disease risks than the second cohort ("likely not exposed") and the third cohort, then, depending on such considerations as the magnitude of the increase in risk, the inference will be clear -- herbicide exposure confers a health decrement. But suppose that the first and second cohort have similar disease risks and that they are both higher than the third. Then, one will be at a loss to say if the lack of difference between the first two and their similar difference with the third is due to exposure misclassification in the first two cohorts or to the difference in service experience.

Another problem of inference will be false positive findings. We plan to make comparisons of presumed herbicide exposure and/or Vietnam service for numerous health outcomes. There is, therefore, a certain probability that several of these will show statistically significant positive associations even if, in truth, there are none. It is difficult to a priori specify how these are to be handled. It may be that some such associations will be "convincing," in and of themselves, whereas others may not. Making such inferences transcends from the cold objectivity of statistics to the art of medicine -- at this stage considerations such as the biological plausibility of associations play a large part. In addition, the following approach may help in making such judgments. If the number of significant associations found is reasonably close to the number expected under the null hypothesis (e.g., 5% significant if working at an alpha = 5% level) and if the associations are relatively well balanced with respect to the direction of the association (e.g., if the number of instances where presumed herbicide exposure and/or Vietnam service appears harmful is approximately the same as where service appears protective), then we might be inclined to attribute the significant findings to chance. Finally, it is not unlikely that we will be left with equivocal positive results.

5. Inferences from Possible Study Findings; Study Limitations

A major concern of Vietnam veterans is that they are at high risk for quite a variety of diseases. The cause of this putative high risk is generally suspected to be exposure to Agent Orange and other herbicides, but there is also concern that other factors incidental to Vietnam service may have conferred an increased risk. The design of CDC's studies should permit an assessment of both general and aome specific concerns. The Agent Orange study will permit an evaluation of the possible health consequences of herbicide exposure, and the Vietnam Experience study will give information regarding health risks that may be associated with the general (Army) service experience.

Unavoidable limitations of the proposed studies, or indeed any other studies which could be done, will preclude describing the results as "definitive." A number of limitations have already been mentioned, but some of them need to be repeated here, and a few more need to be added. An important limitation is that the proposed studies are observational, as opposed to experimental, and observational studies inherently require some tempering of the inferences drawn from them. Another general caveat is that it is not possible to prove a negative -- that is, it will never be possible to say with certainty that herbicide exposure or some other factor connected with Vietnam service did not cause any adverse health effects. In addition, when evaluating negative findings, the study power, or sensitivity, must always be kept in mind. The proposed studies will be quite powerful, but they will not provide answers to all health questions that might arise. However, if no increase in risks is found, these studies should be of substantial value in easing the concerns of veterans.

The ability to detect such specific increases will depend on the magnitude of the risk and the numbers of veterans (cases and controls in the Selected Cancers study) studied; the possibilities for exposure misclassification between the "likely exposed" and "likely not exposed" cohorts in the Agent Orange study have already been mentioned as a cause of concern. Moreover, even in the absence of exposure misclassification, the studies will have low power for rare diseases and/or low increases in risk, or for increases in risk limited to those veterans with prolonged and/or heavy exposure to herbicides or some other harmful factor. Thus, an overall finding of no increase in risk might "hide" a real increase for specific disease categories or special groups of veterans. But if the increase is limited to very rare categories of disease or to special veterans, then the study still has the utility of putting some boundary on the scope of the problem for most veterans.

The lack of strong hypotheses has been mentioned previously and this has led us to propose a rather wide ranging investigation. Thus, we may not give enough emphasis to some crucial factor. Our proposal to keep open the option of modifying our interviews and examinations mitigates this concern somewhat. However, it is conceivable that we will not include some critical item in our investigation, and from this type of omission there is no recovery.

Depending on the results of analysis, the design of the Agent Orange study may present unusual problems of inference. Some examples follow. If the first cohort ("likely exposed") appears to have significantly higher

7. Timetable, Milestones, and Reports

Month 1 in the following timetable is December 1983. The timetable is ambitious and may be difficult to follow. CDC will do its utmost to ensure that there are no avoidable delays. It is projected that the Selected Cancers study will be finished last, at Month 69. The rate limiting factor for this study is the relatively low number of cases that will accrue each year. If CDC can identify other population-based cancer registries that have good case-ascertainment rates and that are willing to participate, the completion date would be sooner than the date currently projected.

Month Number	Major Milestone
1	- begin selecting Vietnam Experience (VE) main study subjects
4	- obtain OMB approval
7	- Random Digit Dialing Contract Award
	- Selected Cancers (SC) Data Collection Agencies Contract Award
9	- Agent Orange (AO)-VE Interview Contract Award
	- begin interviews, AO and VE pilot studies
10	- SC interviews begin
	- SC Pathology Contract Awards
11	- Examinations Contract Award(s)
12	- Company location for first 25 battalions complete, AO study
13	- VE study main interviews begin
14	- assess AO and VE pilot study
16	- begin VE study medical exams
	- begin selecting AO main study subjects
17	- selection of VE study individuals complete
18	- company location for second 25 battalions complete, AO study
23	- complete VE study mortality data collection
29	- report VE study mortality data
30	- complete VE study interviews
33	- complete VE study medical exams
39	- report VE study interview data
42	- report VE examination data
45	- complete AO study interviews
49	- report AO study mortality data
52	- complete AO medical exams
	- report AO study interview data
58	- report AO study exam data
63	- complete SC study histological review
69	- report SC study data

6. Report of Study Findings

CDC will prepare comprehensive reports of the findings for each of the study phases. The credibility of the results will be enhanced if the major findings are released simultaneously in peer-reviewed medical journals.

9. Protocol Review; Study Oversight

A draft of this protocol received wide scientific review. A panel of CDC scientists from programs outside of the division responsible for the studies conducted a scientific evaluation. The Office of Technology Assessment, the Science Panel of the Agent Orange Working Group, and the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants also conducted scientific reviews. In addition, CDC transmitted copies of the draft protocol to the representatives of about 15 veterans' organizations for their consideration. This version of the protocol incorporates a number of changes suggested during these reviews. The written reviews received, and CDC's responses to them, are available on request. Since the detailed interview instruments and examination protocols are currently being developed, CDC will make these available on request to interested parties when they are completed. This version will receive "human subjects review" by CDC's Institutional Review Board and review by the Office of Management and Budget.

CDC will conduct the studies with guidance from a steering committee. It has been requested that a subcommittee of the panel which provides oversight of the Ranch Hand studies be formed for this purpose. CDC proposes that steering committee meetings be held at 6-month intervals, to be supplemented by other meetings as the need arises.

8. Investigators

These studies will be conducted under the direction of staff assigned to the Agent Orange Projects, an organizational entity located in the Chronic Diseases Division of CDC's Center for Environmental Health; oversight of laboratory work will be by the Clinical Chemistry Division, also of CDC's Center for Environmental Health.

The following staff, drawn from CDC's Agent Orange Projects group and Cancer Branch, have contributed to the scientific development of this protocol: Lee Annest, PhD; Edward Brann, MD, MPH; Pamela Byrnes; Pierre Decouflé, ScD; J. David Erickson, DDS, MPH, PhD; Nancy V. Hicks, RN, MS; Michael Kafrissen, MD, MPH; Peter M. Layde, MD, MSc; Maurice LeVois; Marion R. Nadel, PhD, MPH; Thomas K. Welty, MD; Matthew M. Zack, MD, MPH. Robert Diefenbach, John Gallagher, Peter McCumiskey, Melvin Ralston, and Joseph Smith have provided technical and administrative support, and secretarial assistance has been given by Gerri Culpepper, Teresa Ellington, Janiece Myers, Emily Peters, Jean Reynolds, Hazel Riley, and Effie Spencer. The staff of the Army Agent Orange Task Force, under the direction of Richard C. Christian, has given valued advice.

Table 2

Power[1] to Detect Various Relative Risks
in the Agent Orange and Vietnam Experience Studies,
by Prevalence of Condition in "Unexposed" Group

A. Interview Phase (6,000 per group)

Prevalence per 100 of Condition in "Unexposed" Group	Relative Risk 2	4	6	8
0.10	0.321	0.928	0.998	0.999+
0.20	0.576	0.998	0.999+	
0.30	0.750	0.999+		
0.35	0.811			
0.40	0.859			
0.50	0.923			
1.00	0.997			
1.50	0.999+			

[1]Power calculations with 1-tail, alpha = 0.05 by method of Casagrande JT, Pike MC: An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 1978;34:483-6.

Table 1

Cumulative Expected Numbers of Deaths by Cause[1] in a Hypothetical Cohort of 6,000 Men Aged 22 in 1968 and Followed Through 1984 (17 Years)

Cause of death[2]	Expected Number of Deaths
All causes	213.0
Accidents (E800-E949)	79.1
Motor vehicle (E810-E823)	48.3
Other (E800-E807, E825-E949)	30.8
Suicide (E950-E959)	25.5
Homicide (E960-E978)	27.3
Diseases of Heart (390-398, 402, 410-429)	18.6
Malignant Neoplasms (140-204)	17.3
Cirrhosis of liver (571)	6.6
Cerebrovascular diseases (430-438)	3.6
Influenza and Pneumonia (470-474, 480-486)	2.9
Diabetes Mellitus (250)	2.1
Nephritis and nephrosis (580-584)	0.7
Bronchitis, emphysema and Asthma (490-493)	0.5
Septicemia (038)	0.5
All other causes (residual)	28.2

[1]Expected numbers based on 1978 U.S. age-specific rates for males. The age-specific rates were quinquennial (5 years), and the cumulative rates used to derive the expected numbers were computed by weighting the quinquennial rates by the number of years of cohort experience in each quinquennium (constant cohort size). Source of rates: Vital statistics of the U.S.:1978, Vol. II, Mortality Part A, NCHS, 1982.

[2]Numbers in parentheses are the relevant codes from the Eighth Revision International Classification of Diseases, Adapted.

