McIntyre N. The liver. In: Williams DL, Marks V, eds. Biochemistry in clinical practice. New York: Elsevier, 1985:139-54.

Moses M, Lilis R, Crow KD, *et al.* Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: comparison of findings with and without chloracne. Am J Ind Med 1984;5:161-82.

Nebert DW, Negishi M. Multiple forms of cytochrome P-450 and the importance of molecular biology and evolution. Biochem Pharmacol 1982;31:2311-7.

Neel S. Medical support of the U.S. Army in Vietnam 1965-1970. Washington D.C.: Department of the Army, 1973:32-48.

Neumann DA, Benenson MW. Hepatitis B antigen in American personnel with acute hepatitis in the Republic of Vietnam. Milit Med 1974;139:693-5.

Patterson DG Jr, Needham LL, Pirkle JL, *et al.* Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri. Arch Environ Contam Toxicol 1988;17:1[illegible]9-43.

Pazderova-Vejlupkova J, Nemcova M, Pickova J, Jirasek L, Lukas E. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch Environ Health 1981;36:5-10.

Penn R, Worthington DJ. Is serum gamma-glutamyl transferase a misleading test? Br Med J 1983;286:5[illegible]-5.

Poland AP, Smith D, Metter G, Possick P. A health survey of workers in a 2,4-D and 2,4,5-T plant. Arch Environ Health 1971;22:316-27.

Sedman AJ. Cimetidine-drug interactions. Am J Med 1984;76:109-14.

Sherman DJC, Finlayson NDC. Diseases of the gastrointestinal tract and liver. New York: Churchill Livingstone, 1982:527-54.

Simon JB. Occult blood screening for colorectal carcinoma: a critical review. Gastroenterology 1985;88:8[illegible]0-37.

Snitbhan R, Scott RM, Bancroft WH, Top FH Jr, Chiewsilp D. Subtypes of hepatitis B surface antigen in Southeast Asia. J Infect Dis 1975;131:708-11.

Strik JJTWA, Debets F, Koss G. Chemical porphyria. In: Kimbrough RD, ed. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins, and related products. New York: Elsevier/North Holland Biomedical Press, 1980:191-239.

Suskind RR, Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 1984;251:2[illegible]72-80.

Walker AE, Martin JV. Lipid profiles in dioxin-exposed workers [Letter]. Lancet 1979;1:446-7.

Wallach J. Interpretation of diagnostic tests. 4th ed. Boston: Little Brown, 1986.

Webb KB, Ayres SM, Mikes J, Evans RG. The diagnosis of dioxin-associated illness. Am J Prev Med 1986;[illegible] 103-8.

Winawer SJ, Andrews M, Flehinger B, Sherlock P, Schottenfeld D, Miller DG. Progress report on controlled trial of fecal occult blood testing for the detection of colorectal neoplasia. Cancer 1980;45:2959-64.

Winchester DP, Shull JH, Scanlon EF, *et al.* A mass screening program for colorectal cancer using chemical testing for occult blood in the stool. Cancer 1980;45:2955-8.

Yager T, Laufer R, Gallops M. Some problems associated with war experience in men of the Vietnam generation. Arch Gen Psychiatry 1984;41:327-33.

CHAPTER 7

Neurologic System

7. NEUROLOGIC SYSTEM

7.1 INTRODUCTION

In this chapter we describe the neurologic status of the Vietnam and non-Vietnam veterans who participated in the medical examination component of the Vietnam Experience Study (VES). The results of their psychological evaluations and neuropsychological tests are presented in Volume IV (Psychological and Neuropsychological Evaluation) of this monograph.

As noted in the introduction to this volume (Chapter 1), the purpose of the VES was to evaluate health effects that may have resulted from the "general experience" of having served in Vietnam. In designing this study we used a broad approach to identify and examine any neurologic or other medical conditions that may have resulted from this experience. The VES was not designed to examine exclusively the potential health effects of exposure to Agent Orange, but many of the concerns expressed by veterans, the public, and some researchers focused on this issue. Thus, we emphasized the evaluation of health effects that have been suggested as being related to prior exposure to phenoxyherbicides or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the contaminant in the herbicide Agent Orange. Before beginning our analysis, we specified for more detailed evaluation two neurologic conditions that we thought might be more prevalent among Vietnam veterans: peripheral neuropathy and hearing loss.

On the basis of our review of the literature, we reasoned that Vietnam veterans might have higher risks than other veterans of peripheral neuropathy or slowed nerve conduction velocities (NCVs) because of possible exposure to Agent Orange or TCDD. Further, we postulated that certain subgroups of Vietnam veterans might be more likely to have signs of peripheral neuropathy. Persons with diabetes or alcoholism may, in the presence of another contributing factor, be more likely to develop peripheral neuropathy than persons who do not have one of these conditions. If the Vietnam experience produced peripheral neuropathy (via exposure to an environmental toxin), then those veterans with predisposing diabetes or alcoholism might be more likely to have evidence of it.

Exposure to phenoxyherbicides or TCDD has been linked potentially to a wide range of neurologic problems, including peripheral neuropathy. Agent Orange, a mixture of two phenoxyherbicides—2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), was contaminated with TCDD during the manufacturing process. Most of the human health studies have involved persons exposed during the manufacture of phenoxyherbicides and related compounds or following explosions and runaway chemical reactions. In addition, investigators have reported some cases of neurologic effects following exposure to herbicides, primarily to 2,4-D (Berkley and Magee, 1963; Berwick, 1970; Goldstein *et al.*, 1959; O'Reilly, 1984; Sare, 1972; Seabury, 1963; Todd, 1962; Wallis *et al.*, 1970), but also to mixtures containing either 2,4,5-T or TCDD (Oliver, 1975; O'Reilly, 1984).

The results of some of these studies are difficult to interpret because comparison groups were not always included, and the types of neurologic examinations performed were often not well described. In addition, many workers in manufacturing plants were also exposed to other chemicals. Further, the adverse neurologic effects, which were often not described in detail, varied among the different studies and case reports (particularly for effects related to 2,4-D exposure).

Polyneuropathy and slowed NCVs, as well as other neurologic sequelae, such as encephalopathy, neurasthenia, decreased proprioception, tremors, and absent Achilles tendon reflexes, have been found among workers at various manufacturing plants (Jirasek *et al.*, 1973; Pazderova-Vejlupkova *et al.*, 1981; Poland *et al.*, 1971; Singer *et al.*, 1982). Similarly, persons exposed during the explosion at Seveso, Italy, had some evidence of peripheral neuropathy, including abnormal NCVs or motor action potentials, polyneuropathies, and nystagmus (Filippini *et al.*, 1981; Pocchiari *et al.*, 1979).

