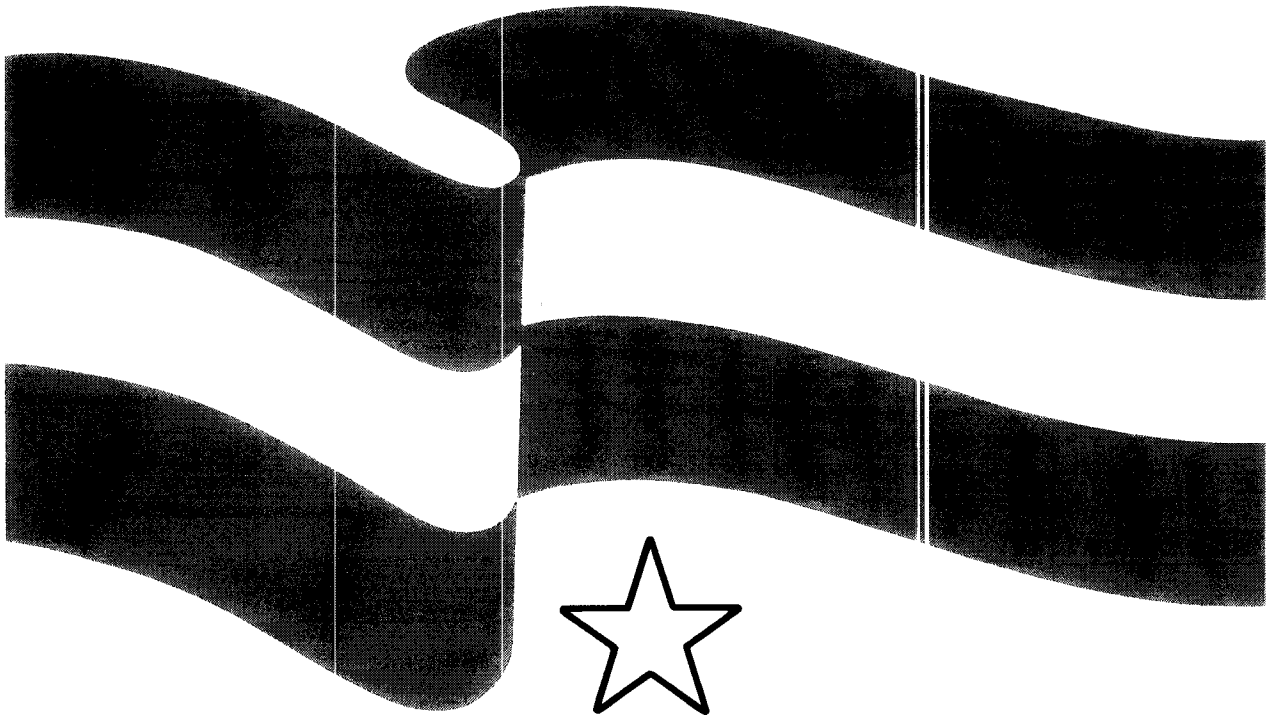

HEALTH STATUS OF VIETNAM VETERANS

VOLUME I
SYNOPSIS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
Centers for Disease Control

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The Centers for Disease Control
Vietnam Experience Study
January 1989

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
Centers for Disease Control
Center for Environmental Health and Injury Control
Atlanta, Georgia 30333

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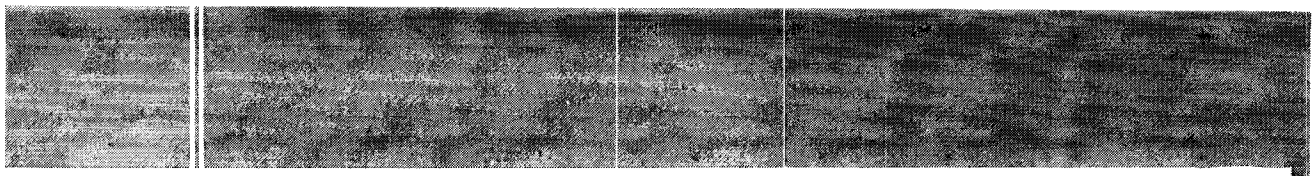