Table 3

Selected Health Outcomes Reported To Be Associated with Exposure to TCDD - Animal and Human Literature*

Dermatologic
- Chloracne
- Hirsutism
- Hyperpigmentation

Hepatic
- Porphyria cutanea tarda
- Hepatomegaly
- Elevated serum levels of hepatic enzymes

Neuropsychologic
- Peripheral neuropathy
- Asthenia and lethargy

Immunologic
- Impaired cutaneous delayed hypersensitivity response
- Increased risk of infection

Reproductive
- Reduced fecundity
- Adverse pregnancy outcomes

Cancer
- Soft tissue sarcoma, lymphoma, and nasopharyngeal and nasal

General
- Lipid metabolism: Hypercholesterolemia and hypertriglyceridemia

*This table is by no means an exhaustive list (see Appendix B for literature review). It is intended to show the wide range of health outcomes postulated to be linked to TCDD exposure.

Table 2 (continued)

Power[1] to Detect Various Relative Risks
in the Agent Orange and Vietnam Experience Studies,
by Prevalence of Condition in "Unexposed" Group

B. Examination Phase (2,000 per group)

Prevalence per 100 of Condition in "Unexposed" Group	Relative Risk 2	4	6	8
0.10	0.108	0.475	0.778	0.923
0.20	0.218	0.794	0.975	0.998
0.30	0.321	0.930	0.998	0.999+
0.35	0.370	0.960	0.999	
0.40	0.416	0.978	0.999+	
0.50	0.502	0.994		
1.00	0.796	0.999+		
1.50	0.926			
2.00	0.976			
2.50	0.993			
3.00	0.998			

[1]Power calculations with 1-tail, alpha = 0.05 by method of Casagrande JT, Pike MC: An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 1978;34:483-6.

Table 5
Power[1] of Selected Cancers Case-Control Study
to Detect Increased Relative Risks

a) 2-fold Increase in Relative Risk for Vietnam Veterans in General

Study Year 1

Type of Participant	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	106	0.45	0.57	0.66
Lymphoma	331	0.67	0.82	0.90
Nasal & Nasopharyngeal	42	0.30	0.37	0.43
Liver	42	0.30	0.37	0.43
Controls	325			

Study Year 2

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	212	0.70	0.83	0.90
Lymphoma	662	0.92	0.98	0.99+
Nasal & Nasopharyngeal	85	0.47	0.58	0.66
Liver	85	0.47	0.58	0.66
Controls	650			

Study Year 4

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	319	0.84	0.94	0.97
Lymphoma	993	0.98	0.99+	0.99+
Nasal & Nasopharyngeal	128	0.60	0.73	0.81
Liver	128	0.60	0.73	0.81
Controls	975			

Study Year 4

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	425	0.92	0.98	0.99+
Lymphoma	1,324	0.99+	0.99+	0.99+
Nasal & Nasopharyngeal	170	0.70	0.82	0.89
Liver	170	0.70	0.82	0.89
Controls	1,300			

Table 4

Estimated Prevalence of Vietnam Service and Expected Number of Cases of Cancer for the Selected Cancers Case-Control Study in Males Aged 30-54 in 1986 in the SEER Areas

Age	Number of Males[1]	Prevalence of Vietnam Service[2]	Estimated Yearly Number of Cases[3]			
			Soft Tissue[4] Sarcoma	Lymphoma[5]	Nasal and[6] Nasopharyngeal	Primary Liver
30-34	980	4.9	20	53	4	3
35-39	907	11.7	14	45	5	3
40-44	740	12.5	17	52	6	5
45-49	590	3.7	22	75	10	12
50-54	552	1.5	33	106	17	20
Total	3,769	7.4	106	331	42	43

1 Estimated number of males (thousands) in SEER areas, 1976 data projected to 1986, National Cancer Institute Monograph 57, 1981.

2 Percent of males who are Vietnam veterans; estimated from VA data on numbers of Vietnam era veterans and assumption that 32.2% of Vietnam era veterans served in Vietnam.

3 Incidence of cancers derived from National Cancer Institute Monograph 57, 1981.

4 Includes the following (morphology-based) tumor types: fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, Kaposi's sarcoma (estimate based on pre-AIDS incidence), blood vessel sarcoma, nerve sheath sarcoma, synovial sarcoma, malignant mesenchymoma, malignant paragarglioma. Incidence estimates also based on categories "sarcoma NOS" and "other sarcoma."

5 Includes Hodgkin's Disease and non-Hodgkin's lymphoma.

6 Includes the following topographic tumor types: nasopharynx, nasal cavity, accessory sinuses.

7 Includes liver and intrahepatic bile ducts.

APPENDIX A
(November 1982)

Protocol Outline
Tentative Timetable
Epidemiological Studies of the Health of Vietnam-Era Veterans (Agent Orange)

Overall Design

The Centers for Disease Control (CDC) recommends two complementary historical or retrospective cohort studies. One study will compare the health of a group of U.S. veterans of the Vietnam conflict with the health of a group of Vietnam-era veterans who did not serve in Vietnam; it may include individuals from all four branches of the military. The purpose of this study will be to make an assessment of the possible health effects of the general Vietnam service experience. The other study, which is designed to evaluate the health effects of possible exposure to herbicide Agent Orange, will compare the health of three groups or cohorts of Vietnam veterans who differ in their probable level of exposure to Agent Orange. This second study will focus primarily on veterans of the Army but will probably include veterans of the Marine Corps.

Each of these two studies will have three major components: 1) a mortality assessment (mortality followup will be repeated every 5 years for the foreseeable future); 2) a health and exposure questionnaire; and 3) a clinical and laboratory assessment. The studies will have several other features in common. However, the sampling plans and some of the health outcomes measured in the questionnaire and clinical assessments will differ between the two studies. Moreover, they will follow different timetables. They are designed to answer related but distinct questions of importance to Vietnam veterans and their families.

These two studies should be sufficient to meet the directive of Congress which instructed the Veterans Administration to conduct an "epidemiological study"; in addition, they are responsive to current veterans' and congressional concern. However, these studies are but a part of the Federal effort to provide answers about the possible health effects of herbicides and their contaminants, and about the effects of military service in Vietnam. Other major Federal activities include: 1) CDC's ongoing study which is designed to determine if Vietnam veterans are at increased risk of fathering babies with birth defects; 2) CDC's NIOSH Dioxin Registry, which will assess the health effects of occupational exposure to dioxin during the manufacture of herbicides and related chemicals; 3) the U.S. Air Force's comprehensive health study of veterans who applied herbicides in Vietnam from fixed-wing aircraft ("Ranch Hand" study); 4) the Veterans Administration's (VA) proportionate mortality study of Vietnam veterans; the VA is also supporting protocol development for a study of twins, one of whom went to Vietnam and one of whom did not.

Composition of Cohorts and Sampling Plans

The choice of individuals for inclusion in the various study cohorts will derive from review of military records from the Vietnam era. Considerable thought about and work with records from Vietnam has been done by the

Table 5 (continued)

b) 2-fold and 5-fold Increases in Relative Risk Under Assumption of 7.5% Control Group Prevalence of Vietnam Service and 3 Levels of Possible Agent Orange Exposure Among Vietnam Veterans (Study Year 4 Only)

2-fold Increase in Relative Risk For Agent Orange Exposed Vietnam Veterans

Type of Participant	Number[2]	Possible Prevalence of Agent Orange Exposure Among Vietnam Veterans 0.10	0.25	0.50
Soft Tissue Sarcoma	425	0.33	0.62	0.85
Lymphoma	1,324	0.49	0.85	0.99
Nasal & Nasopharyngeal	170	0.23	0.41	0.61
Liver	170	0.23	0.41	0.61
Controls	1,300			

5-fold Increase in Relative Risk for Agent Orange Exposed Vietnam Veterans

Type of Participant	Number[2]	Possible Prevalence of Agent Orange Exposure Among Vietnam Veterans 0.10	0.25	0.50
Soft Tissue Sarcoma	425	0.96	0.99+	0.99+
Lymphoma	1,324	0.99+	0.99+	0.99+
Nasal & Nasopharyngeal	170	0.81	0.98	0.99+
Liver	170	0.81	0.98	0.99+
Controls	1,300			

1 Power calculations with 1-tail, alpha = 0.05 by method of Casagrande JT, Pike MC: An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 1978;34:483-6.

2 Estimated number of participants

as the starting point for an historical cohort study. There may be opportunities to assess the accuracy and completeness of the herbicide usage records, and every effort will be made to pursue these opportunities. However, there are no possibilities for similar checking of the company troop records. Thus, the categorization of individuals with respect to their potential for herbicide exposure will be uncertain and will forever remain so.

The desire to ensure that troops classified as "exposed" to Agent Orange are comparable to "non-exposed" troops with respect to other factors which might influence health is another issue which makes it difficult to design an "ideal" study. The underlying problem is that the use of herbicide was not equally distributed in Vietnam. Areas where it was heavily used were generally combat areas and differed in terrain and flora from those areas where it was little used. These areas may also have differed in other important respects, such as, indigenous diseases, level of combat intensity, and type of personnel deployed. It is for these reasons that much of the recent thinking about the subdivision of troops into "exposed" and "non-exposed" groups has been directed at choosing the cohorts from the same area of Vietnam. Unfortunately, because of the inherent limitations of the records, this approach may have the effect of increasing exposure misclassification (especially the categorization of those who are truly "exposed" into the "non-exposed" group). These two competing forces, the desires for comparability and for maximum exposure separation, have drawn CDC to recommend a three-cohort design. Two of the three cohorts will be from the same area of Vietnam (and time during the war) but will differ in regard to their exposure likelihood. These two cohorts will be comparable but suffer from imprecision of exposure separation. The third cohort will be drawn from another area of Vietnam (but from the same time period), an area where there is good evidence of little or no herbicide usage. This cohort will give maximum exposure separation from the "exposed" cohort but may suffer from a lack of comparability in respect of other health-influencing factors. This design is incomplete, as is illustrated in the following 2 x 2 table which cross-classifies exposure by a measure of general experience, which will be called "combat."

