which should appear as a natural and casual part of normal conversation may be used to stimulate a fuller, clearer response.

A brief assertion of understanding and interest: By saying such things as "Uh-huh," or "I see," or "Yes," the interviewer indicates that he has heard the response given so far, that he is interested in it, and that he expects more. These things serve to stimulate the respondent to talk further.

An expectant pause: The simplest way to convey to a respondent that you know he has begun to answer the question, but that you feel he has more to say, is to be silent. The pause--often accompanied by an expectant look or a nod of the head--allows the respondent time to gather his thoughts.

Accepting pauses during an interview is often difficult for the new interviewer. He has the feeling that he must keep things moving. A few seconds of silence seem to last forever. Pauses are useful, however, in encouraging communication, and the art of using them should be acquired.

Some words of caution: The interviewer must be sensitive to each individual respondent in using this technique. Some respondents may be truly out of ideas, and a pause cannot stimulate them to further discussion.

Repeating the question: When the respondent does not seem to understand the question, when he misinterprets it, when he seems unable to make up his mind, or when he strays from the subject, it is often useful to repeat the question just as it is written in the questionnaire. Many respondents, hearing it for a second time, realize what kind of answer is needed. They may not have heard the question fully the first time, or they may have missed the question's emphasis.

Repeating the respondent's reply: Simply repeating what the respondent has said as soon as he has stopped talking is often an excellent probe. This should be done as you are writing, so that you are actually repeating the respondent's reply and recording it at the same time. Hearing his idea repeated often stimulates further thought by the respondent. Interviewer should notate this probe by (R.Q.), which is "Repeat Question."

A neutral question or comment: Neutral questions or comments are frequently used to obtain clearer and fuller responses. Following are examples of the most commonly used probes; their "key word" phrases, which should be recorded in the questionnaire, are in parenthesis:

"Could you tell me more about your thinking on that?" (more)
"Why do you think that is so?" (why)
"Can you give me an example?" (example)
"Could you explain?" (explain)
"Could you tell me why you feel that way?" (why)
"Which figure do you think comes closest?" (which)
"Do you have any other reasons for feeling as you do?" (other)
"What else?" (W.E.) or (else)

Use a probe that makes sense in the context of the question and that will elicit clarification of the respondent's statement. Such probes make a direct bid for more information. This technique takes a while for newer interviewers to master, but it is a dependable and fruitful technique when used correctly. IT REQUIRES THAT THE INTERVIEWER RECOGNIZE IMMEDIATELY JUST HOW THE RESPONDENT'S ANSWER HAS

FAILED TO MEET THE OBJECTIVE OF THE QUESTION, AND THAT THE INTERVIEWER THEN FORMULATE A NEUTRAL TYPE OF QUESTION TO ELICIT THE INFORMATION NEEDED. The interviewer's manner of asking these neutral questions is important.

Please follow the following standards in recording probes:

1. Repeat the KEYWORD e.g., "Convenient." (convenient) "Near shops, schools."

2. Record words you use; e.g., "Convenient (mean) Near shops, schools," or "Convenient (how), Near shops, schools."

3. NEVER use (P), /, X/ i.e., any symbols to indicate probe.

4. The probe "anything else" should never be used...it is too easy for respondent to just say "No" in response. The correct probe is "What else?", which elicits a positive response.

5. NEVER leave an open-end question without an ending probe (e.g., "What else") and the verbatim response (e.g., "That's all.")

Asking for further clarification: In probing, it is sometimes a good technique for the interviewer to appear slightly bewildered by the respondent's answer and to intimate in his probe that it might be he who failed to understand. (For example: "I'm not quite sure I know what you mean by that--could you tell me a little more?") This approach is very useful in dealing with what appears to be an answer that is inconsistent with previous answers. For example, the interviewer might simply say, "I'm sorry, but I'm not sure I understand. Did you mention previously...?" and then briefly mention the respondent's earlier answer. It is most important that you appear to ask this question because you did not understand; do not appear to contradict or "cross-examine" the respondent in any way. If you feel you cannot ask for clarification of an inconsistent answer without upsetting the respondent, simply go right on with the other questions. Later, in editing, you might make a marginal note of the situation.

Final probes: Unless specified, all open-end question must have a final probe. This is your way of telling us the respondent has no further information on a subject. Checking for final probes is a part of the editing process so make sure you always use and record them.

The (W.E.) "What else can you tell me about (...)" is a final probe you will probably use most often. If the respondent gives you no new information, record his response to the (W.E.) verbatim, e.g., "(W.E.) I can't think of anything else."

When you have a question that asks the respondent to list things, e.g., problems in Los Angeles and the United States, you can say, "What other problems..?" and indicate this probe with (OTHER). If the respondent has given two problems and says "Nothing else" to your (W.E.) or (OTHER) probe, record

the probe and his answer verbatim on the next line. This is very important because it tells us he could not think of any more problems, or whatever the question refers to.

3. Probing Methods Should Be Neutral

Remember that we have described probing as the technique that motivates the respondent to communicate more fully and that focuses the discussion on specific topics. We also said these two things must be done without introducing bias.

The potential for bias is great in the use of probes. Under the pressure of the interviewing situation, the interviewer may quite unintentionally imply that some responses are more acceptable than others, or he may probe suggestively, directing the respondent toward a given response. Consider the question:

"How do you think things are going in the world today, I mean--our relations with other countries?"

The respondent's first answer is:

"Well, I don't know too much about our relations with foreign countries."

The respondent has not answered the question, but he has indicated that he has some thoughts on the subject. How might the interviewer handle this situation? An example of a neutral probe might be:

"I see. Well, could you tell me what you have in mind?"

or

"There are no right or wrong answers on things like this, of course. I'd just like to get your thinking."

It is important not to change the content of the question. The following example illustrates a directive probe, which entirely changes the nature of the question:

"Well, what about our relations with Russia?"

The respondent now considers any answer he might give in terms of our relations with Russia, a subject he himself had not mentioned at all and that was introduced by the interviewer. It will be impossible to find out what the respondent really thought about "our relations with other countries."

This principle, of course, applies to interviewing on both factual (For example, "Do you own a car?") and attitudinal (For example, "How do you feel about...?") survey questions. However, in attitudinal interviewing, the interviewer must be especially careful to use neutral methods because the expression of attitudes and opinion is very easily influenced by the interviewer. Sometimes an answer may be suggested unconsciously by the mere inflection of the interviewer's voice.