SUMMARY

Many Vietnam veterans believe that their health, and that of their children, has been affected by their service in Vietnam and, more specifically, exposure to the herbicide Agent Orange. In response to these concerns, Congressional directives led to three epidemiologic studies by the Centers for Disease Control (CDC). The Agent Orange Exposure Study was abandoned as not feasible; the Selected Cancers Study is in progress; and the results of the Vietnam Experience Study (VES), which looked for adverse health effects among men who had served in Vietnam, are summarized here.

In the VES we used a random sample of military records to find 9,324 U.S. Army enlisted men who had served a single tour in Vietnam and 8,989 who had served elsewhere—all of whom had been discharged alive after a single enlistment starting in 1965-1971. The VES had four components: mortality assessment, telephone interview, medical and psychological examination, and a reproductive outcome assessment. In the mortality component we ascertained the vital status of all but 7% of the men and found that, during the first 5 years after discharge, the Vietnam group had 45% excess deaths, largely due to external causes (motor vehicle injuries, homicides, suicides), but thereafter the death rates in the two groups were about the same.

In the telephone interview component, the surviving 9,078 Vietnam and 8,789 non-Vietnam men were traced, with 94% of the eligible Vietnam and 92% of the non-Vietnam men located. Of these, 93% (7,924) Vietnam and 91% (7,364) non-Vietnam veterans were interviewed, producing overall response rates of 87% for Vietnam and 84% for non-Vietnam veterans. For this component the main findings were broad similarities between the two groups in current demographic and social characteristics, with more than 80% of both groups reporting that they were in good health. The Vietnam veterans, however, reported more current use of prescription drugs and more current and previous problems with many types of diseases and somatic symptoms. The Vietnam veterans also reported more health problems among their children and more problems with impaired fertility, yet both groups reported fathering children at the same rate.

In the examination component, a subsample (approximately 42%) of interviewed men were invited to undergo comprehensive medical, psychological, and laboratory examinations. Of those invited, 75% (2,490) Vietnam and 63% (1,972) non-Vietnam veterans participated. Results of physical and laboratory examinations showed few differences between the two groups, despite the many differences reported in the telephone interview. Vietnam veterans did, however, have more hearing loss, particularly among those men with tactical military occupational specialties, and more Vietnam veterans had occult blood in their stools. Semen analysis showed that Vietnam veterans had a lower mean sperm concentration and a lower mean proportion of morphologically "normal" sperm cells. Among Vietnam veterans, 14.7% reported ever having symptoms that met the accepted criteria for combat-related post-traumatic stress disorder (PTSD), and 2.2% reported having had such symptoms during the month before the examination. Despite these psychological problems, Vietnam veterans as a group have attained social and economic status similar to that attained by veterans who did not serve in Vietnam. Although scores for the vast majority of men in both groups fell within normal limits for standard psychological tests, current psychological problems (primarily alcohol abuse or dependence, anxiety, or depression) were more prevalent among Vietnam veterans than among non-Vietnam veterans.

The reproductive outcome component was added because an analysis of responses to early telephone interviews showed that Vietnam veterans were reporting birth defects in their children at a higher rate than were non-Vietnam veterans. Therefore, hospital birth records for a sample of 3,366 births were retrieved. Despite the higher reporting rate, these records did not document a greater risk among children of Vitnam veterans for all types of birth defects combined.

Data from all four parts of the VES show that those Vietnam veterans who report exposure to herbicides in Vietnam also report more postservice diseases and symptoms in themselves and more birth defects in their children. Conversely, those who deny exposure to herbicides in Vietnam tend to report diseases and symptoms at rates very similar to rates for non-Vietnam veterans. Perceived exposure to herbicides (which in itself may lead to additional anxiety and stress) appears to be associated with anxiety, depression, combat-related PTSD, and enhanced recall of diseases and symptoms.