		Agent Orange Exposure	
		Yes	No
"Combat"	Yes	Cohort 1	Cohort 2
	No		Cohort 3

The empty cell, representing the combination of Agent Orange exposure with no "combat," cannot be filled, because it is our understanding from the military that Agent Orange use was inextricably entwined with a certain "combat" experience. Because of its incompleteness, this design will present problems in analysis and interpretation. Moreover, the comparison of the first and third cohorts, which will ensure maximum exposure separation, may be subject to respondent bias; respondent bias should not be a problem in a comparison of cohorts 1 and 2, because individual respondents will probably be

Department of Defense (primarily staff of the Army Agent Orange Task Force--AAOTF), the Veterans Administration, and the White House Agent Orange Working Group. A consensus seems to have been reached that the choice of individual veterans for an Agent Orange study will involve the use of personnel records and company level action records and a variety of herbicide usage records. More thought needs to given to the specific organization and analyses of records which might be used for a Vietnam Experience study, but it is recommended that company level records also be used for this study.

a) Agent Orange Study

A good design for a historical cohort study of the possible health effects of Agent Orange would involve the use of 2 groups of men who were as similar as possible in all respects except for their exposure to the herbicide. One group would ideally be free from all exposure while the others would have been subjected to "meaningful" exposure. (Other attractive designs might include subdivisions of those exposed based on levels and/or duration of exposure, or even continuous measures of exposure for individual veterans.)

It appears that such an ideal is not attainable. Obstacles include: 1) the military records which must be used were made during a war and, therefore, of uneven quality; 2) an inability to define objectively "meaningful" exposure; 3) the difficulty in ensuring that veterans who were possibly or likely exposed (by whatever measure) are comparable (with respect to all things which might influence health) to veterans who were not exposed. Under ordinary circumstances, such obstacles would probably prevent the initiation of an Agent Orange study. It is, therefore, mandatory that advance advice and consent be obtained from veterans' groups with respect to study policies and procedures, especially those directed at defining Agent Orange exposure.

The important company records which give information about troops are the morning reports and the journal files. The morning reports can be used to document the presence or absence of individual servicemen on a daily basis while the daily journal files will indicate the locations of companies in time and space. The major herbicide records are those which document the time and location of fixed-wing aircraft applications of herbicide (Ranch Hand missions--contained on the "Herbs" tape), base perimeter applications records, and information about Ranch Hand mission aborts (dumps). The choice of an individual for inclusion in the "likely-exposed" cohort will be based on a measure of company proximity in time and space to herbicide applications as documented by these records. Members of the "non-exposed" cohort will likewise be chosen because of a measure of their company's distance in time and space from any herbicide applications.

The company records may contain gaps (i.e., whole periods of time missing) and are probably quite variable in terms of quality and detail, because they were created during the war. The herbicide usage records are known to contain errors with respect to the time and location of applications and the degree of their completeness is unknown. They are far from ideal

any given serviceman was at risk of serving anywhere where there was a need for his occupational specialty.

Choice of individuals for the two cohorts of this study should be made after a review of company and personnel files in much the same manner as will be done for the Agent Orange study. A simple random sample or a stratified random sample of Vietnam veterans and non-Vietnam veterans would probably be the method of choice but the filing of the available records probably makes this infeasible. Therefore, we recommend a cluster sampling of military units (much as will be done for the Agent Orange study) and a random sampling within clusters as the method for selecting members of each cohort.

Sample Sizes

It is recommended that each of the 5 cohorts (3 Agent Orange study and 2 Vietnam Experience) be composed of 6,000 servicemen. All of these individuals will be included in the mortality studies, and it is hoped that up to 90% of the surviving cohort members will be included in the questionnaire phase of the studies. (The results of the Ranch Hand study, better than 95% interview completion, give reason to set such an optimistic goal. If, however, the questionnaire pilot studies give indications of completion rates much under 70 or 75%, careful consideration should be given to not proceeding with the main studies.) The number of 6,000 for each cohort was chosen because comparisons between 2 groups of between 5,000 and 6,000 each will be able to detect (alpha = beta = 0.05, 1-tail) 2-fold increases in the relative risk for health outcomes which ordinarily occur at the rate of 0.5%, for example, all cancers (detecting associations for specific cancers would require truly massive cohorts—this problem is probably best approached through specific case-control studies).

For the clinical and laboratory phases, it is suggested that random samples of 2,000 from each cohort be chosen. It is hoped that as many as 80% of those chosen will participate and, as with the questionnaire phases, if the pilot study shows rates much below the 70% level, it will be necessary to question the wisdom of proceeding with the main study phases. The number 2,000 was chosen because samples between 1,500 and 2,000 will give good power (alpha = beta = 0.05, 1-tail) to detect 2.5-fold increases in the risk of outcomes which usually occur at the rate of 1.0%.

(The major health outcome categories from which the questionnaire and clinical laboratory phases will be developed during protocol design and review are listed in a later section of this outline.)

Study Sequences

Three phases are planned for each of the 2 studies and each phase will culminate in a separate report. The 3 reports will concern 1) mortality experience of the cohort members; this phase of the study will also give an indication of the proportion institutionalized, 2) the results of the health questionnaire, and 3) the results of the clinical and laboratory tests. It is anticipated that work will proceed first on the Vietnam Experience study because there will be less work involved in selecting the cohort members than there will be for the Agent Orange study. Within each study, ascertainment of

uncertain about their (study) exposure status. Despite these problems, we believe that this design is better than either of the other alternatives based on an approach which uses only two cohorts--either decreasing exposure misclassification by decreasing comparability or increasing exposure misclassification by increasing comparability. The results of the Ranch Hand study, currently being conducted by the U.S. Air Force, may help in the interpretation of this incomplete design. The Ranch Hand study will compare the health of crews who flew the herbicide spray missions with air crews who did not fly spray missions. Thus, it will provide information about Agent Orange exposure in the absence of the general experience of ground troops.

b) Vietnam Experience Study

The idea of studying ill-health effects which might derive from the "general experience" of having been in Vietnam is at once attractive and unappealing. It is attractive because there may have been many factors which could have adversely affected those who served in Vietnam, in contrast to their counterparts who served elsewhere. And it is also plausible that Vietnam veterans who did not see active combat in Vietnam were subjected to health-influencing events that were not part of the experience of those who served elsewhere. Any study which focuses on Agent Orange alone will obviously not test such a plausible multifactorial hypothesis.

However, the multifactorial nature of this hypothesis makes the study of the "Vietnam experience" unappealing from the scientific point of view. The "experience" comprises many factors, many of which are unknown, poorly defined, or not quantifiable. Nevertheless, it is our opinion that this is an important question to the Vietnam veteran, and one which deserves as much attention as the issue of the possible effects of Agent Orange.

Viewed in the broadest terms, the Vietnam "experience" could have influenced anyone who served there. It is, therefore, suggested that consideration be given to the inclusion of veterans of the Army, Navy, Marines, and, if possible, the Air Force (the records systems of the Air Force might make inclusion of that service's veterans very difficult).

A major concern about the validity of making a comparison of Vietnam and non-Vietnam veterans derives from an undocumented suspicion that there may have been preexisting differences between the two groups in terms of health-influencing factors and behaviors. If such differences existed and if they applied to all veterans, then a valid study of the Vietnam "experience" would not be possible. However, military personnel with whom we have consulted do not feel that such factors would have existed for all Vietnam veterans. Specifically, it is their belief that being sent to Vietnam was a matter of the "luck of the draw" for those who were drafted or who were short-term enlistees. Serving in Vietnam, the U.S., in Europe, or elsewhere was, in their opinion, a matter which depended on occupational specialty and the operational needs of the various commands. Thus,

are listed later in this outline. The goal for both studies will be an interview completion rate of better than 90% of those located.

4) Clinical and Laboratory Examinations

Clinical examinations of the 2,000 individuals from each of the 5 cohorts will take place at 1 or 2 examining facilities, much like that used by the Ranch Hand study. The physical examination will include a standard, good quality review of systems. Multiple laboratories may be used for the various laboratory tests, but each particular test will be performed in a single laboratory. Special emphasis will be given to the clinical and laboratory outcomes which will be chosen during protocol development from among those which are listed later in this outline.

vital status will be a part of the process of locating cohort members for the health questionnaire and clinical/laboratory phases. Thus, mortality analysis will be completed first; reports on the health questionnaire and clinical/laboratory analyses will follow later. Even though these studies are subdivided into phases, it is expected that at some point in time work will be proceeding simultaneously on both studies (see schedule, later in this outline).

The major steps which will be required to complete the two studies are (after full protocol design and approval and after pilot testing of procedures):

1) Selection of individual cohort members by the Army Agent Orange Task Force (AAOTF)

   For the Vietnam Experience study, identifying information about the cohort members will be transmitted to CDC immediately after selection. For the Agent Orange study much more work will be required of AAOTF personnel because of the need to review exposure information. Identifying information about cohort members for each study will arrive at CDC in small batches, possibly on a monthly basis, as they are selected. Therefore, the selection will be done in such a way that an appropriate balance of "exposed" and "non-exposed" for the Agent Orange study and of Vietnam and non-Vietnam veterans for the Vietnam Experience study are included in each batch.

2) Vital Status Determination and Location of Cohort Members

   As soon as a batch of information for study individuals is received, a check will be made against the Beneficiaries Identification and Records Location System (BIRLS) files and the National Death Index to try to ascertain those individuals who are deceased. For those who are found to be dead, collection of death certificates, pathology reports and other relevant material will ensue. Procedures to determine the location of those currently alive will begin simultaneous with the checks against the BIRLS and National Death Index--the first step will be to check against Internal Revenue Service (IRS) files, which is a rapid and inexpensive method to obtain relatively current addresses for taxpayers. For those individuals who are not found on the BIRLS file or National Death Index and who are also not found on the IRS files, more expensive and time consuming methods of location will be used. The goal for both studies will be a location rate of 95% for those who are presumed alive.