4. The "I Don't Know" Response

The "I don't know" answer can mean any number of things. For instance: The respondent doesn't understand the question and answers with a "don't know" to avoid saying he doesn"t understand. The respondent is thinking the question over and says "I don't know" to fill the silence but to give himself time to think, too. The respondent may be trying to evade the issue because he feels he is uninformed and may give the wrong answer, or because the question strikes him as too personal. The respondent may really not know, or he may have no opinion or attitude on the subject. If the respondent actually doesn't have the information requested of him, this is in itself significant to the survey results. But, it is the interviewer's responsibility to make sure this is the case. An expectant pause, a reassuring remark ("Well, we're just interested in your general ideas about this."), repeating the question, a neutral question ("What are your ideas about this?")--all will encourage the respondent to reply.

D. RECORDING AND EDITING THE INTERVIEW

Even though the interviewer does a good job in taking the interview, the survey cannot succeed unless the interviewer conveys the information to the study staff in a full and unbiased form. Ideally, the best way to obtain full and accurate information is to use some sort of recording machine and to tape everything that is said in the interview. This is usually not practical, however, so it is up to the interviewer to accurately record the interview. The best way to do this is to record verbatim as the interview is going on.

Interviewers record the respondent's replies directly on the questionnaire in the spaces provided for each question. Thus, each completed interview contains the original questions asked, the interviewer's probes, and the respondent's answers.

The Center uses two basic types of questions in its questionnaires. These are the write-in question (also called the "open-ended" question) and the check-off question (also called the "closed-ended" or "fixed alternative" question) which is generally precoded. A third type of question, the write-up or "depth" question, requires extensive probing. With this type of question the interviewer takes notes on a separate pad. She then "writes up" a full report immediately after the interview. This type of question is used only in special studies by very experienced interviewers.

The Open-end Question

The survey uses the open-end question when it expects a complete attitudinal answer. For example:

Q1. What do you like about living in your area?_____

_____

The answer must be recorded verbatim while the respondent is talking.

The Closed-end Question

The closed-end question is used for factual items that do not require long answers or when we expect a respondent's attitudes to easily fit into categories. In this type of question the interviewer simply circles the appropriate number. Two sample formats follow:

Q1. How many grades of school did you finish?

8 OR LESS.....1
9 - 11.....2
12 OR MORE.....3

or,

Q1. Would you say that at present business conditions are:

better now.....1
worse now, or.....2
about the same?.....3

RECORD RESPONSES DURING THE INTERVIEW. Experience has shown that the most accurate way to reproduce the responses is to record them immediately, as the respondent is talking. Often, relevant information is lost and distortions occur when the interviewer tries to remember what the respondent is saying and to write it up later.

USE THE RESPONDENT'S OWN WORDS. Interviewers must learn to record the respondent's replies in the very words the respondent uses. This is what is called verbatim reporting. Catch the phrases, grammatical usage, trick and peculiarities of speech characteristic of each respondent so that the interview will reflect something of his individual personality. Do not attempt to record dialect, however.

DO NOT SUMMARIZE OR PARAPHRASE THE RESPONDENT'S ANSWERS. Summarizing or paraphrasing a response creates an artifical--and dangerous--step between the respondent and the analyst for this often results in distortion. A summarized response obscures the respondent's own answer. Consider the difference between the following two examples:

Verbatim recording:	Summarized recording:
"I don't give a doggone what the Russians think of us. I think we should get in there and tell those stinkers off. They're pushing us around too much!"	We should stand up to the Russians.

The summarized recording lacks the true intensity and lustre of the respondent's reply. The problem is even more serious than this, however. The paraphrased answer actually distorts the meaning of the respondent's reply. The specific

terms in which the respondent talks, the words he uses, and the length of his answer all provide important information.

INCLUDE EVERYTHING THAT PERTAINS TO THE QUESTION OBJECTIVES. A recorded response should include everything the respondent said that pertains to the objective of the question, regardless of length.

Some respondents will talk at length during the course of the interview about subjects that have no bearing on the study objectives. Long, irrelevant discourses may be omitted from the recorded interviews if:

(1) the interviewer is certain that what was said has no bearing on or use in fulfilling the aims of the study;
(2) marginal notes are made by the interviewer to indicate that the digression took place.

INCLUDE ALL YOUR PROBES. All comments, probes, and explanations made by the interviewer during the course of the interview should appear in the questionnaire at the point where they were made in the interview. In this way, the coders and analysts can determine what influenced the respondent to reply as he did. Entry of probes and comments by the interviewer should always be made in parentheses.

HOLD THE RESPONDENT'S INTEREST. The interviewer should try to keep his attention focused on the respondent and not become overly absorbed in his notebook or questionnaire. A good technique to hold the respondent's interest and take the verbatim notes is to start repeating what the respondent has said while you are writing that reply. This lets the respondent know you are listening to his every word. As mentioned previously, this technique also serves as a probe. The respondent hears what he has just said and this may stimulate further thought and lead him to amplify or modify his statement. An example of this technique follows:

Question: What would you say are the main differences between schools nowadays compared with what they were like when you went to school?

Answer: "Schools are far more advanced right from the start--in the second and third grades they teach them more than we had at those grades."

Question: (says as he is writing the last few words of the reply) "..they teach them more than we had at those grades?" (pause)

Answer: "Yes. You know--nowadays they teach languages even in grade school."

START RECORDING AS SOON AS THE RESPONDENT STARTS TALKING rather than looking at the respondent all the time he is replying. Naturally, however, you should glance up now and the, especially when you are asking the questions.

SKIP PATTERNS

Certain questions in an interview have follow-up questions (or dependent questions) designed to obtain further information if the original question is answered in a particular way.

The simplest type of skip pattern is shown in this example:

5. Do you plan to buy a new car in the next year?

Yes.....ASK A.....1
No.....SKIP TO Q6.....2

A. What type of car do you plan to buy?

Compact.....1
Sports.....2
Camper.....3
Truck.....4

Obviously if Q5 is answered "No" there is no point in asking "A".

Other skip patterns may deal with a sequence of questions that are to be asked only if respondent (R) fits a certain category determined by a previous question. These appear in a box and are circled by the interviewer for his/her own reference and as a guide to the coder. They are not a question to be re-asked of respondent. The box will appear just above a set of questions and is used as a sort of road map by the interviewer.