Other researchers have found no peripheral neuropathy among persons exposed to phenoxyherbicides. Suskind and Hertzberg (1984), in their study of workers employed in a Nitro, West Virginia, plant that manufactured 2,4,5-T, found no differences between the exposed and control groups in sural or peroneal NCVs. Hoffman *et al.* (1986), in their study of mobile-home park residents exposed to dioxin-contaminated waste oil used to control dust on roadways, found an increased prevalence of two self-reported neurologic symptoms in the resident group compared with the control group: (1) numbness or "pins and needles" in the hands or feet and (2) persistent, severe headaches. Results of physical examinations of the peripheral nervous system, however, showed no differences between groups, and neither did the results of two tests to measure sensory peripheral neuropathy.

Similarly, in the U.S. Air Force Ranch Hand baseline study of Vietnam veterans involved in herbicide spray missions, researchers found no differences between that group and a comparison group in physical examination results for the peripheral nervous system or in measurements of NCVs (Lathrop *et al.*, 1984). Neither did they find a difference in "central functioning" as measured by tremor, finger-to-nose coordination, gait, and balance. In the first follow-up examination of study participants (Lathrop *et al.*, 1987), the investigators found no difference between groups in the prevalence of Babinski reflexes, an abnormality that, in the baseline examination, had been more common among the Ranch Hand personnel.

As stated earlier, the other neurologic condition that we focused on was hearing loss. We emphasized the assessment of auditory acuity among Vietnam veterans because results of prior studies have shown that exposure to noise in a military setting may cause permanent hearing loss. These investigations of noise-induced hearing loss among military personnel have been mostly observational studies of groups of infantrymen (Brown, 1985; Coombe, 1980; Man *et al.*, 1975; Salmivalli, 1979; Walden *et al.*, 1975), with some reviews of case histories (Bender and Mueller, 1981; Ziv *et al.*, 1973). Both types of investigations have shown that hearing loss associated with exposure to military noise, such as blasts and gunfire, occurs in the mid-to-high-frequency range (*e.g.*, 3,000 to 6,000 Hertz), with little occurring at frequencies below 2,000 Hertz (Hz). Thus, we postulated that Vietnam veterans would have more hearing loss than non-Vietnam veterans and, further, that those veterans with more combat exposure would have higher levels of hearing loss than those with less combat exposure.

Our review of the literature suggested no other neurologic conditions, besides peripheral neuropathy and hearing loss, that might be expected to be related to prior military service in Vietnam. Since, however, the VES was designed to provide a comprehensive screening evaluation of the veterans' overall health, the battery of tests included an in-depth evaluation of the neurological system.

7.2 METHODS

In this chapter, we present information obtained from five sources: (1) self-reported medical histories; (2) the general neurologic physical examination; (3) neurodiagnostic tests of the peripheral nervous system; (4) tests of auditory acuity; and (5) tests of visual acuity. During the study all physicians, interviewers, and technicians were unaware of the veterans' cohort status.

7.2.1 Medical History and General Neurologic Examination

Physician's assistants administered a standardized medical history questionnaire to all study participants, as described in Chapter 2. The clinic manager monitored the interviews daily.

Each participant underwent a complete neurologic examination by a board-certified neurologist. Before participating in the study, the 10 neurologists who performed these examinations were trained, by videotapes and other techniques, to conduct a standardized examination, as described in detail in Chapter 2. The physicians were instructed not to ask participants any neurologic or other history questions during their examinations.

The standardized neurologic examination comprised 156 items organized into four sections: cranial nerves, motor systems, reflexes, and peripheral sensory testing. Before the data were analyzed, we selected those items that were most likely to reflect abnormalities due to exposure to a peripheral nerve toxin. These results, which we used to develop a definition of peripheral neuropathy (see Section 7.2.4), are highlighted in this chapter. The results for all items in the neurologic examination are presented in Appendix G

CDC staff physicians monitored the neurologic testing during regular site visits. In addition, a random sample (about 5%) of participants underwent a repeat examination by a second neurologist who was unaware of the results of the first examination. Results of quality control analyses showed variability in the prevalences of physical findings detected by examining physicians, but there was no indication that this variability introduced either confounding or effect modification into the analysis of cohort differences. The results of all quality control analyses are presented in detail in Supplement B (Medical and Psychological Data Quality) of the monograph.

7.2.2 Neurodiagnostic Tests

Three types of neurodiagnostic tests were performed: nerve conduction velocity and amplitude, vibratory sensation, and thermal sensation. Two outside consultants, both experts in the testing of the peripheral nervous system, assisted in test design, technician training, quality assurance, and data analysis.

Tests of Nerve Conduction and Amplitude

All measurements of nerve conduction velocity and amplitude were performed by one of eight trained technicians using standard techniques (Kimura, 1983) and a TECA TD-10 instrument and surface electrodes. Two instruments were in daily use, and a third was available as a backup. The instruments in use were calibrated daily.

The following nerves were tested: median motor, median sensory (both proximal and distal segments), ulnar sensory, peroneal motor, and sural sensory. For the two motor nerves, the technician measured the time from stimulation of the nerve to onset of the response for both proximal and distal supramaximal stimulation. The distance (in meters) between the stimulation sites was divided by the difference in latencies (in seconds) to provide the nerve conduction velocity (NCV) (meters/second). The amplitude, measured in

microvolts, is the depth of the deflection from the baseline to the peak of the M wave response following stimulation. All sensory components were tested antidromically (from proximal to distal, or opposite to the physiological pattern), and motor components were tested orthodromically (also proximal to distal, but, in this case, corresponding to the physiological pattern).

As a rule, the dominant limb was used for the measurements, but limbs with known injuries were avoided. Before the test, the upper and lower limb temperatures were measured at two sites each. If the temperature was below 31°C, the limb was wrapped with a water blanket and warmed. Although the test protocol required that limbs be warmed to 31°C before the test, this temperature was not always achieved. In all, 105 subjects (2.4% of all participants: 63 Vietnam and 42 non-Vietnam veterans) were tested at lower foot temperatures.