1. INTRODUCTION

1.1 GENERAL BACKGROUND OF THE STUDY

Many Vietnam veterans have expressed concern that their military service in Vietnam may have adversely affected their health and the health of their children. This anxiety has focused mainly on exposure to the dioxin contaminant (2,3,7,8-tetrachlorodibenzo-para-dioxin) found in the defoliant mixture named Agent Orange, which was widely used in Vietnam. Because of these concerns and because little objective evidence was available on the relationship of Vietnam veterans' health to the health of other veterans of similar background and age, the U.S. Congress directed that appropriate investigations be conducted (Veterans Health Care, 1981; Veterans Health Programs, 1979). In January 1983, responsibility for the design, conduct, and analysis of studies responsive to these laws, first assigned to the Veterans Administration (VA), was transferred by an Interagency Agreement to the Centers for Disease Control (CDC). In May of 1983, CDC circulated a draft protocol for extensive peer review*, and in November, these reviews resulted in a revised protocol (Centers for Disease Control, 1983).

In response to the concerns of veterans, Congress authorized CDC to carry out three epidemiologic studies:

1. The **Agent Orange Exposure Study** was a historical cohort study, designed to determine whether men exposed in Vietnam to Agent Orange have subsequently developed any health problems related to that exposure. This study was canceled in 1987, after an extensive validation test in a sample of veterans who were in Vietnam at the time of heaviest Agent Orange spraying (Centers for Disease Control, in press). This test showed that of the military record or interviewing methods proposed for classifying "high exposure" and "low exposure" groups needed for analyzing subsequent adverse health effects, none was correlated with current levels of dioxin in blood—the best (though prohibitively expensive) proxy available for Agent Orange exposure in Vietnam. Furthermore, the test showed that current blood levels of dioxin in the vast majority of men who served as ground troops in Vietnam are indistinguishable from levels in the blood of similar veterans who did not serve in Vietnam.
2. The **Selected Cancers Study** is a concurrent, population-based case-control study to ascertain whether Vietnam veterans are at an increased risk of particular types of cancer that have been suggested as being possibly related to dioxin exposure. These cancers occur too infrequently to be evaluated adequately in a cohort study. Collection of data will be completed in 1989, and results will be reported in 1990.
3. The **Vietnam Experience Study** (VES) was a historical cohort study to determine whether adverse health effects are associated with U.S. Army service in Vietnam. The results of the previously published mortality component (Boyle *et al.*, 1987; Centers for Disease Control, 1987) are summarized here, as are the results of the postservice morbidity components of the VES, which are reported in detail in other volumes and supplements of this monograph:

   Volume II. Telephone Interview (Centers for Disease Control, 1988a).
   Volume III. Medical Examination (Centers for Disease Control, 1988b).

* This included formal reviews by the Office of Technology Assessment, the Department of Health and Human Services Advisory Committee, known as the "Ranch Hand Panel," the Agent Orange Working Group Science Panel, and a CDC *ad hoc* review panel.

Volume IV. Psychological and Neuropsychological Evaluation (Centers for Disease Control, 1988c).

Volume V. Reproductive Outcomes and Child Health (Centers for Disease Control, 1988d).

Supplement A. Laboratory Methods and Quality Control (Centers for Disease Control, 1988e).

Supplement B. Medical and Psychological Data Quality (Centers for Disease Control, 1988f).

Supplement C. Medical and Psychological Procedure Manuals and Forms (Centers for Disease Control, 1988g).

1.2 RATIONALE AND RESEARCH QUESTIONS

The Vietnam Experience Study was designed to address the concern that there may have been many factors in addition to herbicide exposure which could have adversely affected veterans who served in Vietnam, in contrast to those who served elsewhere. The "Vietnam Experience" comprises a wide range of health influencing factors operating among those who served in the military in Vietnam. Included in the "experience" are known exposures such as psychological stresses of war, possible exposure to various infectious diseases, possible misuse of drugs and alcohol, as well as many unknown exposures.