EXAMPLE:

R. PLANS TO BUY A NEW CAR - CONTINUE WITH Q10....1
R. DOES NOT PLAN TO BUY CAR - SKIP TO Q15.....2

1. Rules on the Mechanics of Recording and Editing Interviews

The Center requires a uniform procedure for recording interviews. It is easier for the interviewer as well as the coder and the analyst when these procedures are followed:

WRITING MUST BE LEGIBLE. Regardless of how good the actual interview may have been, it is worthless if the record of it cannot be read. In editing an interview please check to be sure that all writing can be read easily.

USE A PENCIL TO RECORD. Please use a black lead #2 pencil to record respondent's answers; do not use a pen. Carry several pencils with you when taking an interview so you will always have a sharp one.

In recording responses, you may leave out small words like "and," "I," and "the," or you may abbreviate words. After leaving the respondent you must then edit the interview immediately so that the responses are clear in both sense and legibility.

ACCOUNT FOR EACH QUESTION IN THE QUESTIONNAIRE. Each question must either be answered by the respondent, or it must have some explanation from the interviewer as to why it wasn't answered. If there are specific skip patterns to follow, an explanation is not necessary.

IDENTIFY EACH INTERVIEW. Proper identification of interviewer and respondent must appear on the cover sheet for each interview as well as on the questionnaire. Such identification is necessary for Center use only; it is never used to identify the respondent. Also include this indentification in the upper right-hand corner of any addtional write-up sheets that may accompany the interview.

2. Tips on Recording Responses

With practice (try recording part of a radio newscast, practice on a friend, etc.) you will be able to record the interview with little difficulty. The following tips can help you become adept at speedy recording.

WHEN THE RESPONDENT STARTS TO TALK, BEGIN TO WRITE IMMEDIATELY. This will help you record verbatim and minimize the time the respondent has to wait for the next question. Always carry a pad with you just in case you need extra writing space. A lengthy answer may be recorded on a separate sheet of paper as long as the paper is properly identified as belonging to a particular interview and a particular question.

3. Summary Tips on Editing

When you edit, please remember that the completed interview will be seen by someone who was not present when you took the interview. Even if you have asked a question, probed, and obtained a full answer, the entire response can be lost if the coder can't understand what you wrote.

The best time to edit an interview is right after you take it, for at this time the entire situation is still clear.

Please be sure that each of the following points is well covered when you edit.

(a) Legibility: As mentioned earlier, the best response is lost if it cannot be read.
(b) Probes: These and any other remarks made by you must be indicated in parentheses; open-end questions must show an appropriate final probe (W.E.) with respondent's ending statement verbatim.
(c) Unclear Responses: Clarify with parenthetical notes.
(d) Comments to clarify any situation at the time of the interview.

After you have edited the interview, you should also carefully go over the cover sheet. Here are some suggestions for editing the cover sheet:

(a) Check to see that all necessary identification is on each cover sheet--name label, your interview number, the date, length of interview in minutes, and the complete specific address of the dwelling unit.
(b) Make sure the specific address appears on the cover sheet in exactly the same words as it appears on the listing sheet.
(c) Complete the call record.
(d) Complete the nonresponse boxes for any address where you were unable to obtain an interview. Give as much information as possible for any non-interview situations.

See Appendix A-1 for example of call record.

E. NONRESPONSES AND CALL-BACK STRATEGY

1. Two Types of Nonresponse

The two kinds of nonresponse situations are the "noninterview" and the "non-sample."

If the interviewer does not get an interview with the eligible respondent, it is a noninterview and may result from conditions beyond the interviewer's control. For instance, the eligible respondent may be too ill to be interviewed, or senile, or unable to speak English (with no interpreter available). The interviewer may also find an eligible respondent who refuses to give the interview, or he may never be able to find the eligible respondent at home.

Noninterviews affect the response rate because there is an eligible respondent who was not interviewed.

The Nonsample

The nonsample situation, on the other hand, does not affect the response rate because there is either no one to be interviewed or no one who is eligible. This can happen when there is no dwelling unit at the assigned address--no such number; no such street; address not a dwelling but a business, school church, etc. It might also happen if a dwelling unit is vacant. It could also occur because there is no one at the assigned address who is eligible by study definition.

2. Refusals

New interviewers frequently ask, "What do you do when a person refuses to be interviewed?" This is a legitimate question, and we know that new interviewers ask it because they want to know how to handle their job. Unfortunately, there are no standard answers; just as one repondent differs from another, the reasons for refusals are many and varied.

Refusals are a source of concern to research organizations like the Center because refusals introduce bias into the survey findings. The Center, is constantly studying nonresponse situations in an effort to discover the reasons behind them, to discover better ways and means of avoiding them, and to measure the extent of the bias they introduce in the survey results. For these reasons, interviewers are asked to give as much information as they can about nonresponse situations, especially refusals. Any personal data on the noninterview respondent--age, sex, marital status, number of children, type of dwelling, and so on--helps. A full account of the meeting with the respondent is particularly helpful.

See Appendix A-2.

3. Call and Call-Back Strategy

Initial call and call-back procedures greatly affect response rates and costs. To increase response rates and keep costs down, please use the following suggestions as a guide.

START CALLS ON ALL ASSIGNED DWELLING UNITS EARLY IN THE STUDY PERIOD. This will get you off to a good start and will allow you time to make repeated call-backs for respondents who are difficult to reach.

NOTICE WHO WILL BE THE SPECIFIED RESPONDENT AND PLAN TO CALL WHEN THE RESPONDENT IS MOST LIKELY TO BE HOME. For example, if you are to interview a male, try to make your first call in the late afternoon, early evening, or on the weekends when he is most likely to be home. (If you know, of course, that he might be home during the day in a neighborhood where men work split shifts, then you might want to plan some other procedure.) Similarly, if you are to interview housewives, try to call in the morning or afternoon. Timing your call to coincide with respondent's likelihood of being home will enable you to take more interviews on the first contact and, therefore, to spend more time trying to reach other respondents.

WHEN MAKING CALL-BACKS FOR A RESPONDENT WHO WAS PREVIOUSLY ABSENT, CALL ON A DAY AND AT AN HOUR OF THE DAY DIFFERENT FROM THE FIRST CALL. It is also a good idea to try asking a neighbor about the best time to find someone at the selected dwelling unit after you have called twice at the address and still can't locate a respondent. As a general rule, plan at least four calls on all addresses.