The quality of the data on the measurements of NCV and amplitude (as well as for the other two neurodiagnostic tests—vibration and thermal sensation) was assessed throughout the study period. Each week onsite supervisors reviewed the worksheets, on which the technicians recorded measurements, for completeness and accuracy. They reviewed any problems or questions that arose with the technician. Each month a 10% random sample of each technician's worksheets was mailed to the consultants for review. During site visits every 3 months, the consultants and the CDC physician responsible for monitoring the neurologic testing reviewed a second 10% sample.

Edit ranges for measurements of NCV and amplitude were set to exclude physiologically improbable values in order to identify probable technician or transcription errors. The lower and upper limits for each measurement were cutoffs suggested by our consultants on the basis of their clinical experience. Table 7.1 shows these edit ranges and the number of participants whose measurements fell outside the edit ranges for each of the nerves tested. These measurements were excluded in all subsequent analyses except where otherwise indicated. Most of the participants listed under "no measurement" were those in whom the technicians could not detect a motor or sensory response for that nerve segment.

Exclusions involving measurements on the sural nerve required special consideration. The sural nerve response is the most difficult of these nerve responses to measure (Kraup and Buchthal, 1985). In a certain percentage of normal individuals, the response is not detectable. This nerve is also one that is commonly affected in diseases of the peripheral

Table 7.1 Edit Ranges and Number of Veterans With Nerve Conduction Velocity or Amplitude Measurements Outside of Edit Ranges, by Type of Measure

	Edit Range Limits		Number of Veterans Excluded			
			Outside Edit Range Limits		No	Total
Measure	Lower	Upper	Lower	Upper	Measurement	Exclusions
Nerve Conduction Velocity, m/sec						
Median motor	15.0	85.0	3	4	4	11
Median sensory-distal	15.0	75.0	0	27	20	47
Median sensory-proximal	15.0	85.0	2	7	31	40
Ulnar sensory	15.0	75.0	0	6	19	25
Peroneal motor	15.0	85.0	2	2	36	40
Sural sensory	15.0	75.0	0	1	159	60
Amplitude, μV						
Median motor	400.0	25000.0	0	0	3	3
Median sensory	0.5	60.0	1	2	19	22
Ulnar sensory	0.5	60.0	1	11	19	31
Peroneal motor	400.0	25000.0	12	2	35	49
Sural sensory	0.5	60.0	3	16	158	77

nervous system. Since we did not know whether the nondetectable responses were due to a peripheral neuropathy or some other cause, we analyzed and presented sural nerve measurements in two ways: by treating the nondetectable responses as though they were abnormal and by excluding them from the analysis.

Among the participants with nondetectable responses (or responses outside of the edit range) for conduction velocity of the sural nerve, 104 (4.2% of the cohort) were Vietnam veterans and 56 (2.8% of the cohort) were non-Vietnam veterans. Among those with nondetectable sural nerve amplitude measurements (or responses outside of the edit range), 109 (4.4%) were Vietnam veterans and 68 (3.4%) were non-Vietnam veterans. For both the conduction velocity and amplitude measurements of this nerve, the proportion of participants who could not be measured did not vary by technician, and the distribution of nonresponses across time was uniform for each technician.

Test of Vibratory Sensation

The Vibratron (Arezzo *et al.*, 1983; Arezzo and Schaumburg, 1980) was used to measure vibratory sensation. This instrument consists of two identical rods connected to a variable voltage source that controls the vibration of the rods. At the beginning of the testing procedure, one of the two rods, chosen by the examiner, vibrates at a frequency of 120 Hz. The examiner controls which rod is vibrating and progressively reduces the intensity of the vibration. The examinee is forced to choose which rod is vibrating until his incorrect responses become as frequent as his correct ones. The sensitivity threshold is calculated in volts. A lower threshold indicates greater sensitivity (or ability to sense vibration). Each participant's index finger and great toe were tested. Among the 4,462 veterans tested, 6 vibratory sensations for the finger and 6 for the toe were not obtained.

Test of Thermal Sensation

The Pfizer Thermal Tester (Arezzo *et al.*, 1986) was used to measure thermal sensation. This instrument has two identical thermal plates whose temperature can be controlled within ± 0.1°C over a 50.0°C temperature range. The temperature of one plate (the steady state plate) is always kept at 25°C; the temperature of the other plate (the active plate) is controlled by the examiner. The examiner, who controls whether the temperature of the active plate is higher or lower than that of the steady state plate, tests the participant by progressively reducing the difference between the temperatures of the two plates. The examinee is forced to choose which plate is cooler until his incorrect responses become as frequent as his correct responses. The threshold of sensitivity is calculated in degrees Centigrade. A lower threshold indicates greater sensitivity (or ability to sense temperature differences). Each participant's index finger and great toe were tested.

Among the 4,462 veterans tested, 32 thermal sensations for the finger and 120 for the toe were not obtained. Of the nonresponses for the toe, 71 (2.9% of the cohort) were for Vietnam veterans and 49 (2.5% of the cohort) were for non-Vietnam veterans. An absent response can mean that the subject could not feel the maximum difference in temperature of 25°C, which can be a sign of peripheral neuropathy. As we did in our analysis of nondetectable sural nerve responses, we handled these thermal nonresponses of the toe in two ways: (1) by treating them as though they were abnormal and (2) by excluding them from the analysis.

7.2.3 Reference Ranges for Neurodiagnostic Tests

Before the analysis, we developed reference ranges for all diagnostic tests listed above. To do this we used the values of the tests for those veterans who were least likely to have a peripheral neuropathy or localized nerve damage—that is, those *without* any of these four conditions:

1. Diabetes—a fasting blood glucose ≥140 mg/dL, current use of a glucose-regulating medication, current adherence to a diabetic diet, or a history of physician-diagnosed diabetes;
2. Heavy alcohol consumption—either having ≥5 drinks per day >15 times during the past 4 weeks, or having an average of >150 drinks per month;
3. Peripheral neuropathy—a history of peripheral neuropathy diagnosed by a physician; or
4. Medication use—current use of any medication (listed in Table 7.2) known to be associated with peripheral neuropathy (LeQuesne, 1984).

By using these restrictions we eliminated values for 573 of the 4,462 veterans (Table 7.3). The 573 are equally represented in the two cohorts. We used the remaining 3,889 to create reference ranges for all quantitative diagnostic tests. Measurements from the nerve conduction velocity (NCV) and amplitude tests that were outside the edit ranges were not used in developing the reference ranges.

We defined a reference range for each neurodiagnostic test among this group of 3,889 veterans. The cut point for the reference range was defined by the 5th percentile for each NCV and amplitude measure; values below this cut point were considered outside the reference range. For the vibration and thermal sensation tests, values above the 95th percentile were considered outside the reference range. Table 7.4 lists the value for the cut point for each test.