3) Health Questionnaire

   Interviews of about 45 minutes in length will be conducted by telephone where possible. For potential respondents without telephones, personal interviews will be conducted at a place convenient for the respondent; for potential respondents who are institutionalized, personal interviews will be conducted at the place of institutionalization. The major outcomes from which questionnaire items will be chosen during the stage of full protocol development

Vietnam Experience Study
Tentative Timetable (continued)

Study Phase	Month Number		Major Milestones
	7	o	begin questionnaire pilot study
	10	o	award contract for clinical and laboratory studies
	11	o	begin clinical and laboratory pilot study
		o	evaluate questionnaire pilot study
	12	o	begin questionnaire main study
	16	o	evaluate clinical and laboratory pilot study
	17	o	begin clinical and laboratory main study
	23	o	complete study sample selection
	32	o	complete mortality study data collection
	35	o	REPORT mortality study analysis
	36	o	complete questionnaire data collection
	41	o	complete clinical and laboratory data collection
	42	o	REPORT questionnaire analysis
	47	o	REPORT clinical and laboratory data collection

Vietnam Experience Study
Tentative Timetable

This tentative timetable is divided into 2 phases - protocol development and study implementation. However, some tasks which are formally a part of the implementation phase are scheduled to begin during the development phase. This approach is proposed so that there will be no unnecessary delays in the event that the protocol review goes smoothly and according to schedule. Month number 1 for each study phase begins at the time resources are made available to CDC by the VA.

Study Phase	Month Number		Major Milestones
Protocol Development	1	o	recruit new personnel and short-term consultants for protocol development
	2		
	3	o	complete development of protocol
	4	o	complete peer review of protocol
		o	complete preliminary work with military files for sample selection
		o	begin developmental work for contracts for questionnaire administration, clinical and laboratory work
	6	o	complete OMB review
		o	complete selection of pilot study samples
Study Implementation	1	o	begin selection of main study samples
		o	begin final formatting of questionnaires and clinical instruments
	2	o	begin data collection for main study mortality analysis
	6	o	award contract for questionnaire administration

3. (Continued)
   Antimalarials--primaquine, chloroquine, fansidar, dapsone, etc.
   Antifungals--griseofulvin, etc.
   Other medications (also include reason for use)
   Illicit drug use (amount of use, dates of use):
   Marijuana, barbiturates, amphetamines, opiates, cocaine, PCP, hallucinogens
   Specific chemical exposures (how, how much, and when exposed; CF.):
   Agent Orange--include 2,4-D and 2,4,5-T
   Other herbicides
   Pesticides, insect repellants
   Riot control agents
   Occupational history (type of job, dates, chemical exposures, if any)
   Hobbies (e.g., chemical exposures, risk-taking behaviors)
   Habits: L. Breslow's healthy habits, index of social linkage

4. Medical history:
   Family history:
   Immediate family: age now or at death; if dead, cause of death; Illnesses requiring hospitalization, surgery, or medication
   Personal history (before, during, and after military service):
   Personal physician: name, address, telephone number
   Specific illnesses (who, what specifically, when, how severe, source of verification):
   high blood pressure, heart disease, cancer, stroke, lung disease, diabetes, mental or nervous diseases, liver disease, arthritis, repeated infections, malaria, parasitic diseases
   Hospitalizations (reason, year, duration, source for verification)
   Surgical procedures (reason, year, duration, source for verification)
   Blood transfusions (reason, year, source for verification)
   Injuries (year, severity, source for verification)
   Allergies (year, severity, source for verification): asthma, rash, hay fever, medication reactions
   Time lost from work $\geq$1 week (reason, year, duration, source for verification)
   Review of systems: (date, duration, severity when positive response)
   Weight on discharge from military, 1 year ago, and today
   General: change in weight (if loss, intentional or unintentional), loss of appetite, weakness
   Head: headaches, change in hair pattern
   Eyes: change in vision, irritated eyes
   Ears: change in hearing, ear noises, ear infections
   Nose: sinus infections, nosebleeds
   Mouth: sore tongue, sore throat
   Neck: swollen glands, goiter (large thyroid), stiffness, pain
   Chest: shortness of breath, cough, wheezing, phlegm, chest pain, heart attack, heart failure, heart murmur, palpitations
   Abdomen: difficulty swallowing, vomiting, gallstones, difficulties with digestion, change in bowel habits, blood in bowel movement, hemorrhoids, hernia

Agent Orange Study
Tentative Timetable

Timetable for this study will parallel the Vietnam experience study timetable in the early phases (i.e., protocol development and review). Because of the extra time required to review military records for determination of Agent Orange exposure, data collection for the 3 study phases (mortality, questionnaire, clinical) will begin approximately 6 months after the comparable phase of the Vietnam experience study. Accordingly, the reports will appear 6 months later:

Study Phase	Month Number	Major Milestones
Study Implementation	41	o REPORT mortality study analysis
	48	o REPORT questionnaire analysis
	53	o REPORT clinical and laboratory data collection

Tentative List of Items for Health Questionnaire, Physical Examination and Laboratory Analysis

The questionnaire and physical examination instruments will be drawn up during the protocol development phase. The following is a list of important elements which will serve as the starting point for development of the final instruments.

Questionnaire Information:

1. Locator and Tracing Information

2. Demographic Information

3. Other Potential Confounders:
   - Military History:
     - Drafted vs enlisted status
     - Military occupational specialty
     - Combat vs noncombat experience: Duties, places, dates
       (develop combat index from casualty rates, # enemy attacks, etc., from sample of records as well as asking men)
     - Area of service
     - Discharge status
   - Tobacco (types of use, amount of use, dates of use)
   - Alcohol (types of use, amount of use, dates of use)
   - Medications (amount of use, dates of use):

7. Laboratory tests:

Blood:

Complete blood count: hematocrit, hemoglobin, red cell count, white cell count and differential, platelet count

Liver function tests: SGPT, GGTP, total protein, albumen (SGOT, bilirubin, and alkaline phosphatase not necessary but may occur on SMA-12)

Kidney function tests: BUN, creatinine

Lipid function tests: total and HDL cholesterol, fasting triglycerides

Hepatitis B surface and core antigens

Immunoglobulin quantitation: IGG, IGM, IGA, IGE, IGD

Two hour post-prandial blood glucose

VDRL

Free T4 and T3 uptake

Serum stored for serological testinG (CF., Ranch Hand positives, melioidosis)

Urine:

Urinalysis: microscopic and dipstick (protein, glucose, hemoglobin)

Urine total porphyrins and porphyrin profile

Stool:

Qualitative test for blood (during physical exam)

Other tests depending on results from Ranch Hand study:

Chest X-ray

Electrocardiogram

B- and T-lymphocyte quantitation

4. (Continued)

Genitourinary: venereal diseases, kidney stones, kidney infections, blood in urine, impotence, decreased sex drive, infertility, children with birth defects
Limbs: swelling, change in skin color, joint pain, difficulty with movement, difficulty with coordination, numbness, tingling, pains
Neuropsychiatric: concussion, forgetfulness, sleep disorders, paralysis, seizures, dizziness, depression
Skin: rashes, boils, acne, scars, sunburns easily, bruises easily

5. Physical examination (CF., NCHS and Ranch Hand physical exam sheets):

General: appearance, weight, height, blood pressure, pulse, respiratory rate
Head: movements, hair pattern
Eyes: movements, conjunctivitis
Ears: hearing, infections
Nose: polyps, sinusitis
Mouth: teeth, tonsils, tongue, cheeks, throat
Neck: movement; thyroid enlargement, nodules, tenderness; parotid enlargement or tenderness; cervical lymphadenopathy
Chest: movements, bony abnormalities, axillary lymphadenopathy
Lungs: rales, rhonchi, wheezes, dullness, hyperresonance
Heart: extra sounds, murmurs, rubs, size
Abdomen: liver size, spleen size, tenderness (location), masses, hernia, testicular masses, inguinal lymphadenopathy, rectal exam,
Back: scoliosis, kyphosis, tenderness (location)
Limbs: movements, edema, arthritis, varicose veins, nail clubbing, peripheral pulses

The following exams should be done by a dermatologist and a neurologist, respectively:

Skin: rash, scars, ulcers, acne, masses, spider angiomata, etc.;
Neurological exam:
Mental status:
Emotional responses:
Cranial nerves:
Motor systems: gait, movement, tremors, muscle bulk, muscle tenderness
Reflexes:
Sensory tests:

6. Psychological testing (CF., Ranch Hand set of tests--need consultation):

Minnesota Multiphasic Personality Inventory
Wechsler Adult Intelligence Scale
Reading Subtest of Wide Range Achievement test
Halstead-Reitan Neuropsychological Test Batteries
Wechsler Memory Scale
Cornell Index

Chloracne may persist for many years. For example, 14 of 122 persons with chloracne following the Nitro accident had lesions evident 28 years later (Crow, 1980). One case remained 18 years after the explosion in Ludwigshafen (Goldmann, 1972). Thirteen years after the explosion in Amsterdam, 10 of 50 original cases remained (Hay, 1976). Of 41 employees surveyed 10 years after the U.K. accident, 22 still had mild chloracne (May, 1982). A followup of 55 subjects with chloracne who had worked in the Czech factory revealed that 15% still had florid manifestations after 10 years (Pazderova-Vejlupkova et al., 1981).

Hyperpigmentation and hirsutism may accompany chloracne. Many of the Newark workers with chloracne also developed hyperpigmentation of the sun-exposed areas of the head, neck, and hands or hirsutism, which was always located on the temples. The severity of these conditions paralleled that of chloracne (Bleiberg et al., 1964; Poland et al., 1971). About one-quarter of the Czech workers with chloracne had either hyperpigmentation or hirsutism of the face or both (Jirasek et al., 1973). Mucous membrane irritation has also been reported in several groups of workers (Schulz, 1957; Poland et al., 1971; Goldmann, 1972).