F. SAMPLED ASSIGNMENTS

1. The sampling section of the Center makes a selection of dwelling units within each block for each study.

It is the responsibility of the interviewer to interview at the selected (sampled) address and/or unit number. If the wrong address is sampled by the interviewer, we are unable to use the interview.

Therefore, the interviewer must carry out correct sampling procedures carefully and conscientiously in the field.

The interviewer must not substitute one address for another. The sample was mathematically drawn to represent the entire county. If we made substitutions we would quickly destroy the representativeness of our sample. Call your supervisor if you find any problems with a sampled address.

2. Selecting the Respondent

After a sample of occupied dwelling units has been identified and their occupancy has been ascertained, the interviewer must use further sampling procedures to select the proper respondent from among the residents of each sample DU.

When interviewing in blocks, we usually use one of two procedures for selecting respondents:

(a) Designating the Respondent by Family Relationship: This is usually done when we want to represent family units and believe that a certain type of person within each family will be the best source of information. For example, on an economic study we may want to talk with the head, but on a health study we may wish to speak with the wife.

(b) Designating the Respondent With the Selection Table: When, for example, we wish to represent all adults in the County or all citizens of voting age or all persons between eighteen and twenty-five, we are likely to find more than one eligible person in a DU. Since we may not wish to confine our choice to head, or wife, or another specific family relationship, we must use a method which gives all eligible persons in the DU a chance of selection. For this reason, certain studies will require the use of selection tables.

At the beginning of each survey you will receive instructions indicating which procedure to use. If a survey requires a selection procedure different from either of the two mentioned above, you will receive special instructions.

LIST ALL MEMBERS OF THE DU IN THE FIRST COLUMN OF THE HOUSEHOLD ENUMERATION TABLE. List the head first, and then the other members in whatever order they're given to you using first names. You must see the instruction book for each study to determine which DU members should be listed because requirements vary from study to study.

RECORD RELATIONSHIP TO THE HEAD. Designate as son or daughter (not child), and wife or husband (not spouse). List persons not related to the head by position in the household: roommate, roomer, maid, chauffeur, cook, etc.

CHECK FOR OTHER MEMBERS OF THE DU. Be sure all residents of the DU are listed by asking "Anyone else living here whom we may have missed?" Unless you take special pains to find out about them, you are quite likely to miss roomers and unrelated persons, or even family members. If you do not know whether to list persons who are temporarily present or absent, refer to the following rules:

Persons staying in the DU at the time of contact should be included as members of the household, if:

- this is their usual or only place or residence, or if
- this is their legal address.

Persons absent* at the time of contact should be included as members of the household if a place of residence is held for them here and no place of residence is held for them elsewhere.

If any of these criteria cannot be determined, the person should be included in the household, but you should tell us what you can about the situation.

RECORD ADDITIONAL INFORMATION CALLED FOR IN THE HOUSEHOLD LISTING BOX. Normally, sex will be evident from relationship to the head and can be recorded as you list without additional inquiry. Ages may be learned by saying "I'd like to know the ages of the people. How old is...?" (MENTION ONE)

EACH DU IN THE SAMPLE SHOULD BE ACCOUNTED FOR WITH A COVER SHEET REGARDLESS OF WHETHER OR NOT IT YIELDS AN INTERVIEW. If no interview is obtained, record the type of nonresponse and fill out the nonresponse form on the cover sheet as completely as possible.

Head of Family Unit: The most common listing situation is a married couple alone or with their minor children. In this situation the husband is always the head of the family. This rule holds true even if the husband is disabled or unemployed and the wife is supporting the family.

In any other situation we consider the family head to be the economic dominant. In order to determine who is the economic dominant, you will have to obtain some additional information about the family financial arrangements. At this stage of the interview it is generally not a good idea to inquire about income. However, you can ask such general questions as "Who provides the major share of financial support for your family?" or "Who pays the rent?" Questions like these should enable you to determine fairly accurately who we would consider to be the economic dominant.

Sometimes different members of a family have equal economic power, such as two unmarried sisters with the same income who share expenses equally. In such cases, with all other things equal, you would designate the older one as family head.

---

* Persons absent at time of contact who are not to be listed are those:

1. having a country or town house;
2. having a summer home or winter home;
3. away at school or in the service;
4. in prison, nursing home or special hospital (long-term).

To help you in deciding who is the family head, the above rules can be summarized with the following mnemonic device:

Husband

Economic dominant

Age oldest

Don't ask your informant who is the head. Determine it yourself on the basis of these criteria.

(a) Designation of Respondent with the Selection Table

When the respondents are to be selected by this means, a selection table appears on the cover sheet. In order to select different kinds of respondents eight kinds of tables have been devised. In order to assure randomness, cover sheets with selection tables must be used in a certain sequence. Study instructions will specify how this is to be done.

The steps you are to follow are:

Assign numbers to each eligible person (eighteen years or older and as defined by the special study instructions.) The usual procedure will be: Assign the number "1" to the oldest male, "2" to the next oldest male, and so on until all eligible males are numbered. Continue by numbering females; the oldest female is assigned the next number after the youngest male, etc.

Refer to the selection table on the cover sheet. Circle the number corresponding to the total number of eligible persons listed in the DU. Below this number you will find the number of the person to be interviewed; circle that number. Find the person whose number you have selected and circle his or her number in the "number" column of the enumeration table. THIS IS THE SELECTED RESPONDENT: YOU ARE TO INTERVIEW HIM OR HER AND NO ONE ELSE. (See the following, Figures 1,2,3).

Interview only the person selected by the selection table.. If the selected person is not at home, ask about the best time to return to interview. If the selected respondent will not be home during the survey, do not substitute anyone else for the original selection. If an interview couldn't be obtained with the selected respondent, the DU would be classified as a noninterview. Since interviews with wrong respondents cannot be used in the analysis, in some cases the interviewer may be asked to return to the DU and interview the proper respondent. This inconveniences the household, embarrasses the interviewer, and WE DO NOT PAY FOR INTERVIEWER ERROR.

If the respondent does not speak English, NON-BILINGUAL INTERVIEWERS do not interview. Note on the schedule that the respondent speaks Spanish only and return questionnaire to the field office. Each interviewer will carry Spanish versions of all the introductory materials and a card explaining in Spanish that a bilingual interviewer will be assigned that household; the card should be left with the respondent. If any other foreign language is spoken, record as LANGUAGE BARRIER (Note Lang. Spoken) on Non-Interview Form.