We introduced one refinement in defining reference ranges for conduction velocity and amplitude measurements of the distal median sensory nerve. Entrapment at the wrist (carpal tunnel syndrome) frequently affects this nerve segment alone and thereby decreases NCV and amplitude. To distinguish this condition from a peripheral neuropathy also affecting other distal nerves, we looked at the ratio of the velocity or amplitude on this nerve segment to that on the distal ulnar sensory segment. If the ratio was lower than the 5th percentile among the referent group, we ruled that the reduced value on the median nerve was an isolated phenomenon and reclassified this value from our list of those below the reference range for the median nerve to those within the reference range. With this procedure we reclassified measurements for about half of each group of veterans (velocity and amplitude).

Table 7.2 Medications Associated With Peripheral Neuropathy

Chloramphenicol	Hydralazine
Cisplatin	Isoniazid
Clioquinol	Metronidazole
Dapsone	Nitrofurantoin
Diphenylhydantoin	Perhexiline Maleate
Disulfiram	Pyridoxine
Ethionamide	Sodium Cyanate
Glutethimide	Thalidomide
Gold	Vincristine

Table 7.3 Percent and Number of Vietnam and Non-Vietnam Veterans Excluded in Developing Reference Ranges for Neurodiagnostic Tests, by Reason for Exclusion

	Vietnam		Non-Vietnam	
Reason for Exclusion	**%**	**No.**	**%**	**No.**
Diabetes[a]	1.8	46	1.4	28
Heavy alcohol consumption[b]	6.8	168	4.9	96
Physician-diagnosed peripheral neuropathy[c]	5.4	134	5.2	102
Use of neurotoxic medication[d]	0.9	22	0.8	16
Any of above	13.9	345	11.6	228
None of above	86.1	2145	88.4	1744
Total	100.0	2490	100.0	1972

[a] Fasting blood glucose ≥140 mg/dL, adherence to a diabetic diet, current use of glucose-regulating medication, or diabetes diagnosed by a physician.
[b] During the past 4 weeks: ≥5 drinks/day on >15 days; or an average of >150 drinks/month.
[c] Reported in medical history.
[d] See Table 7.2.

Table 7.4 Reference Values for Neurodiagnostic Measurements

Measure	**Reference Value[a]**
Nerve Conduction Velocity, m/sec	
Median motor	50.55
Median sensory-distal	43.15
Median sensory-proximal	54.85
Ulnar sensory	45.44
Peroneal motor	39.89
Sural sensory	36.16
Ratio of median sensory-distal to ulnar sensory	0.784
Amplitude, μV	
Median motor	4394.0
Median sensory	10.54
Ulnar sensory	8.98
Peroneal motor	2148.0
Sural sensory	4.10
Ratio of median sensory to ulnar sensory	0.571
Vibration Threshold, V	
Index finger	3.92
Great toe	10.62
Thermal Threshold, °C	
Index finger	1.92
Great toe	2.38

[a] Reference values were defined as the 5th percentile for the Vietnam and non-Vietnam veterans combined for nerve conduction velocity and amplitude measurements; for vibration and thermal thresholds the reference value was the 95th percentile in the combined cohorts.

7.2.4 Definition of Peripheral Neuropathy

No definition of peripheral neuropathy, whether based on historical information, clinical signs, or diagnostic tests, is universally accepted. In the clinical setting, a severe case of peripheral neuropathy can be easily recognized. In the context of the VES, an epidemiologic study, we needed an operational definition that could be used to analyze the prevalence of peripheral neuropathy in a large group of men, many of whom might show only minimal signs of clinical impairment. Therefore, before beginning our analysis, we developed definitions by combining elements from each segment of the examination. First, we identified those items from the history, the neurologic examination, and the special diagnostic tests that were most likely to indicate the presence of a peripheral neuropathy.

In the medical history, we identified six relevant items. Each participant was asked whether he had experienced any of the following symptoms during the past year:

1. Numbness of the arms or legs;
2. Tingling of the arms or legs;
3. Burning of the arms or legs;
4. Weakness (needed help getting out of a chair);
5. Weakness of the fingers or hands; or
6. Twitching or rippling of the muscles of the arms or legs.

If the respondent answered "yes" to any of the questions, he was also asked about the location and duration of the symptom and if he had seen a physician about the symptom.

In the neurologic examination, we identified the following relevant clinical signs:

Leg (left or right)

1. Absent ankle reflexes
2. Decreased strength
   - Foot dorsiflexors
   - Foot plantar flexors
   - Toe extensors
3. Absent pinprick sensation
   - Distal dorsal or ventral
4. Decreased or absent vibratory sensation
   - Lateral malleolus
   - Patella

Arm (left or right)

1. Decreased strength
   - Wrist extensors
   - Grip
   - Finger abductors
2. Absent pinprick sensation
   - Distal dorsal or ventral

In forming definitions of peripheral neuropathy, we used, from the neurodiagnostic tests, values outside the reference range. These values included the six from the nerve conduction tests, the five from the nerve amplitude tests, and those from the vibration and thermal sensation tests.

Using these symptoms, signs, and test results, we developed four definitions of peripheral neuropathy for use in comparing the two cohorts. We constructed these definitions to reflect increasing amounts of objective information. The definitions are—

1. Two or more symptoms from the symptom list, and the veteran must have consulted a physician for at least one of them.
   Too few clinical signs or abnormal neurodiagnostic measurements to qualify under Definition 2.
2. Symptoms as in Definition 1 and at least one of the following:
   a. Two or more clinical signs.
   b. Two or more abnormal nerve conduction velocities or amplitudes.
   c. One or more abnormal vibration thresholds or thermal thresholds.

3. Symptoms as in Definition 1 and at least two of the following:
   a. Two or more clinical signs.
   b. Two or more abnormal nerve conduction velocities or amplitudes.
   c. One or more abnormal vibration thresholds or thermal thresholds.
4. Too few symptoms to qualify under Definition 1 with at least two of the following:
   a. Two or more clinical signs.
   b. Two or more abnormal nerve conduction velocities or amplitudes.
   c. One or more abnormal vibration thresholds or thermal thresholds.

7.2.5 Audiometry

In the standardized pure-tone audiometric screening, we used one instrument, an RA400 Microprocessor Audiometer, for all participants. A test run of the instrument was conducted daily, and it was calibrated daily with an internal voltmeter. In addition, a biomechanical engineer periodically performed external calibration.