The study protocol developed by CDC called for one group of men, selected to be representative of most U.S. Army men who served in Vietnam, to be compared with another group, selected to be like the Vietnam group in every respect except that they were not sent to Vietnam. The basic research questions for the VES components were—

1. Is there an excess risk of postservice mortality for the Vietnam group? (If so, due to what causes?)
2. Is there an excess risk of specific illnesses (including psychological) or groups of postservice illnesses for the Vietnam group?
3. Is there an excess of adverse reproductive outcomes or childhood illnesses among children of the Vietnam group?

2. STUDY GROUP SELECTION AND DATA COLLECTION METHODS

2.1 CRITERIA FOR INCLUSION

The primary objective in defining the Vietnam and non-Vietnam study groups was to obtain two groups that were as similar as possible with regard to pre-existing factors which could influence health. Achieving this objective does not result in representative samples of all military personnel who served in Vietnam and elsewhere. The comparability of the two study groups, however, was considered of paramount importance because it increased the probability that any observed differences in subsequent mortality or morbidity would relate to Vietnam experiences rather than to differences in preexisting characteristics of the men in the two groups. To achieve this objective, we decided that only those veterans meeting the following criteria were eligible for random selection into the study:

1. ***U.S. Army veterans.*** The majority of military personnel who served in Vietnam were in the Army. Marines were deployed in Vietnam in ways very similar to soldiers, but in smaller numbers, and such a high proportion of Marines went to Vietnam that it would have been difficult to find a comparison group of Marines who had not been there. Air Force and Navy personnel were often stationed for at least part of their tours of duty in offshore locations or in other parts of Asia.
2. ***Military occupational specialty (MOS)*** other than "duty soldier" (someone likely to have had behavior or conduct problems identified during training) or "trainee" (someone who never successfully finished training in the United States).
3. ***Single term of enlistment.*** Those who reenlisted may well have differed from the vast majority who did not do so. Because of the method of selection, however those who later enlisted into another branch of the service could have been included in this study.
4. ***Minimum of 16 weeks of active duty time.*** Army regulations stated that men could not be sent to duty such as in Vietnam until they had completed at least 16 weeks of active duty.
5. ***Pay grade E-1 to E-5 at discharge.*** These grades correspond to the ranks of private through sergeant (or specialist fifth class). The majority of those in some combat specialties who had ranks higher than E-5 had more than one tour in Vietnam, making it difficult to find a comparison group above that rank without service in Vietnam.
6. ***Entered military service for the first time during 1965-1971.*** This was the period during which a large number of single-term volunteer or drafted soldiers were assigned to Vietnam.

The non-Vietnam group was limited to those with duty stations only in the U.S.A., Germany, or Korea. The assignment process was believed to be different for men sent to countries other than these three during that era; therefore, their health-related characteristics might be different from the characteristics of men sent to Vietnam.

The study was limited to men because, as stated in the study protocol, of CDC's belief that if women are to be studied, they should be studied separately in sufficient numbers to allow meaningful conclusions to be reached about them as a group. A separate study of female Vietnam veterans is currently under consideration by the Veterans' Administration.

2.2 SAMPLE SIZE AND POWER

Sample sizes required for the VES telephone interview and examination components were discussed in the protocol (Centers for Disease Control, 1983). The objective was to have sufficient numbers in the interview component to have a power of 0.95 and a Type I error probability of 0.05 (one-sided) of detecting a twofold increase in health outcomes that normally occur at a rate of about 5 per 1,000. It was estimated that 6,000 interviewed veterans in each group would be sufficient to achieve this objective. For the medical examination component, the goal was to examine 2,000 men in each cohort to provide sufficient power (beta error = alpha error = 0.05, one-sided) to detect a twofold increase in relative risk for conditions that ordinarily occur with a prevalence rate of 1.5%-2%.