SELECTION OF THE PROPER RESPONDENT

In the training sessions, we stressed the fact that we would obtain a proper and representative cross section of the people of Los Angeles County ONLY IF the selection process was done accurately. Any deviation automatically distorts our sample and, therefore, over- or underrepresents certain types of people.

Having recorded the family/household, 18 years of age and older, (son, daughter, wife, etc.), you are to assign numbers according to sex and age: From oldest to youngest, all men and then all women are assigned numbers. For example, a man eighteen years of age is always assigned a number after his father aged 47 but before his grandmother aged 95.

After assigning the numbers, in the appropriate column, to each member listed on the 18 years and older roster, check the SELECTION TABLE on the computer-generated label for the size of the household. That is, if the number of adults is

	1,	2,	3,	4,	5,	6,	7,	or 8 or more,
select adult number	1	1	1	1	2	2	3	3.

Select the number which is directly below the total number of people in the household; that is, select THE PERSON (respondent) you will interview. NO SUBSTITUTIONS ARE PERMITTED UNDER ANY CIRCUMSTANCES.

As you examine the summary of the selection tables (attached), you will note that tables lettered A, B_1, and B_2, have low numbers (1's and 2's); since men have been numbered first, they will be assigned the low numbers. Hence, it is more likely, other things being equal, that such tables will yield male respondents. Tables lettered E_1, E_2, and F have higher numbers (3's, 4's, 5's, and 6's) and will generally yield women respondents (because females are assigned numbers after all the males).
ONLY ONE COMPUTERIZED SELECTION TABLE WILL APPEAR FOR AN ASSIGNED (SAMPLED) ADDRESS.

We hope this will give you a little headstart in planning your first calls on your assigned households. There is no reason to make a daytime cal at an address for which you have a "TABLE A," because the table is likely to indicate a male respondent and he will probably be away at his job.

FIGURE 1 (CONTINUED)

Summary of Selection Tables

TABLE LETTER	If the Number of Adults in Household is: 1	2	3	4	5	6	7	8
	Select Adult Numbered:							
A	1	1	1	1	1	1	1	1
B_1	1	1	1	1	2	2	2	2
B_2	1	1	1	2	2	2	2	2
C	1	1	2	2	3	3	3	3
D	1	2	2	3	4	4	4	4
E_1	1	2	3	3	3	5	5	5
E_2	1	2	3	4	5	6	6	6
F	1	2	3	4	5	6	6	6

FIGURE 2

1234 03 1302	3 204	TABLE E2
ADDRESS:	452 10TH STREET SANTA MONICA	90403
OPTIONS:	Q9 9Y	
IF THE # OF ADULTS IS:	1 2 3 4 (5) 6	
THEN SELECT ADULT #:	1 2 3 4 (5) 6	

CONFIDENTIAL
BEGIN DECK 01

Selection Table Example

A1. INTERVIEWER: Jane Smith I.D. 012 22-23

A2. TIME BEGINNING: _____ AM/PM TIME ENDING: _____ AM/PM # OF MINUTES: ___ 24-

Good morning/afternoon/evening. I'm from the UCLA Survey research Center. You may have received a letter from our Center telling you about the survey we are doing in Los Angeles. We are interested in finding out how people in the Los Angeles Metropolitan Area feel about the community, what problems there are and what is needed for the future. The information we collect will be written up in reports for local officials and in the local newspapers. Your opinions are very important because you have been chosen scientifically to represent hundreds of other people in Los Angeles. The more people who cooperate, the more successful we can be in reporting the needs of all the people in this city. EVERYTHING YOU TELL US WILL BE STRICTLY CONFIDENTIAL. YOUR NAME WILL NOT BE CONNECTED IN ANY WAY WITH THE FINDINGS OF THIS IMPORTANT STUDY.

A3. First, I would like to make a list of the persons 18 years old or over, who live here as members of your household. This will tell me which adult I am to interview. (AFTER RECORDING INFORMATION IN "A," ASSIGN NUMBERS IN "E" WITH OLDEST MALE = 1, SECOND OLDEST MALE = 2, ETC. AFTER ALL MEN ARE NUMBERED, CONTINUE WITH WOMEN BEGINNING WITH OLDEST TO YOUNGEST.)

	A. Name	B. Relationship to Head	C. Sex CIRCLE ONE M	C. Sex CIRCLE ONE F		D. Age	E. Number & CIRCLE # SELECTED	F. Marital Status* INSERT
A.	Mary	27-28/ Wife	1	(2)	41/	48-49/ 63	62/ 3	69/ 2
B.	John	29-30/ HEAD	(1)	2	42/	50-51/ 66	63/ 1	70/ 2
C.	DAVid	31-32/ son	(1)	2	43/	52-53/ 28	64/ 2	71/ 1
D.	Susan	33-34/ daw	1	(2)	44/	54-55/ 26	65/ (5)	72/ 1
E.	Amy	35-36/ daw	1	(2)	45/	56-57/ 29	66/ 4	73/ 1
F.		37-38/	1	2	46/	58-59/	67/	74/
G.		39-40/	1	2	47/	60-61/	68/	75/

MARITAL STATUS CODE:
1 = Never married
2 = Married
3 = Divorced
4 = Separated
5 = Widowed

OFFICE USE ONLY
LINE # OF RESP. _____ 76/
LINE # OF HEAD _____ 77/
TOTAL LISTED _____ 78/

LAMAS V #3005

ID	REC TRACT	BG/ED	BLK	TABLE
5	06 1043	5	508	D

ADDRESS: 11307 WOODCOCK AVE
PACOIMA 91331
OPTIONS: Q9
9X

IF THE # OF ADULTS IS: 1 2 3 (4) 5 6
THEN SELECT ADULT #: 1 2 2 (3) 4 4

CONFIDENTIAL
BEGIN DECK 01

Selection Table Example

A1. INTERVIEWER: B. Mitchell I.D. 002 22-23/

A2. TIME BEGINNING: ____ AM/PM TIME ENDING: ____ AM/PM # OF MINUTES: ____ 24-26/

Good morning/afternoon/evening. I'm from the UCLA Survey Research Center. You may have received a letter from our Center telling you about the survey we are doing in Los Angeles. We are interested in finding out how people in the Los Angeles Metropolitan Area feel about the community, what problems there are and what is needed for the future. The information we collect will be written up in reports for local officials and in the local newspapers. Your opinions are very important because you have been chosen scientifically to represent hundreds of other people in Los Angeles. The more people who cooperate, the more successful we can be in reporting the needs of all the people in this city. EVERYTHING YOU TELL US WILL BE STRICTLY CONFIDENTIAL. YOUR NAME WILL NOT BE CONNECTED IN ANY WAY WITH THE FINDINGS OF THIS IMPORTANT STUDY.