1.2. Hepatic Effects

Hepatic porphyria, a disorder of heme pigment metabolism, can either be inherited or acquired by exposure, in both experimental animals and humans to certain polyhalogenated aromatic compounds, medications, and other environmental factors such as excessive alcohol consumption (Strik, 1979; Kimbrough, 1980). All of these chemicals inhibit uroporphyrinogen decarboxylase in the liver, but not in red blood cells. Porphyria cutanea tarda (PCT) is the most severe form of this type of porphyria. A diagnostic indicator of PCT is the simultaneous increase of both uro- and heptacarboxylic porphyrin in urine. It has been found that chronic hepatic porphyria without clinical symptoms begins with accumulation of these porphyrins in the liver, followed by their gradually increasing excretion in the urine. In PCT, skin findings are often associated with increased porphyrin excretion and include excessive skin fragility, vesiculobullous lesions on sun-exposed areas, hirsutism, and hyperpigmentation. However, it appears that PCT and chloracne are independent syndromes (Poland et al., 1971). Porphyria was observed after exposure to TCDD in rats, mice, and chick embryo cells (Goldstein et al., 1973; Kociba et al., 1976; Sinclair and Granick, 1974). It has also developed in several groups of exposed workers. Eleven of 29 Newark workers with chloracne had abnormal excretion of urinary uroporphyrins; of these, three had definite cases of PCT (Bleiberg et al., 1964). A re-examination of the same plant 6 years later revealed no clinical PCT and only one employee with mild persistent uroporphyrinuria (Poland et al., 1971). At least 11 cases of PCT were reported among Czech workers (Jirasek et al., 1973, 1974).

Other hepatic effects of TCDD include structural alterations, changes in serum enzyme levels, and changes in the biliary system, in a number of animal species (IARC, 1977; VA, 1981). Many of the reports of human exposures also mention hepatic effects (see also section on carcinogenicity, below). Liver damage was reported in workers in the factories in Hamburg, West Germany, Grenoble, France, Czechoslovakia, and the U.S.S.R. (Kimmig and Schulz, 1957; Dugois et al., 1958; Jirasek et al., 1974; Telegina and Bikbulatova, 1970). Three workers in Middle Rhein, West Germany, had morphological changes in

APPENDIX B

Literature Review

1. Health Effects of Herbicides and Dioxin

1.1. Dermatologic Effects

Chloracne is a refractory skin disease characterized by inclusion cysts, comedones, and pustules, with eventual scarring of the skin, produced by environmental exposure to certain halogenated aromatic compounds in humans (Taylor, 1979). A similar condition is also seen in animals. TCDD is an active skin irritant and produces local lesions resembling human chloracne in the skin of rabbit ears (Kimmig and Schulz, 1957). An analogous hyperkeratosis and modulation of sebaceous structures to keratin cysts was observed in monkeys and hairless mice. Since in these species the skin areas affected by TCDD all lack major hair growth, and, in men, lesions usually do not occur in the follicles of beard hair, it has been suggested that the hair shafts on the unaffected portions of the body may facilitate drainage of sebum and keratinaceous debris (Greig, 1979). After acute exposure to TCDD, blepharitis, loss of fingernails and eyelashes, and facial alopecia were observed in monkeys (McConnell et al., 1978a). Horses accidentally exposed to salvage oil containing TCDD in Missouri had hyperkeratotic skin lesions and hair loss, and dogs, cats, and mice similarly exposed had ulcerative dermatitis and hair loss (Case and Coffman, 1973; Carter et al., 1975).

In humans, chloracne is the most frequent and consistent acute health outcome of exposure to TCDD. It is often observed in exposed individuals who have no other apparent health effects. However, since it is usual that only patients with chloracne are studied further, it is not possible to accurately estimate the relative frequency of other adverse effects of exposure. There are, however, reports of individuals without chloracne who developed other acute symptoms possibly related to TCDD exposure (Jirasek et al., 1973; Oliver, 1975).

Cases of chloracne were reported after the explosions which occurred at factories in Nitro, West Virginia, in 1949 (Suskind, 1978), in Ludwigshafen, West Germany, in 1953 (Goldmann, 1972, 1973), in the Netherlands in 1963 (Dalderup, 1974; Hay, 1976), in Grenoble, France, in 1966 (Dugois et al., 1968), and in the United Kingdom in 1968 (May, 1973). Chloracne has also been reported in occupational exposures that did not involve explosions. These were reported from factories in Middle Rhein, West Germany (Bauer et al., 1961), Hamburg, West Germany (Kimmig and Schulz, 1957; Schulz, 1957), Grenoble, France (Dugois et al., 1958), Newark, New Jersey (Bleiberg et al., 1964), the U.S.S.R. (Telegina and Bikbulatova, 1970), and Czechoslovakia (Jirasek et al., 1973). In addition to these industrial exposures, chloracne developed in two government scientists involved in the experimental preparation of TCDD (Oliver, 1975). In 1976, the explosion at the ICMESA factory near Seveso, Italy, resulted in the contamination of a large, densely populated area; 187 cases of chloracne have been reported, mostly in children (Malizia et al., 1979). A few of the individuals exposed to the TCDD-contaminated horse arenas in Missouri may have had chloracne (Carter et al., 1975; Kimbrough et al., 1977).

observed between the severity of active acne and the score on the hypomania scale of the MMPI (Poland et al., 1971). Abnormal EEG patterns were noted among workers in Czechoslovakia and Middle Rhein, West Germany (Jirasek et al., 1974; Bauer et al., 1961).

Neurological studies were conducted following the Seveso accident. A higher percentage of cases of idiopathic clinical or subclinical neuronal damage was found in the most highly contaminated zone than in zones with lower levels of contamination, for both adults and children. The most frequent pathological signs were detected in the peripheral nervous system. Signs of subclinical neuronal damage included reduced nerve conduction velocity (Boeri et al., 1978; Pocchiari et al., 1979). Altered nerve conduction velocity was more prevalent among exposed individuals with chloracne or increased levels of serum hepatic enzymes than among exposed individuals without these manifestations (Filippini et al., 1981). Of about 200 workers from the ICMESA plant and another factory in the same area who were examined for neurological function, 8 were diagnosed as having polyneuropathy of peripheral nerve fibers (Pocchiari et al., 1979). An increased prevalence of slowed nerve conduction velocities was observed among workers employed in the manufacture of 2,4,5-T and 2,4-D in Arkansas (Singer et al., 1982).

1.4. Immunological Effects

Acute and subacute doses of TCDD have produced atrophy of the thymus and other lymphoid tissues with loss of lymphocytes in monkeys, rats, mice, and guinea pigs (McConnell et al., 1978a & b; Vos and Moore, 1974). Changes in thymic weight appeared to be a very sensitive indicator of exposure to TCDD, since decreases in thymic weight occurred at doses which had no effect on body weight in rats, mice, and guinea pigs (Harris et al., 1973). Horses exposed to TCDD-contaminated salvage oil were found to have spleens reduced to one-third the normal size and small and inactive lymph nodes (Case and Coffman, 1973).

TCDD has also been shown to suppress immune function in animals, primarily thymic-dependent immune function. Suppression of mitogen responsiveness, skin-graft rejection, and delayed hypersensitivity responses have been observed (Vos and Moore, 1974; Vos et al., 1973; Faith and Moore, 1977). Suppression of these T-cell-dependent immune functions appears to occur without helper cell function being affected; thus, different functional subsets of T-cells seem to be selectively affected (Faith et al., 1978). Sensitivity to the immunosuppressive effect of TCDD appears to decrease with age. Exposure of the developing immune system during pre-, and/or post-natal life results in more severe effects than exposure during adult life (Vos and Moore, 1974; Luster et al., 1979). A slight suppression in humoral immunity has been noted (Vos et al., 1973).

Low doses of TCDD, which did not elicit clinical or pathological effects, did reduce host defenses in mice to Salmonella infection, while defense to pseudorabies virus was not affected (Thigpen et al., 1975). Susceptibility to Salmonella was found to result from increased sensitivity to bacterial endotoxin (Vos et al., 1978). Non-specific killing by macrophages or specific killing of Listeria was not impaired by TCDD treatment (Mantovani et al., 1979; Vos et al., 1978).

liver biopsies taken 5 years after their exposure ended (Bauer et al., 1961). Liver enlargement and tenderness were reported after the Nitro explosion, and liver damage and hepatitis were reported after the explosion in Ludwigshafen (Zack and Suskind, 1980; Goldmann, 1972). Hepatomegaly was reported among residents of the contaminated region of Seveso (Pocchiari et al., 1979).

Effects on enzyme levels have also been reported in humans. TCDD is known to be a potent inducer of a number of hepatic microsomal enzymes (Huff et al., 1980). Increased levels of urinary d-glucaric acid, an indirect measure of hepatic microsomal enzyme activity, were found in children living in the Seveso area (Ideo et al., 1982). Altered levels of other enzymes, mainly transaminases and gamma-glutamyl transferases, were also noted (Pocchiari et al., 1979). A slight elevation in the levels of urinary d-glucaric acid and gamma-glutamyl transpeptidase were also observed in a 10-year survey of U.K. workers (May, 1982). Slightly increased elimination of delta-amino levulinic acid has also been reported (Jirasek et al., 1974; Poland et al., 1971).

1.3. Neurological/Psychological Effects

Neurological effects of exposure to 2,4-D have been observed in both experimental animals and man. Myotonia of skeletal muscles was produced by 2,4-D administration to rats, guinea pigs, dogs, and rabbits (Danon et al., 1978; Eberstein and Goodgold, 1979; Drill and Hiratzka, 1953; Hill and Carlisle, 1947). Symptoms of asthenia, lethargy, and ataxia were observed in pigs, calves, rats, and mice (Hill and Carlisle, 1947; Bjorklund and Erne, 1966). Irregularities of EEG pattern have been observed in rats, cats, and dogs as well as demyelinization of the spinal cord (Desi et al., 1962).