For continuous outcome variables, such as the results of most laboratory tests, this sample size would provide sufficient statistical power to detect even modest differences between the two groups.

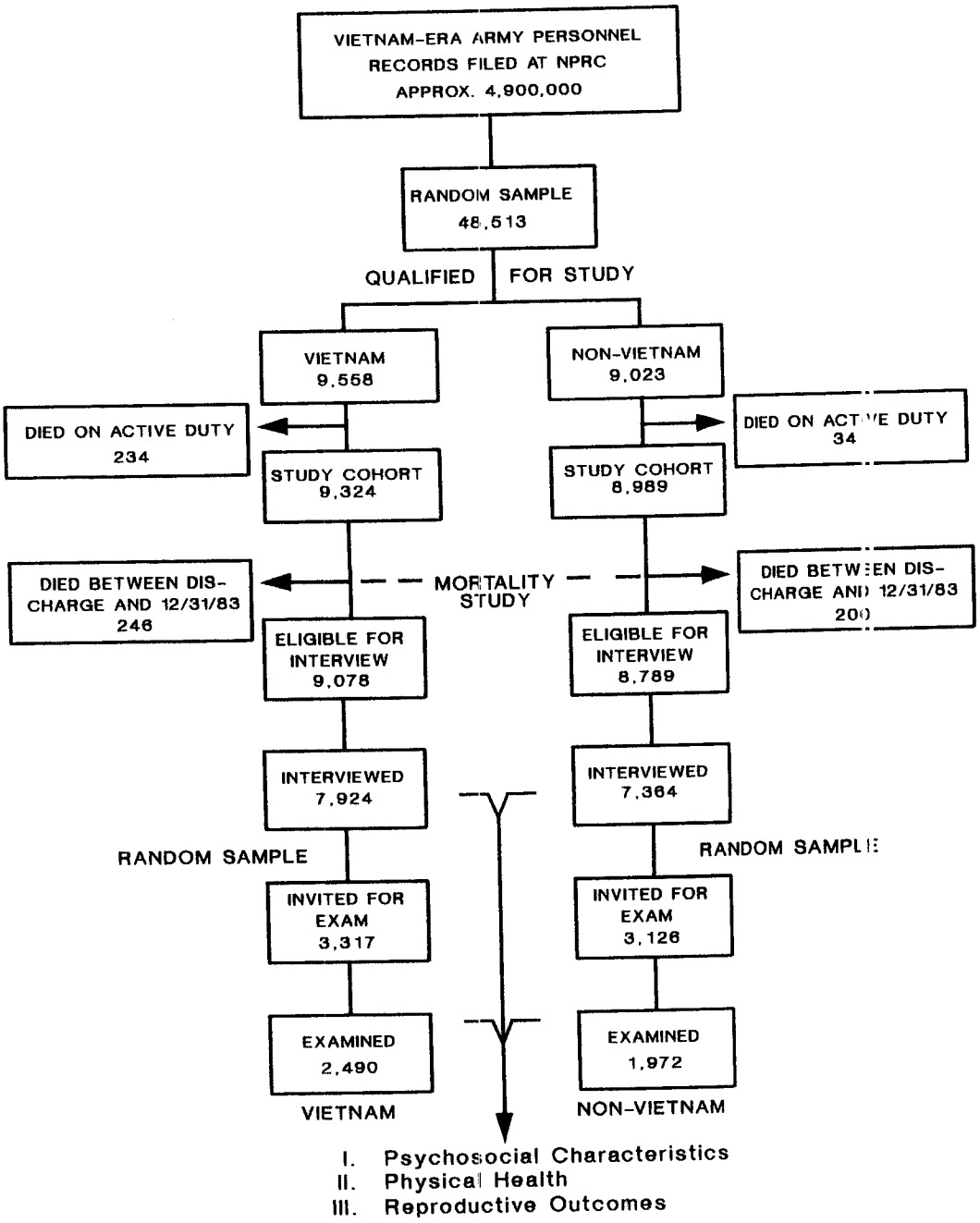
Because of small numbers of births, we recognized from the outset that, for the reproductive outcome component of the study, birth defects would have to be counted in broad categories rather than as specific conditions.