A3. First, I would like to make a list of the persons 18 years old or over, who live here as members of your household. This will tell me which adult I am to interview. (AFTER RECORDING INFORMATION IN "A," ASSIGN NUMBERS IN "E" WITH OLDEST MALE = 1, SECOND OLDEST MALE = 2, ETC. AFTER ALL MEN ARE NUMBERED, CONTINUE WITH WOMEN BEGINNING WITH OLDEST TO YOUNGEST.)

	A. Name	B. Relationship to Head	C. Sex CIRCLE ONE M	C. Sex CIRCLE ONE F		D. Age	E. Number & CIRCLE # SELECTED	F. Marital Status* INSERT
A.	Bob	27-28/ roomate	(1)	2	41/	48-49/ 31	62/ 2	69/ 3
B.	Carol	29-30/ roomate	1	(2)	42/	50-51/ 25	63/ 4	70/ 4
C.	Ted	31-32/ head	(1)	2	43/	52-53/ 33	64/ 1	71/ 3
D.	Alice	33-34/ roomate	1	(2)	44/	54-55/ 26	65/ (3)	72/ 1
E.		35-36/	1	2	45/	56-57/	66/	73/
F.		37-38/	1	2	46/	58-59/	67/	74/
G.		39-40/	1	2	47/	60-61/	68/	75/

MARITAL STATUS CODE:
1 = Never married
2 = Married
3 = Divorced
4 = Separated
5 = Widowed

OFFICE USE ONLY
LINE # OF RESP. ____ 76/
LINE # OF HEAD ____ 77/
TOTAL LISTED ____ 78/

ID	REG	TRACT	BG/ED	BLK	TABLE
1	06	1043	5	502	A

ADDRESS: 13361 FILMORE ST
PACOIMA 91331
OPTIONS: Q9
9X

IF THE # OF ADULTS IS:	1	2	3	4	5	6
THEN SELECT ADULT #:	1	1	1	1	1	1

CONFIDENTIAL

LAMAS V
3005

1ST INT. ID___22-23/
OF CALLS____24-25/
2ND INT. ID___26-27/
OF CALLS____28-29/

	A. DATE	B. DAY OF WEEK	C. TIME	D. PERS	CONTACT TEL	E. RESULT (CODE MUST BE ENTERED ON EVERY LINE.)
1.	31-34/	35/	AM 36-39/ PM		40/	41-42/
2.	43-46/	47/	AM 48-51/ PM		52/	53-54/
3.	55-58/	59/	AM 60-63/ PM		64/	65-66/
4.	07-10/	11/	AM 12-15/ PM		16/	17-18/
5.	19-22/	23/	AM 24-27/ PM		28/	29-30/
6.	31-34/	35/	AM 36-39/ PM		40/	41-42/
7.	43-46/	47/	AM 48-51/ PM		52/	53-54/
8.	55-58/	59/	AM 60-63/ PM		64/	65-66/
9.	07-10/	11/	AM 12-15/ PM		16/	17-18/
10.	19-22/	23/	AM 24-27/ PM		28/	29-30/
11.	31-34/	35/	AM 36-39/ PM		40/	41-42/
12.	43-46/	47/	AM 48-51/ PM		52/	53-54/
13.	55-58/	59/	AM 60-63/ PM		64/	65-66/

no one home/no answer (NH)-01
respondent not at home (RNH)-02
appointment made (AM)-03
initial contact busy-no appt.(IBY)-04
respondent busy-no appt. (RBY)-05
initial contact ill-no appt. (I ill)-06
respondent ill-no appt. (R ill)-07
appt. cancelled by initial contact(ACI)-08
appt. cancelled by respondent (ACR)-09
non-interview (NI)-82
completed on appt. (CA)-90
completed no appt. (CNA)-91

1ST INTERVIEWER

F. FIRST PERSON CONTACTED: 67/
Black, non-Spanish surname..1
Spanish surname.....2
Oriental.....3
Non-Spanish surname (not Black/Oriental).....4
Other - SPECIFY:_____

G. male.....1 68/
female.....2 69-70/

H. AGE ESTIMATE 1ST PERSON:_____

2ND INTERVIEWER

I. FIRST PERSON CONTACTED: 71/
Black, non-Spanish surname..1
Spanish surname.....2
Oriental.....3
Non-Spanish surname (not Black/Oriental).....4
Other - SPECIFY:_____

J. male.....1 72/
female.....2 73-74/

K. AGE ESTIMATE 1ST PERSON:_____

APPENDIX A-2

FOR NON-INTERVIEWS ONLY

FIRST INTERVIEWER

F.

Vacant.....01
Address not a dwelling unit....02
No such address.....03
No one at home, final call.....04
Respondent not at home, final call.....05
Language barrier.....06
(What language:_____)
Secure residence.....07
Secure apt. building.....08
Manager refuses.....09
Initial contact incapable.....10
WHY:_____

Initial contact refused.....20
VERBATIM:_____

Respondent never contacted.....30
DESCRIBE:_____

Respondent incapable.....40
WHY:_____

Respondent refused.....50
VERBATIM:_____

Refused to open door.....60
COMMENTS:_____

Other.....70
SPECIFY:_____

SECOND INTERVIEWER

J.