All participants were tested while seated in an audiometry booth. In most cases, the audiometer operated in the automatic mode. The left ear was always tested first, then the right. Stimulus presentations were random, in order to minimize the possibility of fraudulent responses. Hearing level was tested at the following frequencies: 500, 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 Hz. Responses were recorded in decibels (rounded to the nearest five). These responses reflect hearing level "thresholds," which are the lowest number of decibels at which a person can hear the frequency-specific acoustic signal.

Responses were grouped into three categories to reflect increasing hearing difficulty: normal or mild impairment (0-30 decibels), moderate impairment (31-50 decibels), and severe to profound impairment (≥51 decibels). To summarize cohort differences, we treated hearing loss as a dichotomous variable (≥51 decibels versus the other two response categories combined). We adopted this approach because similar results were found (regardless of how the three categories were reduced to two) when the data were analyzed by using special cumulative logit models designed for the analysis of ordinal categorical data (Agresti, 1984).

Hearing level thresholds were analyzed for each separate frequency. In addition, we defined mid-to-high-frequency hearing loss as an average hearing threshold ≥51 decibels at three combined frequencies (3,000, 4,000, and 6,000 Hz).

7.2.6 Visual Acuity

Each participant's monocular and binocular visual acuity was tested by using an OPTEC 2,000 Vision Tester medical testing model. This automated instrument permits screening of near and far vision as well as measurement of peripheral vision fields.

7.2.7 Statistical Methods

The general approach to statistical analysis for outcomes covered in this chapter is described in detail in Chapter 2. Multiple logistic regression was used for statistical modeling of dichotomous outcomes, and multiple linear regression was used for the modeling of continuous outcomes.

All neurodiagnostic measurements (nerve conduction velocities, amplitudes, and vibration and thermal thresholds) are continuous variables, so we checked the normality assumption of multiple regression for each of them. We calculated skewness and kurtosis, made various plots, and estimated the Box-Cox power transformation (Draper and Smith, 1981; Stead,

1987) to determine which transformation best satisfied the assumption of normality. Twelve of the fifteen neurodiagnostic measures required some transformation (log, square root, quadratic, or cubic) to make them normal, but the other three were approximately normally distributed. The crude results of the linear regression of the transformed variables were similar to those of the untransformed variables. Therefore, for ease of interpretation we present all results for the neurodiagnostic measurements without the variables having been transformed.

In all multivariate analyses, Model 1 included the six entry characteristics, as described in Chapter 2. For analyses of neurodiagnostic tests and peripheral neuropathy, Model 2 regression analyses included current alcohol consumption (as defined in Chapter 2) and diabetes. Diabetes was defined as a fasting serum glucose $\geq$140 mg/dL, current use of a glucose-regulating medication, current use of a diabetic diet, or a prior physician-diagnosis of diabetes.

For analysis of audiometric and visual acuity data, statistical models included covariates for preservice auditory and visual acuity, respectively. Information on the physical health of the veteran at entry into the service was recorded on Army personnel records. Two of the health categories were hearing (and ears) and visual acuity (and eyes) (U.S. Department of the Army, 1980). Each category was rated on a four-point scale, ranging from a score of 1, indicating no impairment, to a score of 4, indicating maximum impairment, which was below Army retention standards.

Because many of the measures (examination of physical signs, tests of auditory and visual acuity) reported in this chapter are bilateral, and thus correlated, special statistical techniques were occasionally used to account for this correlation. For several of these paired-data outcomes we performed multiple logistic regression analyses while accounting for the intraclass correlation between paired measurements (Connolly and Liang, in press; Rosner, 1984). With this technique, the estimate of serving in Vietnam has an odds ratio interpretation similar to that given by ordinary logistic regression, yet the estimate has the advantage of summarizing data for both measures in the pair simultaneously. In the results we indicate where we have summarized data by using this paired-data odds ratio.

7.3 RESULTS

7.3.1 Medical History

Few Vietnam (2.1%) or non-Vietnam (1.5%) veterans reported being hospitalized for neurologic conditions (including disorders of the eye and ear) since being discharged from active duty. Specific neurologic conditions of interest that were reported by at least one participant are listed in Table 7.5. Nine Vietnam and seven non-Vietnam veterans were hospitalized for mononeuritis of the upper or lower extremity. Only one, a Vietnam veteran, reported hospitalization for an inflammatory and toxic neuropathy.

There were similar proportions of Vietnam (3.4%) and non-Vietnam (2.8%) veterans who reported having surgical procedures on the nervous system since being discharged (Table 7.6). The distribution of sites of operations was also the same in the two groups. The most common procedures, those involving the spinal cord and spinal canal structures, were reported by 1.4% of the Vietnam veterans and by 1.3% of the non-Vietnam veterans.

Vietnam veterans reported having symptoms that may be related to peripheral neuropathy during the year preceding examination more frequently than did non-Vietnam veterans

Table 7.5 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Selected Neurological Hospitalizations Since Discharge

Reason for Hospitalization (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Neurasthenia (300.5)	<0.1	1	0.0	0
Physiological malfunction arising from mental factors (306)	0.1	3	0.1	1
Meningitis of unspecified cause (322)	0.2	4	0.0	0
Encephalitis, myelitis, and encephalomyelitis (323)	0.0	0	0.1	1
Intracranial and intraspinal abscess (324)	<0.1	1	0.0	0
Multiple sclerosis (340)	0.1	2	0.1	1
Hemiplegia (342)	0.0	0	0.1	1
Other paralytic syndromes (344)	0.1	3	0.1	1
Epilepsy (345)	<0.1	1	0.0	0
Facial nerve disorders (351)	<0.1	1	0.0	0
Nerve root and plexus disorders (353)	0.0	0	0.1	1
Mononeuritis of upper limb and mononeuritis multiplex (354)	0.2	6	0.3	5
Mononeuritis of lower limb (355)	0.1	3	0.1	2
Hereditary and idiopathic peripheral neuropathy (356)	0.0	0	0.1	2
Inflammatory and toxic neuropathy (357)	<0.1	1	0.0	0
Disorders of the globe (360)	<0.1	1	0.0	0
Retinal detachments and defects (361)	0.0	0	0.1	1
Other retinal disorders (362)	<0.1	1	0.0	0
Disorders of iris and ciliary body (364)	0.1	2	0.0	0
Glaucoma (365)	<0.1	1	0.0	0
Cataract (366)	<0.1	1	0.2	3
Visual disturbances (368)	0.0	0	0.1	1
Blindness and low vision (369)	0.0	0	0.1	1
Corneal opacity and other disorders of cornea (371)Disease of conjunctiva (372)	<0.1	1	0.0	0
	0.2	5	0.0	0
Strabismus and other disorders of binocular eye movements (378)	0.0	0	0.1	2
Hearing loss (389)	0.2	4	0.1	1
Syncope and collapse (780.2)	0.3	7	0.4	8
Malaise and fatigue (780.7)	0.3	8	0.2	3
Symptoms involving nervous and musculoskeletal systems (781)	0.1	2	0.1	2

(Table 7.7). Overall, 25.1% of Vietnam and 18.4% of non-Vietnam veterans had had at least one of these symptoms: numbness, tingling or burning sensations, weakness, and muscle twitching. The absolute difference between cohorts in the prevalence of each symptom was less than 5%; the largest relative difference was for the symptom twitching or rippling of muscles in the arms or legs.