In humans a number of case reports have described symptoms of peripheral neuropathy following poisoning by 2,4-D herbicides. Typical symptoms observed included asthenia, hypesthesia, and myotonia in the muscles of the extremities, hyporeflexia, and general muscular weakness leading to ataxia. Decreased nerve conduction velocities were measured in some cases (Goldstein et al., 1959; Berkley and Magee, 1963; Wallis et al., 1970; and see VA literature review). Irregularities in EEG patterns were observed in farmers exposed to 2,4-D (Kontek et al., 1973). In a survey of 292 workers in a factory that produced 2,4-D, reports of weakness, fatigue, and headaches were very common (Bashirov, 1969).

Neuropsychological effects were reported after most of the human exposures to TCDD. Typical complaints among factory workers included fatigue, headaches, weakness and pain, especially in the extremities, sexual dysfunction, loss of appetite, and irritability (Jirasek et al., 1973; Poland et al., 1971; Baader and Bauer, 1951; Goldmann, 1972; Bauer et al., 1961; Kimmig and Schulz, 1957; Crow, 1980; Dugois et al., 1958; Telegina and Bikbulatova, 1970). Two to three years following their exposure to TCDD, two laboratory scientists had similar complaints, including loss of energy and drive, irritability, visual problems, and diminished sense of taste (Oliver, 1975). Headaches were reported among people exposed to the contaminated horse arenas in Missouri (Carter et al., 1975; Kimbrough et al., 1977). Decreased auditory acuity and decreased sense of proprioception were noted among Newark workers. The Minnesota Multiphasic Personality Inventory (MMPI) was administered to the Newark workers. A significant positive correlation was

At least two epidemiologic studies suggest a slight excess risk of stomach cancers in cohorts exposed to phenoxyherbicides and related compounds. Theiss et al. (1982) reported a significant excess of stomach cancers (3 observed vs. 0.6 expected) in 74 German workers who were exposed to trichlorophenol and dioxin 20 years before. Axelson et al. (1980) observed an apparent excess of stomach cancer (3 observed and 0.71 expected) among 348 railroad workers exposed to phenoxyherbicides and amitrol.

Hardell et al. (1982) reported that exposure to phenoxy acid herbicides doubled the risk of nasal and nasopharyngeal cancer (relative risk 2.1, not statistically significant). The controls used for this study were the same as those used in the previously mentioned Swedish studies of sarcomas and lymphomas.

Tung reported that primary liver cancer occurred in excess in Vietnam as a result of Agent Orange exposure of the general population, but this reported excess was not verified when his report and pathologic specimens were reviewed (VA lit rev., 1981). Even though human liver damage has been reported as a result of dioxin exposure (see above), no excess liver cancer has been reported.

1.6. Reproductive Effects

The reproductive effects of 2,4-D, 2,4,5-T, and TCDD, alone or in combination, have been examined in a number of different animal species. The effects are variable, depending on dosage, species, and strain. Only animal studies of the effects of 2,4,5-T with levels of TCDD contamination which either are unknown or known to be at least 1 ppm and of the effects of combinations of 2,4-D, 2,4,5-T, and TCDD will be discussed, in the light of the composition of Agent Orange.

A study of the effect of exposure of male mice to contaminated 2,4,5-T before mating with unexposed females showed no effect on the loss of fetuses before or after implantation (Buselmaier et al., 1972). Lamb et al. (1980) examined the effects of "simulated Agent Orange" -- i.e., mixtures of 2,4-D, 2,4,5-T, and TCDD -- administered to male mice followed by mating to untreated females. No effects were reported in fertility, implantation, fetal malformations, germ cell toxicity, sperm concentration, motility, or abnormalities and survival of offspring.

Most of the reproductive studies in animals have involved exposure only of the female after conception. In monkeys, fetal size was reduced but no malformations were observed (Wilson, 1971). In the rat, low doses of 2,4,5-T produced cystic kidney and intestinal hemorrhage (Courtney et al., 1970; Sparschu et al., 1971). A slightly increased incidence of cleft palate in the rat was reported in one study (VA, 1981 lit. rev.). 2,4,5-T administered throughout gestation produced maternal toxicity, fetal death or decreased fetal growth (Hall, 1972). In the mouse, 2,4,5-T produced cleft palate, and cystic kidney, the necessary dosage depending on the strain (Bionetics, 1968; Courtney et al., 1970; Gaines et al., 1974). In the hamster, cleft palate was rarely encountered; instead abnormal cranial development was observed (Collins et al., 1971).

Reports of immunologic effects following human exposure to TCDD have been very rare. An increased susceptibility to infection was noted among workers following the Ludwigshafen accident (Goldmann, 1972). Following the explosion in Seveso, there did not appear to be an increase in number or severity of childhood infections, nor were results of immunological tests found to be abnormal (Reggiani, 1979, 1980; Malizia et al., 1979; Pocchiari et al., 1979).

1.5. Carcinogenic Effects

Several studies indicate that TCDD is carcinogenic in rodents, producing increased incidence of hepatocellular carcinomas and neoplasms in the lung, hard palate, nasal turbinates, and thyroid of the rat (Kociba et al., 1978; Toth et al., 1979; National Toxicology Program, 1982). Hepatocellular tumors, thyroid tumors, and fibrosarcoma of integumentary tissue have been produced in mice (National Toxicology Program, 1982a & b). TCDD may act as a promoter of liver tumors in the rat (Pitot et al., 1980).

An association between phenoxyherbicide exposure in forestry workers and soft tissue sarcoma has been noted in two Swedish case control studies as well as in the combined analysis of four American cohorts of workers industrially exposed to phenoxyherbicides (Coggon and Acheson, 1982; Editorial, 1981). Hardell and Sandstrom (1979) found a significant excess of malignant mesenchymal tumors in individuals occupationally exposed to phenoxyherbicide 10-20 years beforehand (relative risk 5.3, with 95% confidence limits 2.4-11.5). Eriksson et al. (1981) also found a significant association between exposure to phenoxyherbicides and soft tissue sarcoma (relative risk 6.8 with 95% confidence limits 2.6-17.3). The histologic distribution of tumor types in the exposed and unexposed groups was not recorded in either study.

Honchar and Halperin (1981) combined individuals from 4 cohorts industrially exposed to phenoxyherbicides and related compounds and found that 3 of 105 deaths had been due to soft tissue sarcoma compared with 0.07% of deaths in the total U.S. white male population aged 20-84. A fourth (recently deceased) case was subsequently reported in one of these cohorts (Cook, 1981). Additionally, three other individuals with soft tissue sarcomas were reported to have worked in 2,4,5-T production facilities (Moses and Selikoff, 1981; Johnson et al., 1981).

Other studies of workers exposed to phenoxyherbicides during their application have so far failed to confirm this association (e.g., Coggon and Acheson, 1982). However, in most cases the design of these investigations was such that only very high relative risks for soft tissue sarcoma were likely to be detected.

Hardell et al. (1981) found a significant excess of lymphomas in Swedish individuals occupationally exposed to phenoxyherbicides (relative risk 6.0, 95% confidence limits 3.7-9.7). The excess risk was similar for Hodgkin's and non-Hodgkin's lymphomas when analyzed separately. No other epidemiologic studies of this association have been reported. Compromised immunity is the strongest risk factor for development of lymphomas (Greene, 1982). Dioxins have immunosuppressant properties in animal species (see above), which presents an attractive hypothesis for the etiology of their postulated association with both soft tissue sarcoma and lymphomas.

Meselson et al. (1971). Cutting et al. (1970) found no increased incidence of congenital abnormalities, stillbirths, and hydatidiform moles with heavy herbicide spraying. However, the conclusions of both of these studies were seriously limited by incomplete and unrepresentative sampling of births, unreliable birth records, and inadequate estimation of exposure (Advisory Committee, 1971). A subsequent study found an increased prevalence of isolated cleft palate and spina bifida compared with earlier years before widespread defoliant use, which might, however, be attributable to better case-finding and referral (Herbicide Assessment Commission, 1970; Nelson et al., 1979). Tung et al. (1971) and Rose and Rose (1972) reported on malformations and abortions among South Vietnamese refugees in North Vietnam. Lack of specific information about exposure and the lack of an unbiased selection procedure preclude any causal inferences. Studies conducted in South Vietnam in 1972 and 1973 by the National Academy of Sciences (1974) found no conclusive evidence of association between human birth defects and herbicide exposure, although study limitations were recognized.

A report has just been released on a large study (Donovan et al., 1983) designed to determine if Australian Vietnam veterans are at increased risk of fathering babies with birth defects. Vietnam veterans had no greater risks than veterans who served elsewhere or than men who were not veterans.

1.7. Other Effects

Gastrointestinal problems have been reported after a number of human exposures. A health survey of workers involved in 2,4-D production revealed that about half complained of dyspepsia, abdominal pains, and constipation (Bashirov, 1969). About 30% of the workers studied at the Newark plant complained of gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pains, or blood in stool) (Poland et al., 1971). Digestive disorders were reported among workers in the factories in Grenoble, France, and in Hamburg and Middle Rhein, West Germany (Dugois et al., 1958; Schulz, 1957; Bauer et al., 1961). Gastrointestinal symptoms, including abdominal pains and indigestion, were among the delayed symptoms which developed 2 to 3 years after TCDD exposure in two of the three government scientists in England (Oliver, 1975).

High levels of serum cholesterol and lipids were also commonly reported among exposed workers. Serum lipids tended to be high among workers following the explosion at the Nitro factory (Suskind, 1978). Ten percent of Newark workers had elevated serum cholesterol levels (Poland et al., 1971). Hyperlipemia and hypercholesterolemia were reported among workers in Grenoble (Dugois et al., 1958). Similar findings were described for the Czech workers, who also exhibited elevated levels of pre-beta lipoprotein and of total blood proteins (Jirasek et al., 1974; Pazderova-Vejlupkova et al., 1980, 1981). All three of the English scientists had hypercholesterolemia (Oliver, 1975). Walker and Martin (1979) reported high cholesterol and triglyceride levels and low high-density-lipoprotein levels in a small group of exposed workers.