Vacant.....01
Address not a dwelling unit....02
No such address 03
No one at home, final call.....04
Respondent not at home, final call.....05
Language barrier.....06
(What language:_____)
Secure residence.....07
Secure apt. building.....08
Manager refuses.....09
Initial contact incapable.....10
WHY:_____

Initial contact refused.....20
VERBATIM:_____

Respondent never contacted.....30
DESCRIBE:_____

Respondent incapable.....40
WHY:_____

Respondent refused.....50
VERBATIM:_____

Refused to open door.....60
COMMENTS:_____

Other.....70
SPECIFY:_____

G. IF REFUSAL, REFUSER WAS:

Black, non-Spanish surname.1
Spanish surname.....2
Oriental.....3
Non-Spanish surname (not Black/Oriental).....4
other-SPECIFY:_____

H. male.....1
female.....2

I. AGE ESTIMATE OF REFUSER:_____

K. IF REFUSAL, REFUSER WAS:

Black, non-Spanish surname.1
Spanish surname.....2
Oriental.....3
Non-Spanish surname (not Black/Oriental).....4
other-SPECIFY:_____

L. male.....1
female.....2

M. AGE ESTIMATE OF REFUSER:_____

III. TELEPHONE INTERVIEWING

The basic procedures and techniques employed in face-to-face interviewing and defined in the manual are applicable to telephone interviewing as well. There are obvious differences and unique problems in a telephone survey. Communication in any interviewing situation is not simple, and in telephone interviewing communication is complicated by the elimination of normal face-to-face contact.

In the telephone interview, the respondent reacts to the interviewer's voice rather than to a personality. This emphasizes a need for the interviewer to be courteous, to sound pleasant, and to speak slowly and clearly. It is important that the interviewer identifies himself immediately and addresses the respondent (or whoever may answer the phone) by name, whenever possible. The person who answers the phone may not be the person you must interview. You must establish friendly relations with the person on the other end of the line by concisely stating the purpose of the call and by expressing enthusiasm for the project, with true sincerity. Be brief in your introduction so you do not lose the interest of your respondent.

If you sense suspicion or wariness on the part of the respondent, stress the confidentiality of the information you seek. Since contacts are made mainly through telephone listings, you already know the name of the respondent, or at least of someone residing in the household. It is important to explain that the respondent's name is in no way connected to the data you collect.

As in all interviews, the question of selection arises. The respondent may ask, "How did you get my phone number?" You must always have a clear and satisfactory answer, explaining that a computer has selected the number at random from all those numbers listed in the directory. Assure the respondent that this is the only method possible to reach a cross-section of L.A. County residents by telephone.

The instructions for recording responses in a telephone interview are the same as in a face-to-face interview; all responses are recorded verbatim. However, in a telephone interview it is more imperative to be completely familiar with the questionnaire to avoid embarrassing pauses. A constant flow is essential; otherwise you will lose the interest of the respondent which can result in premature termination.

Accordingly, all the probes must be verbal and, of course, nondirective. The telephone interviewer cannot rely on a facial expression, a raised eyebrow, or an expectant pause. It is more difficult to elicit information over the telephone without falling into the pitfall of prodding, suggesting, or rushing the respondent. A pleasant, nicely modulated, and interested voice is the most effective technique, coupled with the "know-how" of probing effectively.

Adjust your approach to the personality of the respondent. If he is formal and businesslike, be formal. Be receptive and sensitive to the wishes of the respondent.

Be courteous at all times and thank the respondent for his cooperation. Be certain to explain that he may be phoned again for a verification of the validity of the interview.

GENERAL RULES FOR INTERVIEWING

1. Write in black lead pencil.

2. Write legibly.

3. Write verbatim (in the first person).

4. Do not abbreviate.

5. Do not use ditto (") marks or write "same as above" in answer to a question.

6. There must be an answer to each question.

7. Get an answer pertaining to the question. Write related comments in the lefthand margin.

8. Never write over the code numbers.

9. Never change the wording of a question.

10. Never change the sample or quota requirements.

11. Never count an incomplete questionnaire as part of your quota unless otherwise specified.

12. In classification data, always include the first initial or first name of the respondent, indicating the Mr., Miss or Mrs. (If "Mrs." obtain husband's initials for easier phone identification.) Please print name of respondent.

13. In obtaining occupation, get both the specific and the general occupation and duties. If retired, ask for previous occupation, or what respondent considers was "main" occupation.

14. Edit your questionnaires carefully. Make sure that each question is answered and that the answers are understandable.

15. Check your instructions carefully after the briefing and after your first interview.

16. Do not interpret instructions. Follow them exactly as stated. If any portion of questionnaire or procedure is not clear, contact your supervisor. (Do not call any unauthorized person.)

17. Keep careful daily records of time and expenses as specified on the job. Turn in time sheet with last completed interview. Be sure that the time sheet is completed, including title of job and/or job number, your name and other personal data requested.

18. Before accepting an assignment be sure you can meet the required deadline. If an emergency should arise, call your supervisor immediately.

19. All surveys are confidential.

SYMBOLS

1. Use an "X" mark, not a check mark. (unless otherwise specified.)

2. (ELSE) Probes are indicated by (....). Key word probes are always used. Interviewers words put into (....). Examples of keyword probes: (ELSE) (EXPLAIN) (CONVENIENT) (LIKE).

3. D.K. is used for "Don't Know."

4. N.A.H. for "Not At Home."

5. REF. for "Refused."

6. N.A. for "No Answer."

7. N.Q.R. for "not a Qualified Respondent."

8. Est. for Estimate

9. D.U. for "Dwelling Unit."

10. W.E. for "What else."

11. D.N.A. for "Does Not Apply."

12. H.H. for "Household."

13. N.F.I. for "No Further Information."

14. N.E. for "Nothing Else."

15. R. for "Respondent."

16. D.R. for "Don't Remember."

17. R.Q. for repeat question.

EQUIPMENT

1. Clipboard, #2 pencils.

2. Maps, City Guide (Thomas) (Optional)

3. Identification

4. Car - Insured.

K

APPENDIX K

INTRODUCTION TO RAMIS II USERS MANUAL

Appendix K

PREFACE TO RAMIS USERS MANUAL

The purpose of the RAMIS Users Manual is to provide a detailed explanation of how the facilities made available by the RAMIS II family of systems can be used.

The purpose of this preface is first, to provide an overview of the philosophy that led to the development of RAMIS II and then to survey the components of the RAMIS II family of systems in order to outline the structure both of this documentation and of RAMIS II.

RAMIS II is the next generation of RAMIS. A complete data base management system, it permits users to store, manipulate, retrieve, and display large quantities of data. RAMIS II can be invoked either through English-like RAMIS II nonprocedural languages or traditional procedural languages such as Cobol, Fortran, or PL/1. The RAMIS II system was generated in response to the need of the community of users to access data for both routine business operations and special decision-making procedures.