Although study participants in each group commonly reported symptoms, only 4.1% of the Vietnam and 3.1% of the non-Vietnam veterans reported that they had current neurological problems. Selected problems of interest are listed in Table 7.8. The largest single category of neurological problems involved diseases of the ear, which 2.1% of Vietnam veterans and 1.3% of non-Vietnam veterans reported. Of these diseases, hearing loss was described as a current problem by nearly twice as many Vietnam veterans (1.0% versus 0.6%).

Only 1.2% of the participants in each group reported current use of neurologic medications (exclusive of central nervous system drugs such as sedatives and antipsychotics). Within this category of medications (National Drug Code Category 1300), anticonvulsants were the type most frequently reported; 0.7% of Vietnam veterans and 0.6% of non-Vietnam veterans reported current use.

Table 7.6 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Neurosurgical Procedures Since Discharge, by Site or Type of Surgery

Site or Type of Surgery (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Incision and excision of skull, brain, and cerebral meninges (01)	<0.1	1	0.1	1
Other operations on skull, brain, and cerebral meninges (02)	0.1	3	0.1	1
Spinal cord and spinal canal structures (03)	1.4	34	1.3	25
Cranial and peripheral nerves (04)	0.6	15	0.6	11
Sympathetic nerves or ganglia (05)	0.0	0	0.1	1
Eye (08-16)	0.5	13	0.5	9
Ear (18-20)	0.7	18	0.4	3
Any of above (01-05, 08-20)	3.4	84	2.8	55

7.3.2 Neurologic Physical Examination

Table 7.9 shows the prevalence of clinical signs detected during physical examination that may be related to peripheral neuropathy. The most common finding in the lower extremities was absent ankle reflexes, noted in about 11% of the veterans in each group. The next most frequent finding, detected in about 5% of participants in each group, was that of absent pinprick sensation in the distal ventral aspect of the upper extremity. All other findings were noted in less than 3% of either Vietnam or non-Vietnam veterans. The odds ratios are ≥ 1.0 for clinical signs in the lower extremity, but ≤ 1.0 for those in the upper extremity. All confidence intervals for odds ratios include 1.0, except for absent pinprick sensation in the distal dorsal aspect of the leg.

7.3.3 Neurodiagnostic Tests

There were few cohort differences in the mean values for the 15 neurodiagnostic measurements performed (Table 7.10). For the nerve conduction velocity tests, the average values for five of the six nerves tested were similar for Vietnam and non-Vietnam veterans. The Vietnam veterans' average value for the median sensory nerve (distal segment) was lower than that for non-Vietnam veterans—a statistically significant difference that persisted even after the results were adjusted for the six entry characteristics, diabetes, and alcohol consumption. The adjusted difference in mean conduction velocity for this nerve, 0.89 meters per second, was, however, small.

Table 7.7 Percent and Number of Vietnam and Non-Vietnam Veterans With Self-Reported Symptoms of Peripheral Neuropathy in Past Year

Peripheral Neuropathy Symptom	Vietnam		Non-Vietnam	
	%	No.	%	No.
Numbness of arms or legs	6.6	164	4.8	95
Tingling sensation in arms or legs	15.9	393	11.4	225
Burning sensation in arms or legs	3.7	92	3.3	64
Weakness (need help getting out of chair)	1.5	38	1.1	22
Weakness of finger or hand	4.9	122	3.8	74
Twitching or rippling of muscles in arms or legs	8.5	212	4.6	91
Any of above	25.1	626	18.4	363

Table 7.8 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Selected Current Neurological Problems[a]

	Vietnam		Non-Vietnam	
Condition (ICD9-CM Codes)	**%**	**No.**	**%**	**No.**
Physiological malfunction arising from mental factors (306)	0.2	4	0.2	3
Extrapyramidal disease and abnormal movement disorders (333)	0.1	2	0.1	1
Multiple sclerosis (340)	0.1	3	0.1	1
Other paralytic syndromes (344)	<0.1	1	0.1	1
Epilepsy (345)	0.1	3	0.2	3
Facial nerve disorders (351)	0.0	0	0.1	2
Mononeuritis of upper limb and mononeuritis multiplex (354)	0.2	4	0.4	7
Mononeuritis of lower limb (355)	0.1	3	0.1	1
Disorders of the globe (360)	<0.1	1	0.0	0
Other retinal disorders (362)	0.0	0	0.1	1
Glaucoma (365)	0.2	5	0.0	0
Cataract (366)	0.1	3	0.1	1
Visual disturbances (368)	0.3	8	0.2	3
Blindness and low vision (369)	0.4	9	0.5	9
Disease of conjunctiva (372)	0.2	5	0.0	0
Disorders of optic nerve and visual pathways (377)	<0.1	1	0.0	0
Hearing loss (389)	1.0	26	0.6	12
Syncope and collapse (780.2)	0.2	4	0.2	3
Malaise and fatigue (780.7)	0.6	14	0.5	10
Symptoms involving nervous and musculoskeletal systems (781)	0.4	11	0.4	8

[a] From medical history: conditions that the veterans would like to discuss with a physician or that were currently being treated.

The differences in unadjusted average median motor and median sensory amplitudes were small but statistically significant; however, after the results were adjusted, these differences decreased and became nonsignificant. Likewise, Vietnam and non-Vietnam veterans differed in mean index finger vibration thresholds and great toe thermal thresholds, but these differences were small, and after the results had been adjusted for diabetes and alcohol consumption, the differences were no longer statistically significant.