2. Diseases Affecting U.S. Troops in Vietnam

This section is included to provide background on the health of U.S. servicemen while they were stationed in Vietnam. Fifty-six to seventy-four percent (mean 70.6%) of hospital admissions during the Vietnam war were for

Reproductive outcomes have been examined after many human exposures. However, the significance of most of these studies is questionable because of limitations in study design, population size, and inadequate handling of confounding factors. Pazderova-Vejlupkova et al. (1980) considered the frequency of abortion to be normal among wives of workers in the Czech factory. Following the explosion at Seveso, no increase in congenital malformations or developmental abnormalities was noted, but it was not possible to assess the frequency of spontaneous abortions due to an increase in elective abortions following the accident, and no baseline data were available for miscarriages (Reggiani, 1979; Homberger et al., in VA lit. rev.). In the U.S.A., a study of the incidence of spontaneous abortions among women whose husbands were occupationally exposed to 2,4-D as farmers, forest workers, or herbicide applicators revealed no overall association (SRI International, 1981). Human miscarriages near a spray project near Globe, Arizona, were found not to be related to herbicide use; a similar lack of association was found with human malformations in Swedish Lapland (Binns and Balls, 1971; Advisory Committee, 1971). In Arkansas, facial clefts were not associated with the agricultural use of 2,4,5-T (Nelson et al., 1979). A study of birth defects in children born to Long Island Railroad maintenance employees exposed to 2,4,5-T used for weed control revealed that all major birth defects combined and inguinal hernia were less frequent than expected. An excess observed for metatarsus adductus and tear duct obstruction probably resulted from variability in diagnosing these "minor" defects (Honchar, 1982). Reproductive outcomes of wives of Dow Chemical employees exposed to dioxins were surveyed. No statistically significant association between exposure and spontaneous abortions, stillbirths, infant deaths, and congenital malformations was observed (Townsend et al., 1982). The reported association between 2,4,5-T spraying and an increased incidence of miscarriage in the Alsea basin of Oregon (EPA, 1979) has been severely criticized (Wagner et al., 1979; Mantel, 1979).

A number of studies of reproductive outcomes were conducted in Australia and New Zealand. A study in Australia revealed no relationship between 2,4,5-T use and birth defects (Aldred et al., 1978). Another showed a correlation between the season of conception of babies with neural tube defects and the season of maximum 2,4,5-T spraying; a correlation was also found between neural tube defects in animals and 2,4,5-T (Field and Kerr, 1979). Two studies in New Zealand found no association between 2,4,5-T exposure and neural tube defects (McQueen et al., 1977; Hanify et al., 1981). One of these also found no association with cleft lip and palate or malformations of the heart or male genitalia, although it did reveal an association with talipes (malformations of the foot). A study in Western Australia that suggested an association between cleft lip and palate and herbicide exposure (Brogan et al., 1980) has been criticized on methodologic grounds (Bower and Stanley, 1980). A survey of ground agricultural sprayers showed no differences in the occurrence of malformations, stillbirths, miscarriages, or ectopic pregnancies (Smith et al., 1981).

The reports of human birth defects alleged to result from exposure to Agent Orange, which appeared in South Vietnamese newspapers in 1969, caused public and scientific furor (Advisory Committee, 1971; Young et al., 1978). In response, two independent surveys of South Vietnamese hospital records were conducted. An apparent increase in certain birth defects relative to others, which seemed to be associated with periods of herbicide spraying, was noted by

disorders increased among all army troops and particularly among those stationed in Vietnam and became the second leading disease problem by 1970. Concomitantly, the problem of drug abuse escalated during this period, especially among younger, lower ranking enlisted men (Neel, 1973).

3. Current Health of Vietnam Veterans

Very little is known about the health of Vietnam veterans relative to the health of other men of similar age. Some indication of veterans' and others' perceptions about the veterans' health can be found in the reports of Bogen, 1979; Stellman and Stellman, 1980; Texas Dept. of Health, 1983; UCLA-VA Protocol literature review; and Wolfe, 1980. The most frequently reported conditions include dermatologic disorders, neurologic and psychologic disorders (including numbness and tingling in the extremities, headaches, fatigue, depression, memory loss, sleep disturbances, and sexual dysfunction), reproductive problems (birth defects, miscarriages, abortions, reduced fertility), cancer, gastrointestinal disorders, infections, hypertension, hepatic hematologic, genitourinary, respiratory, and cardiovascular problems.

Although there is a lack of data on organic disease outcomes among Vietnam veterans, there are a number of reports on the occurrence of health-related outcomes — outcomes which may be considered by some to be disease outcomes and by others as possible causes or effects of disease.

Several large surveys have been conducted which provide psychological and sociological data on Vietnam veterans, veterans who served in the Vietnam era but not in Vietnam, and contemporary non-veterans (Starr et al., 1973; Martindale and Poston, 1979; Hammond, 1980; Harris and Assoc., 1971; Egendorf et al., 1981). These surveys present objective data concerning several aspects of social adjustment, subjective reports of psychological adjustment, and attitudes held by and about Vietnam era veterans. Although these surveys employed a variety of methods and focused on different aspects of adjustment, it can be concluded from this literature that Vietnam veterans have encountered more problems in adjusting to civilian life than the other men (Figley, 1977; 1978).

The general areas of observed or suspected sociological differences among Vietnam veterans, other Vietnam era veterans and non-veterans include educational and occupational status, stress-related psychological difficulties, drug and alcohol use, medical problems, and arrests (Boscarino, 1981; Boscarino and Figley, 1981; Segal, 1977; Borus, 1975; Gover and McEaddy, 1974; Stinson, 1979; O'Brien et al., 1980; Mintz et al., 1979). These problems have been found to vary among subgroups of these populations defined by ethnicity, exposure to combat, urban or rural residence, and period of service in Vietnam (Egendorf et al., 1981; Penk et al., 1981).

Post Traumatic Stress Disorder (PTSD) and its association with Vietnam service, exposure to combat, and drug and alcohol use has been widely investigated (Roberts et al., 1982; Boman, 1982; Lipkin et al., 1982; Frye and Stockton, 1982; Wilson & Kruass, 1982; Boscarino, 1980; 1981; Helzer et al., 1979; DeFazio et al., 1975; Horowitz, 1975). PTSD is thought to be a very common condition among Vietnam veterans (Wilson, 1980). However, large-scale psychiatric epidemiology research, which treats PTSD as a distinct diagnosis, has not yet been reported. Reliable estimates of the prevalence of PTSD in

medical disorders, as compared with battle casualties (15.6%) and non-battle injuries (13.8%), during the period 1965-69 (Ognibene and Barrett, 1982). Despite this fact, the average annual disease admission rate (351 per 1,000 per year) was one-third lower than for the China-Burma-India and Southwest Pacific theaters in WWII, and 40% less than for the war in Korea (Neel, 1973).

Malaria has been identified as the most significant medical problem, accounting for the greatest number of man-days lost from duty during the war. The emergence of a chloroquine-resistant form of malaria, P. falciparum malaria, led to the use of Dapsone^{R} (4,4'-diaminodiphenylsulfone), which is also used to treat leprosy (Neel, 1973).

Infectious hepatitis did not pose a major problem during the Vietnam war, as it did in previous wars. The incidence of hepatitis (6.9 cases per 1,000 per year) varied with the intensity of combat operations and with troop interaction with the civilian population (Neel, 1973). In Vietnam, serum hepatitis was of more concern, occurring most commonly among men who received multiple blood transfusions related to battle injury or among those using illicit drugs intravenously (Ognibene and Barrett, 1982).

Diarrheal disease rates were also lower compared with earlier wars. The prevalence rate ranged from 69 per 1,000 in 1965 to 35 per 1,000 in 1969. Diarrheal diseases may have been related to viruses, bacteria or parasitic agents, but the cause of most cases could not be identified. Troops at greatest risk were those who were unacclimatized and those under combat conditions. Incidence peaked in May or June, corresponding with the monsoon season (Neel, 1973).

Skin diseases were quite prevalent among troops in Vietnam. Those cases severe enough to require hospitalization or retention in quarters varied from 30 per 1,000 in 1965 to 20 per 1,000 in 1968. In 1970, however, skin problems increased again, to 30 per 1,000. The reason for the increase is unexplained. The three major skin problems identified were superficial fungal infection, bacterial infection, and immersion foot (Neel, 1973; Allen, 1977).

Plague and cholera, endemic in the Vietnam population, did not pose a significant problem for U.S. troops. Melioidosis, an infectious disease of humans and animals endemic in tropical areas, presented a problem to U.S. physicians unfamiliar with its diagnosis or treatment. Two hundred and thirty cases, diagnosed between 1965 and 1971, resulted in 14 deaths (Neel, 1973). The problem of fever of undetermined origin (FUO) presented some of the most challenging diagnostic dilemmas for military physicians in Vietnam. The diagnosis of FUO ranked second only to venereal disease. During the period 1966 through 1969, 58 cases per 1,000 were reported each year, including hospitalized and non-hospitalized patients (Ognibene and Barrett, 1982).

Venereal diseases have been prevalent during most military engagements. In Vietnam, it led other common medical problems in prevalence from 1965 to the conclusion of the war. Gonorrhea accounted for 90% of all venereal disease cases. The second most frequently occurring condition of venereal origin was chancroid (Ognibene and Barrett, 1982).

Neuropsychiatric diseases did not differ appreciably among troops serving in Vietnam and those serving elsewhere until 1968. During this year, the prevalence of psychosis, psychoneurosis, and of character and behavior

A summary of the studies reviewed follows, even though they are not especially useful for the task at hand.