2.3 SELECTION OF VETERANS FROM MILITARY PERSONNEL FILES

The National Personnel Record Center (NPRC) supplied CDC with accession numbers corresponding to nearly 5 million records of U.S. Army veterans whose records were received between September 1964 and June 1977, a period that would include records of most Vietnam veterans. A random number generating program was used to select the sample of 48,513 accession numbers (see Figure 1). Individual records were then located and reviewed for the inclusion criteria; fewer than 1% of the records were eliminated because information needed to judge these criteria was missing. Each month for 14 consecutive months, lists containing 3,500 accession numbers were sent to NPRC, where corresponding military records were located and sent to the Army Reserve Personnel Center. There each file was reviewed to confirm eligibility and to initiate a data abstraction form. These forms, along with the corresponding personnel files, were then forwarded to the U.S. Army and Joint Services Environmental Support Group, where a second qualification process was completed. The abstract forms were then completed in detail for those veterans found to be fully qualified for the study. Through this process 9,558 Vietnam and 9,023 non-Vietnam veterans were qualified. Two different systematic sampling methods for reabstraction demonstrated no substantial misclassification by place of service.

The completed abstract forms were then forwarded to CDC for data entry and editing via computer. Ascertainment of vital status and the most recent address for each study subject was sought through computer matching with a variety of agencies (Veterans Administration, Social Security Administration, Internal Revenue Service via the National Institute for Occupational Safety and Health, and the National Center for Health Statistics). After we deducted the 234 Vietnam and 34 non-Vietnam subjects who died while on active duty and the 246 Vietnam and 200 non-Vietnam subjects who died after discharge (Figure 1), 9,078 Vietnam and 8,789 non-Vietnam veterans remained eligible for interview. From this pool of study subjects thought to be alive, random sample batches of about 1,400 names (with location information) were sent each month to the contractor (see Section 2.4) for tracing, obtaining informed consent, and telephone interviewing. Each batch contained roughly equal numbers of Vietnam and non-Vietnam veterans.

Figure 1. The Vietnam Experience Study Components



2.4 INTERVIEW METHODS

The process of locating, contacting, and interviewing veterans was conducted via a contract with Research Triangle Institute (RTI), including a subcontract with Equifax, Inc., to provide multilevel locating and contacting services. After a field-test in late 1984, tracing and

interviewing began in early 1985 and ended in July of 1986. In tracing the veteran, RTI and Equifax used telephone directory assistance, searches of automated credit bureaus, state motor vehicle operator records, city directories, other local records, and contacts with relatives, neighbors, and employers.

Study procedures were aimed at maximizing the number of interviews conducted by telephone. In-person interviews were conducted for nine veterans who wanted to participate, but who could not or would not be interviewed by telephone. The use of computer-assisted telephone interviewing with concurrent data entry for each item and prompting for the next question made it easier to do some immediate data editing. Vietnam and non-Vietnam veterans were intermingled in the interviewing process, and interviewers were unaware of each veteran's place of service until late in the interview, when Vietnam veterans were asked questions about experiences unique to Vietnam. All participants were given special assurances of confidentiality regarding the interview and other components of the study. RTI supervisory staff monitored 10% of all interviews in a manner that prevented the veteran or the interviewer from being aware of the monitoring. CDC staff also did periodic on-site monitoring, and regular feedback sessions were held to correct errors and to ensure continuing interviewer consistency. Partially edited data tapes were sent to CDC monthly for further editing and data analysis.