For the past 20 years, data processing research has been directed toward two ends: to simplify communication between the user and the computer and to make applications responsive to business and technological change. Most recently, two technologies—nonprocedural languages and data base management—have been evolving separately, each answering one of the two objectives. With RAMIS II, these two technologies are completely integrated for the first time.

With RAMIS II data base management, the user can input and access data without knowing how or where the data is actually stored and changes to the data storage structure do not affect existing applications. This data independence results in better use of both human and computer resources.

In addition, the RAMIS II data base management system enables many users to share data so data need be stored only once. Data redundancy is minimized, reducing both the possibility of inconsistency from one application to the next and the computer resources required to store the data. Nonredundant storage also permits the creation of standards to control the use of the data while balancing the conflicting requirements of the various user groups.

RAMIS II provides two nonprocedural languages: a report preparation language that obtains data from the data base and a records management language that inputs it into the data base. These languages simplify communication between the user and the computer by eliminating the need to translate a request into a computer program and then debug it. With RAMIS II, the original request is fed directly into the computer and this permits the user to proceed directly from problem definition to the analysis of results.

The RAMIS II nonprocedural languages now solve a very large segment of the problems facing business. To handle the few remaining problems and bring the benefits of data independence and reduced redundancy to all operations, a procedural language interface is provided that permits any standard procedural language to use the RAMIS II data base management system to access a RAMIS II data base.

RAMIS II can be used for almost any information-processing problem. The language used to solve a problem can vary with the type of problem as well as the background of the problem solver. For example, nonspecialists in data processing can use RAMIS II nonprocedural languages to determine pricing policy or profitability ratios while data processing specialists use the same data, RAMIS II nonprocedural languages, and, perhaps, the RAMIS II procedural interface, to support routine business operations such as accounts receivable and inventory control. RAMIS II can be used effectively in any business area that involves data storage and manipulation to produce reports.

THE RAMIS II FAMILY OF SYSTEMS

RAMIS II consists of a set of component systems that work together to provide a complete data base management system. These components are described in the RAMIS II Users Manual. A brief summary follows.

The **RAMIS Data Base** is structured as a network of data segments. It can be interconnected to form what appears to the user to be a single hierarchical file even when the segments may be contained in many different physical files or even in different data bases. The system designer controls the Data Base Management System, and thus the data base, through file design. A file description is stored in a file dictionary within the data base. These file descriptions are used by the Data Base Management System to control the storage and access of data. Once a file is described, the user can access data without being concerned with the structure of the file. In most cases, all the user needs to know is the names of the data fields. Designing files, establishing file descriptions, and the structure of the data base are covered in Part 1 of the users manual.

The **Data Base Management System** provides complete data independence, automatic maintenance of logical relationships among all data elements, and algorithms to ensure efficient utilization of computer resources. It is used by all the other component systems to access the data base. This system is not described in any single part of the users manual, but aspects of data base management are presented where relevant in Parts 1, 2, 3, and 4.

The **Records Management System** provides the user with a nonprocedural language for reading, processing, validating, and logging data transactions used to create and maintain a file in the data base. This language and its implementation are described in Part 2.

The **Report Preparation System** provides the user with an English-like nonprocedural language for retrieving, sorting, calculating, and formatting data into tabular or graphic reports. The sequence of the data in the report need not be the same as that in which data is stored, and calculations can be made from data retrieved from one or more files as well as from information provided by the request. Thus, the contents and format of the report are controlled by the user; they are not dependent on the structure of the data and file. This language and its implementation are described in Part 3.

The **Procedural Language Interface (RPI)** provides facilities for inputting, updating, deleting, and retrieving data from procedural languages such as Cobol, Fortran, and PL/1. The format in which data is stored is provided to and obtained from the calling program and can be determined at the time that a program is executed. The details of this interface are described in Part 4.

The **Executive** enables the user to catalog, interconnect, and control complex sequences of RAMIS II activities. The RAMIS II Executive acts as control monitor over the Records Management and Report Preparation Systems and permits the implementation of complete data processing systems. Records Management and report procedures can be cataloged for future or recurrent use. When needed, they can then be recalled and executed by a single statement. Several request activities can be combined and the results of one activity can be made to determine the next activity to be executed. The procedure can prompt for information, which can then be used either to control further processing or as transaction data once it has been validated within the procedure. The Executive language and facilities are described in Part 5.

The **SCAN** mode provides the user with the facility to look at the actual data in the file and to add, change, or delete data in a conversational mode. This facility is described in Part 6.

The **Linking to User-Written Programs** facility permits the user to insert special programs that perform functions such as special or complex transaction editing before data is added, updating before data is changed, and processing of report lines before they are printed. This procedure is described in Part 7.

The description and usage of **RAMIS Data Sets** in each operating system environment is explained in Part 8.

The **Directed Format Option (DFO)** permits the use of a formatting model to specify the data, text, and calculations used for each line of a report. Most often used for financial reports, it is also useful for any report which requires a linear rather than columnar format. This option is discussed in Part 9.

The **Reporting from External Files Option (REF)** permits the use of the RAMIS II report preparation language to access non-RAMIS files whether these files are maintained by normal IBM access methods or by other data base systems such as ADABAS or IMS. This option is discussed in Part 10.

The **Usage Accounting Option** permits an installation using RAMIS II to assemble and manage a complete range of data and statistics to account and bill for RAMIS II usage and to improve overall system utilization and efficiency. This option is discussed in Part 11.

RAMIS II Service Procedures expedite the display of frequently required information such as file descriptions, cataloged procedures, and DFO models. They are described in Part 12.

PREFACE

This edition of the RAMIS Users Manual has been rewritten and reorganized to reflect the RAMIS II system. It replaces previous editions and various users guides. Each part is separately bound and can be obtained both by itself and in combination with other parts as required. Each part is divided into sections. Sections prefixed by bullets are more advanced and can be bypassed during the first reading. A cover is provided for your convenience.

Reference cards are enclosed in appropriate parts of the manual. These can be removed and placed where they will be handy for quick reference. Extra copies of these cards can be obtained from your local MPG office.

Your comments on the manual are invited and should be addressed to:

RAMIS Technical Publications Group
Mathematica Products Group
P. O. Box 2392
Princeton Station Office Park
Princeton, New Jersey 08540
609-799-2600

From: Ramis II Users Manual, Vol. 1, Mathematica Products Group, Princeton, N.J., 1980.