Hawryzluk (1975) studied prevalence ratios of diagnosed conditions among 813 army officers. Hearing loss, musculoskeletal disorders, and skin disorders were among the most frequently occurring medical problems. This study was limited to officers, most of whom were between 33 and 37 years old and had had 10-14 years of military service. They were selected for leadership positions and for their potential ability to do college work; thus, they were probably not representative of the general military population.

Medical records from the Armed Forces and the VA offer opportunities for followup studies. The Armed Forces system records all illnesses and injuries, even minor ones, among its active duty members, and it stores the clinical records in a central repository when the individual is separated from service. In the VA system, records documenting most of the agency's contacts with a veteran are maintained in a single file. Because benefits to veterans are many and varied, the VA maintains contact with most veterans, and many thousands of records are thus accessible for study (DeBakey and Beebe, 1962), (Beebe, 1951), (Cohen, 1953). However, because only a fraction of veterans receive their health care at VA facilities, and because those who do may be less educated and have more severe service-connected physical and mental disabilities, the records are of questionable usefulness for epidemiologic purposes, since their health experiences may not reflect those of the overall veteran population.

Armed Forces and VA records have been used for clinical followup studies of various medical and traumatic conditions, such as leprosy (Brubaker et al., 1969), rheumatic fever (Engleman et al., 1954), missiles in the heart (Blano and Beebe, 1966), and psychoneuroses (Brill and Beebe, 1951). These studies have been conducted for the purpose of describing the natural history and progression of the disease or condition and were conducted without control groups. Other studies with control groups, on the basis of the Armed Forces and VA data bases, have been directed at the veteran population receiving health services through the VA system, for example: studies of amyotrophic lateral sclerosis (Kurtzke and Beebe, 1980), asthma (Robinette and Fraumeni, 1978), scrub typhus (Elsom et al., 1961), coronary heart disease (Hrubec and Zukel, 1974), lumbar disc lesions (Hrubec and Nashold, 1975), splenectomy (Robinette, 1977), infectious mononucleosis (Miller and Beebe, 1973), cirrhosis of the liver (Beebe and Simon, 1970), esophageal cancer (Rogers et al., 1982), traumatic limb amputations (Hrubec and Ryder, 1980), and learning and reaction time (Milligan and Powell, 1981). Generally, the controls for these studies have been other veterans. Since the diseased and control veterans in these studies were not stratified with respect to their combat participation, the effect of that experience on the occurrence of the disease or its clinical course cannot be evaluated.

Veterans or their families have been participants in several studies on the effect, on subsequent health, of exposure to certain risk factors. Wallis (1968) reported on stress in service families, but his study did not include control families. Other studies have examined the effect on veterans of exposure to adjuvant influenza virus vaccine (Beebe et al., 1972), microwave radiation (Cleary et al., 1965), mustard gas (Beebe, 1960), (Norman, 1975), and smoking (Rogot and Murray, 1980). These studies included control groups,

the Vietnam veteran population cannot be derived from the current literature because of the frequent use of unusual (e.g., treatment seeking) samples and because symptom frequencies instead of validated diagnostic criteria have been used as outcome measures.

4. Long-Term Health Status of Servicemen and Veterans

This literature was reviewed to provide background for the Vietnam Experience study. The writers of these protocols expected to find a rich literature, but did not.* Numerous health studies of veteran populations have been conducted, but there are few, if any, which deal with long-term health effects of the general war experience. Disease incidence and prevalence among army personnel is well documented for World War II (WWII) (Anderson, 1968), the Korean War (Army Medical Service Graduate School, 1954), and the Vietnam conflict (Ognibene and Barrett, 1982) (see part 2, this Appendix); however, these reports cover only the period of military action.

*For reports of studies on the long-term health effects of war experience, we reviewed the Cumulated Index Medicus for the years 1975 through March 1983. In addition, several computer-based literature searches were conducted against these on-line data bases: Medline, 1966-83; Cancerlit, 1963-83; American Statistics Index, 1974-82; Social Science Citation Index, 1972-83; Psych Info, 1967-83; and Sociological Abstracts, 1963-83. The holdings of the libraries maintained at the Centers for Disease Control, Veterans Administration (VA) Hospital (Atlanta), VA Central Office (Washington) and Emory University School of Medicine were reviewed for appropriate reports. Finally, relevant studies completed on veteran populations by the Medical Follow-up Agency of the National Research Council within the National Academy of Sciences were included in the literature search. When relevant studies were identified, we used a branching technique to search for other cited references. A total of 135 journal articles and books were brought to CDC offices and reviewed.

In two studies which covered 29 years (1946-1974), Jablon and Miller (1970, 1978) found no statistically significant differences between army x-ray technologists (n=6,560) and controls (n=6,826) who served as medical, laboratory, or pharmacy technologists for total deaths from cancer, individual site of cancer, or deaths from other causes. Norman et al. (1981) investigated exposure to tetrachloroethane by comparing age-specific mortality among 1,099 males assigned to chemical processing companies during WWII and 1,319 veterans not involved in the impregnation process of protecting clothing against mustard gas. Overall cancer mortality for exposed subjects was 1.26 times higher than for controls. The risks for leukemia, lymphoma, and cancers of the genital organs were moderately elevated, but the numbers were small and no significant excesses were observed.

The Medical Followup Agency of the National Academy of Sciences - National Research Council established a Twin Registry comprising 16,000 pairs of white male twins, both members of which had been in military service, mainly in WWII. This data base has provided information for the study of multiple sclerosis (Bobowick et al., 1978), cardiovascular and respiratory symptoms (Cederlof et al., 1969), (Hrubec et al., 1973), psychopathology (Pollin et al., 1969), (Allen and Pollin, 1970), (Hoffer and Pollin, 1970), (Stabenau et al., 1970), intraocular pressure (Schwartz et al., 1972, 1973), corticosteroid response (Schwartz et al., 1973), allergy (Bazaral et al., 1974), skin diseases (Lynfield, 1974), hypertension (Oglesby, 1975), headache (Ziegler et al., 1975), plasma cholesterol and triglycerides (Christian et al., 1976), personality traits (Horn et al., 1976), earnings (Taubman, 1976), dietary intake (Fabsitz et al., 1978), weight changes (Fabsitz et al., 1980), electrocardiographic characteristics (Havlik et al., 1980), alcoholism (Hrubec and Omen, 1980), and familial factors in early deaths (Hrubec and Neel, 1981). These studies have not classified the veterans according to their combat experience.

Seltzer and Jablon (1974) found evidence for a "healthy warrior" effect when they examined the effect of health selection at induction on subsequent cause-specific mortality in a series of 85,491 white male WWII U.S. Army veterans followed for 23 years, 1947-1969. They found that mortality rates were well below those of the general population during the first few years after discharge. After 23 years the mortality rates of the veterans were still lower than, but approaching, those of the general population. The effect of military selection varied considerably according to the nature of the cause of death.

Three studies have demonstrated an association between mortality and military rank at separation from military duty. Keehn et al. (1978, 1974) and Seltzer and Jablon (1977) found that mortality during 24 years following separation declined with each successive advance in rank through the enlisted grades. Furthermore, mortality of privates was very close to expectation based on population rates; non-commissioned officers had a 23% advantage and commissioned officers about a 40% advantage. The advantage held for deaths from all causes and also for most specific causes examined. Over the 24-year period of followup, the tendency for the differences to diminish was only small.

but they were also selected from among other veterans. For the reasons discussed above, these data cannot be used to evaluate the effect of war service.

The literature contains reports from several studies that examined the morbidity and mortality experience of prisoners of war (POW's). Nefzger (1970) found that standardized mortality ratios and death rates indicated a clear early excess of deaths among prisoners held by the Japanese in WWII. Prisoners from the European and Mediterranean theatres of WWII did not have an adverse mortality experience to 1965. Keehn (1980) followed the same groups through 1975 and found that their increased risks of death, though diminished over time, persisted for 9 and 13 years, respectively. Mortality in Korean War prisoners has been more like that in Pacific than European WWII prisoners (Nefzger, 1970). Mortality from tuberculosis and from trauma contributes to the increase among Pacific ex-prisoners, whereas for Korea the increase is limited to trauma. An excess of deaths due to cirrhosis of the liver was apparent in all three former prisoner groups, WWII (Europe, Pacific) and Korean, from about the 10th followup year (Keehn, 1980).

Beebe (1975) studied morbidity, disability, and maladjustments among WWII and Korean prisoners and compared them with veteran controls from the same wars who were not taken captive. In this study, sequelae of the POW experience were both somatic and psychiatric and were of greatest extent and severity among Pacific WWII POW's. Among European WWII POW's, only psychiatric sequelae were apparent. Somatic sequelae were most prevalent in the early years after liberation, but for Pacific WWII POW's they persist in the form of higher hospital admission rates for many specific causes. Klonoff et al. (1976) investigated the long-term or residual effects resulting from severe and extended exposure to stress among POW's captured in Japan (high-stress group) or Europe (low-stress group) during WWII. The low-stress group was divided into long-term and short-term internment periods. Neuropsychological, psychiatric, and physical/neurological outcomes were compared, and significant differences were found among these three groups. The high-stress group scored significantly lower in operational intelligence, exhibited more signs of psychiatric maladjustment, and had more physical illnesses, especially of the neurological and musculoskeletal systems. Residual effects increased in proportion to length of internment, though numbers in each category were small when stratified in this way. The authors concluded that terms such as "survival syndrome" (Chodoff, 1963) and "war neurosis" (Maskin, 1966) describe identifiable phenomena with long-term residual effects (Klonoff et al., 1976).

Davies (1978) found an excess of leukemias, lymphomas, myelomas, and polycythemia vera among Australian servicemen with overseas and tropical area service as compared with those serving in temperate Australia; however, he did not control for confounding variables (such as age) and, for some controls, the area of service was doubtful. A diagnosis of malaria and/or an interaction of nitrates and nitrites with the malaria prophylactic drug chloroquine were suggested as possible risk factors. In a followup study, Giles et al. (1980) investigated the possibility that exposure to malaria may have led to later development of lymphoma in 62 men resident in Tasmania, Australia, and found no association.