The structured interview averaged 32 minutes and was designed to cover past and present health status and demographic and behavioral characteristics. It included open-ended questions about health problems while in the Army and questions about current psychosocial and physical health status. It also contained questions about specific post-service conditions or disease categories, including hospitalizations; reasons for current use of prescribed medications or for current limitations in activities; neurologic symptoms; skin conditions; psychological symptoms related to post-traumatic stress disorder (PTSD); treatment for drug, alcohol, or emotional problems in the past 12 months; current health problems not already mentioned; and difficulties in conceiving children.

2.5 EXAMINATION METHODS

For the examination component, a number of veterans randomly preselected for examination were included in each monthly batch of names sent to RTI. The proportion of men preselected for examination was adjusted each month to account for current interview and examination rates; the proportion averaged about 42% of the men listed in each batch. Preselected men who were successfully located and interviewed were invited at the end of their interview to participate in the examinations, and they were told that they would soon receive more information. CDC then supplied the Lovelace Medical Foundation (LMF), the examination contractor, with monthly lists of names and location information so that it could make appointments for those who had been invited for examination.

The examinations were all held at one site (LMF); all travel expenses were paid, and an honorarium was given for loss of pay during the examination. The general approach was to limit examinations and tests to those that measure health deficits in the most direct way possible, and invasive procedures were limited to venipuncture. After a pilot test of procedures in April 1985, the examinations began in the summer of that year and ended in September 1986.

Men typically arrived at LMF in Albuquerque, New Mexico, in the afternoon before their first examinations, and they were given an orientation late that afternoon, when they signed the

informed consent statement. The next morning, before eating, they reported for venipuncture, then proceeded with the examinations and tests. During the following day, they completed psychological and neuropsychological tests, and on the last morning each veteran had separate meetings with an internist and a psychologist, who reviewed available results, discussed the findings, and suggested any medical or psychological follow-up that the veteran should seek after returning home. Problems found during the screening examinations and tests described below did not lead to any further evaluation at LMF.

The LMF staff received intensive training, followed written protocols, and were monitored periodically by their own supervisors and by visiting CDC personnel. Repeat tests or independent rereadings of examination results (*e.g.*, chest roentgenograms) were done according to a quality control protocol. All laboratory equipment was standardized, periodically retested, and used only for this study. Two full-time laboratory quality control supervisors assured that protocols were followed. Laboratory assays were controlled by using both bench and "blind" control specimens. External quality control included CDC monitoring of data and LMF enrollment in proficiency testing programs of the College of American Pathologists, the CDC Lipid Standardization Program, and the World Health Organization. Partially edited data tapes were sent monthly to CDC for further editing and analysis.

A physician's assistant administered a standardized medical history questionnaire; an internist performed a general medical examination; a dermatologist performed a dermatologic examination; and a neurologist performed a neurologic examination. Registered nurses measured blood pressure. Technicians administered chest roentgenogram, pulmonary function, skin hypersensitivity (cell-mediated immunity—CMI), neurodiagnostic, and Doppler examinations. The peripheral arterial system was evaluated by using a Parks Dual Frequency Bidirectional Doppler instrument.

Standard 12-lead electrocardiograms (ECGs) were interpreted by Board-certified cardiologists. Chest roentgenograms were interpreted by radiologists. Pulmonary function was tested by using a MedScience 570 wedge spirometer, and the results were analyzed by a computer. Nerve conduction velocity and the amplitude of upper and lower extremity sensory and motor nerves were measured by using standard techniques (Kimura, 1983), with a TECA TD-10 instrument and surface electrodes. Vibratory sensation and thermal sensation were tested by using a Pfizer Vibratron (Arezzo *et al.*, 1983) and a Pfizer Thermal Tester (Arezzo *et al.*, 1986). Auditory acuity was tested by using a RA400 Microprocessor Audiometer operating in the automatic mode.