For all of the neurodiagnostic tests (except sural nerve sensory amplitude), the proportion of Vietnam veterans with values outside the reference ranges was higher than the proportion of non-Vietnam veterans (Table 7.11). For most, the differences were small and the 95% confidence intervals of the odds ratios included 1.0 (*i.e.*, the ORs were not statistically significant). Relative cohort differences were largest for nerve conduction velocity (OR = 1.7) and amplitude of the peroneal nerve (OR = 1.5), and after the results had been adjusted for entry characteristics, diabetes, and alcohol consumption, they were the only two statistically significant differences between cohorts.

For three of the tests—nerve conduction velocity and amplitude of the sural nerve, and great toe thermal sensation—results were analyzed by treating undetectable responses as abnormal, as well as by excluding them. Relative cohort differences were similar, regardless of the method of analysis. Furthermore, relative differences in conduction velocity of the distal median sensory nerve were unchanged when results for participants with possible carpal tunnel syndrome were reclassified as being within the reference range.

Table 7.9 **Percent and Number of Vietnam and Non-Vietnam Veterans With Abnormalities[a] of the Peripheral Nervous System Noted During Neurologic Physical Examination**

	Vietnam		Non-Vietnam			
Sign	%	No.	%	No.	OR[b]	95% CI
Leg						
Absent ankle reflex	11.2	224	10.7	173	1.0	0.9-1.2
Decreased strength						
Dorsiflexors	1.4	36	1.1	21	1.2	0.8-1.9
Plantar flexors	0.8	21	0.8	16	1.1	0.7-1.7
Toe extensors	1.5	37	1.4	27	1.1	0.7-1.6
Absent pinprick						
Distal dorsal	2.4	58	1.3	26	1.6	1.1-2.4
Distal ventral	2.7	65	2.6	51	1.1	0.8-1.4
Decreased or absent vibratory sensation						
Lateral malleolus	2.4	57	1.8	34	1.3	1.0-1.7
Patella	1.5	34	1.5	27	1.1	0.7-1.6
Arm						
Decreased strength						
Wrist extensors	0.9	22	0.9	17	1.0	0.6-1.7
Grip	0.6	16	0.9	17	0.8	0.5-1.5
Finger abductors	0.5	13	0.8	16	0.9	0.5-1.6
Absent pinprick						
Distal dorsal	2.0	48	1.9	36	1.0	0.7-1.5
Distal ventral	5.3	128	5.4	104	0.9	0.8-1.1

[a] Defined as a clinical sign on either or both sides.
[b] Paired-data ORs and 95% CIs (see Section 7.2.7 for explanation).

7.3.4 Peripheral Neuropathy

Only a small proportion of veterans in either cohort had any evidence of peripheral neuropathy (Table 7.12). More Vietnam than non-Vietnam veterans had peripheral neuropathy, regardless of how this condition was defined, but the largest absolute difference between cohorts was less than 2%, and confidence intervals for all odds ratios included 1.0. The largest relative difference between groups was for those veterans who had primarily subjective criteria (symptoms without signs) of neuropathy. Among those who met more objective criteria (asymptomatic but with two or more signs) for peripheral neuropathy, the prevalence was higher in both groups but cohort differences were less. Only about 1% of veterans (24 Vietnam and 15 non-Vietnam) in either group had both symptoms and ≥2 neurologic signs of peripheral neuropathy.

7.3.5 Auditory Acuity

At entry into the service, the Vietnam and non-Vietnam veterans had similar auditory acuity (rated on a scale from 1 to 4), according to their military personnel records. No veteran had "significant" (scale = 4) hearing impairment at induction; only two, both Vietnam veterans, had "moderate" (scale = 3) impairment; and 5.5% of Vietnam veterans and 6.7% of non-Vietnam veterans had "mild" (scale = 2) hearing impairment. The remainder had no hearing impairment (scale = 1).

At examination, Vietnam veterans had greater hearing level thresholds than non-Vietnam veterans in each ear at all frequencies tested except one (the left ear at 1,000 Hz) (Table 7.13). The results were about the same after they had been adjusted for the six entry characteristics or preservice auditory acuity. Mean hearing level thresholds, in decibels (dB),

Table 7.10 Means and Difference Between Means for Neurodiagnostic Tests of Vietnam and Non-Vietnam Veterans, by Measure

	Crude Mean		Crude Results			Multivariate Results					
						Model 1[a]			Model 2[b]		
Measure	Vietnam	Non-Vietnam	Diff	95% CI		Diff	95% CI		Diff	95% CI	
Nerve Conduction Velocity, m/sec											
Median motor	57.32	57.42	-0.10	-0.36,	0.16	-0.08	-0.35,	0.19	-0.05	-0.31,	0.22
Median sensory-distal	53.53	54.03	-0.50	-0.87,	-0.12	-0.42[c]	-0.80,	-0.03	-0.89[c]	-1.44,	-0.35
Median sensory-proximal	61.75	61.99	-0.23	-0.57,	0.10	-0.11	-0.46,	0.23	-0.05	-0.39,	0.30
Ulnar sensory	55.04	55.32	-0.28	-0.63,	0.08	-0.19	-0.55,	0.17	-0.14	-0.50,	0.22
Peroneal motor	46.28	46.48	-0.20	-0.45,	0.05	-0.12	-0.38,	0.14	-0.03[d]	-0.29,	0.23
Sural sensory	44.50	44.48	0.02	-0.33,	0.37	0.01	-0.36,	0.37	0.02	-0.35,	0.38
Amplitude, μV											
Median motor	10273.60	10503.67	-230.07	-435.85,	-24.28	-184.42	-397.57,	28.74	-176.50	-390.38,	37.39
Median sensory	23.25	23.89	-0.65	-1.16,	-0.14	-0.32	-0.85,	0.20	-0.26	-0.78,	0.27
Ulnar sensory	21.35	21.74	-0.39	-0.92,	0.14	-0.01	-0.55,	0.54	0.06	-0.48,	0.61
Peroneal motor	6824.47	6973.19	-148.72	-324.62,	27.18	-149.66	-331.75,	32.43	-145.11	-327.96,	37.73
Sural sensory	16.52	16.94	-0.42	-1.04,	0.20	-0.28	-0.92,	0.37	-0.29	-0.94,	0.36
Vibration Threshold, V											
Index finger	2.26	2.18	0.08	0.02,	0.15	0.07	0.01,	0.14	0.04[d]	-0.02,	0.11
Great toe	5.48	5.32	0.16	-0.03,	0.34	0.12	-0.07,	0.31	0.04[d]	-0.15,	0.23
Thermal Threshold, °C											
Index finger	0.84	0.81	0.02	-0.02,	0.07	0.02	-0.03,	0.06	0.01	-0.03,	0.06
Great toe	0.90	0.82	0.07	0.01,	0.14	0.07	0.00,	0.14	0.07	0.00,	0.14

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and diabetes and alcohol consumption.
[c] Standardized for age at entry.
[d] Standardized for diabetes.