Laboratory measurements included standard hematologic assays and quantification of T and B lymphocyte subset populations by flow cytometric fluorescence (Edwards *et al.*, 1987). Delayed-type hypersensitivity to standardized recall antigens was assessed with the Multitest CMI (Kniker *et al.*, 1984). Immunoglobulin levels (IgG, IgM, IgA) were measured by immunoprecipitin reaction (Centers for Disease Control, 1988e). Most serum chemistry assays were performed on a Kodak Ektachem 700 autoanalyzer. Commercial radioimmunoassays were used to test serum for markers of hepatitis B infection and a variety of hormones (Centers for Disease Control, 1988e).

A 12-hour overnight collection of urine was tested for creatinine, D-glucaric acid, and porphyrins. Porphyrin levels, measured by using high-performance liquid chromatography (Hill *et al.*, 1982), were classified by chronic hepatic porphyria patterns (Hill, 1985). Stool was tested for occult blood via Hemoccult (SmithKline).

The physicians, nurses, and technicians who did these examinations were blinded as to the cohort status of each veteran, and they were trained not to ask any questions that might reveal the place of service. The personnel who administered the psychological tests were also blinded as to place of service until near the end of the psychiatric interview, when questions about post-traumatic stress disorder were asked.

Because of early indications in the telephone interview that Vietnam veterans were reporting more problems with conceiving children than were non-Vietnam veterans, a semen analysis was added to the list of examinations. Of the 705 veterans who were examined toward the end of the study and who had not had vasectomies, 571 (81%) participated in the semen study. Semen specimens, collected after a minimum of 2 days of sexual abstinence, were processed within 2 hours after they were collected. The Cellsoft system (Ast *et al.*, 1986), which employs computer analysis of digitized video images of sperm heads, was used to measure several characteristics of semen quality, including concentration, movement, and sperm-head shapes and dimensions. Sperm-head morphology was classified according to World Health Organization criteria (Belsey *et al.*, 1980).

Case Definitions

Chloracne-like lesions were defined as (1) comedones in a malar crescent or auricular and postauricular distribution, with nasal sparing, or (2) a history of chloracne with postinflammatory scars in chloracne-prone locations. Alteration of peripheral arterial hemodynamics was defined as the presence of a femoral bruit, the absence of a posterior tibial pulse waveform (upon using a Doppler probe), or a resting ankle/brachial blood pressure ratio <1. Pulmonary function values of "never smokers" without lung disease from the two combined cohorts were used to develop prediction equations of expected pulmonary function values based on a veteran's race, age, and height (Hankinson, 1986).

High-frequency hearing loss was defined as an average hearing threshold $\geq$51 decibels (dB) at three frequencies (3,000, 4,000, and 6,000Hz) (Brown, 1985). Symptoms of peripheral neuropathy included numbness, tingling, a burning sensation, and weakness of the arms or legs. Signs included findings from the neurologic physical examination and out-of-reference-range values for nerve conduction velocity and amplitude or for vibration and thermal thresholds.

Unless otherwise specified, the reference range for most continuous measures (neurodiagnostic tests and laboratory assays) was determined by the 5th or 95th percentile (depending on the outcome of interest) in the distribution of both cohorts combined.

2.6 PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL EVALUATIONS

Psychological evaluation was based on the Minnesota Multiphasic Personality Inventory (MMPI), a well-established self-administered questionnaire, and the Diagnostic Interview Schedule (DIS), version 3A, used to assess the cumulative prevalence of certain psychiatric conditions that have ever been experienced. For this study, questions were added to the DIS on symptoms during the past month for five conditions of special interest (generalized anxiety, depression, alcohol abuse or dependence, drug abuse or dependence, and post-traumatic stress disorder).

Trained technicians administered standard neuropsychological tests (Delis *et al.*, 1987; Lezak, 1983), including the General Technical (GT) section of the Army Classification Battery, which these men had also taken during their induction into the Army. Concept-formation and problem-solving abilities were measured by using the Wisconsin Card Sorting Test (WCST),