Table 7.11 Percent and Number of Vietnam and Non-Vietnam Veterans With Neurodiagnostic Test Results Outside of the Reference Range and Odds Ratios, by Measure

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[a]		Model 2[b]	
Measure	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Nerve Conduction Velocity										
Median motor	5.6	139	5.3	104	1.1	0.8-1.4	1.0	0.8-1.4	1.0	0.8-1.3
Median sensory-distal	6.0	147	4.4	85	1.4	1.1-1.8	1.3	1.0-1.8	1.3	1.0-1.7
Median sensory-distal after subjects reclassified[c]	2.6	64	1.8	35	1.5	1.0-2.2	1.4	0.9-2.1	1.3	0.8-2.0
Median sensory-proximal	6.6	162	4.8	94	1.4	1.1-1.8	1.4	1.0-1.8	1.3	1.0-1.7
Ulnar sensory	5.7	141	5.4	106	1.1	0.8-1.4	1.0	0.8-1.3	1.0	0.7-1.3
Peroneal motor	6.7	164	4.0	78	1.7	1.3-2.3	1.7	1.2-2.2	1.6	1.2-2.2
Sural sensory	5.4	128	4.9	93	1.1	0.8-1.5	1.1	0.8-1.5	1.1	0.8-1.5
Sural sensory-undetectable included as abnormal	9.2	228	7.5	148	1.2	1.0-1.5	1.2	1.0-1.5	1.2	1.0-1.5
Ratio of median sensory-distal to ulnar sensory	5.4	133	4.6	90	1.2	0.9-1.6	1.1[d]	0.9-1.5	1.1[d]	0.8-1.5
Amplitude										
Median motor	4.9	122	4.6	90	1.1	0.8-1.4	1.1	0.8-1.4	1.0	0.8-1.4
Median sensory	5.5	136	4.2	83	1.3	1.0-1.7	1.2	0.9-1.6	1.2	0.9-1.6
Median sensory after subjects reclassified[c]	3.1	77	2.1	40	1.5	1.0-2.3	1.4	1.0-2.1	1.4	0.9-2.1
Ulnar sensory	5.6	138	4.9	96	1.1	0.9-1.5	1.0	0.8-1.4	1.0	0.7-1.3
Peroneal motor	5.6	137	3.8	75	1.5	1.1-2.0	1.5	1.1-2.0	1.5	1.1-2.0
Sural sensory	4.9	116	5.0	95	1.0	0.7-1.3	1.0[d]	0.7-1.3	1.0[d]	0.7-1.3
Sural sensory-undetectable included as abnormal	8.7	215	7.6	148	1.2	0.9-1.4	1.1	0.9-1.4	1.1	0.9-1.4
Ratio of median sensory to ulnar sensory	5.1	126	4.8	94	1.1	0.8-1.4	1.0	0.8-1.4	1.0	0.8-1.4
Vibration Threshold										
Index finger	5.8	144	4.8	94	1.2	0.9-1.6	1.2	0.9-1.6	1.2	0.9-1.6
Great toe	5.6	140	4.7	92	1.2	0.9-1.6	1.1	0.9-1.5	1.1	0.9-1.5
Thermal Threshold										
Index finger	5.5	136	4.7	91	1.2	0.9-1.6	1.1	0.9-1.5	1.1	0.8-1.5
Great toe	5.5	133	4.8	93	1.1	0.9-1.5	1.2	0.9-1.5	1.2	0.9-1.5
Great toe-undetectable included as abnormal	7.3	180	6.3	122	1.2	0.9-1.5	1.2	1.0-1.6	1.2	1.0-1.6

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and diabetes and alcohol consumption.
[c] Participants with a possible carpal tunnel syndrome were reclassified to be within reference range (see text for explanation).
[d] Standardized for race.

at each tone frequency are shown in Figure 7.1. The difference in mean decibel thresholds between cohorts increases at higher tone frequencies.

Vietnam veterans were more likely to have mid-to-high-frequency hearing loss than non-Vietnam veterans (Table 7.14). This loss was defined as an average hearing threshold ≥51 dB at three combined frequencies: 3,000 Hz, 4,000 Hz, and 6,000 Hz. For either ear, or both, the prevalence of hearing loss was about 40% higher among the Vietnam veterans. Adjustment for the six entry characteristics and preservice auditory acuity did not alter these findings. When bilateral hearing loss (adjusted for the six entry characteristics and preservice auditory acuity) was further evaluated by using paired-data statistical techniques, the odds ratio decreased to 1.3 (95% CI = 1.2-1.5), but was still statistically significant.

Differences between the two cohorts in hearing loss were greatest among men with a tactical military occupational specialty (MOS) (Table 7.15). Veterans with a tactical MOS (infantrymen, armored vehicle crewmen, combat engineers, and artillery crewmen) who

Table 7.12 Percent and Number of Vietnam and Non-Vietnam Veterans With Peripheral Neuropathy and Odds Ratios, by Definition of Peripheral Neuropathy

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results			
							Model 1[a]		Model 2[b]	
Definition[c]	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
≥2 Symptoms and 0 Signs	3.0	74	1.9	38	1.6	1.0-2.3	1.5	1.0-2.2	1.5	1.0-2.2
≥2 Symptoms and ≥1 Signs	2.8	69	2.5	50	1.1	0.8-1.6	1.0	0.7-1.4	1.0	0.7-1.4
≥2 Symptoms and ≥2 Signs	1.0	24	0.8	15	1.3	0.7-2.4	1.2[d]	0.6-2.3	1.1[d]	0.6-2.2
0 Symptoms and ≥2 Signs	8.2	204	6.5	128	1.3	1.0-1.6	1.2	1.0-1.6	1.2	0.9-1.5

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and diabetes and alcohol consumption.
[c] See text for exact definitions. Undetectable responses for the conduction velocity and amplitude of the sural sensory nerve and for the thermal threshold of the great toe are treated as abnormals in forming the case definitions.
[d] Standardized for age at entry.

Table 7.13 Distribution of Hearing Level Thresholds, in Decibels, Among Vietnam and Non-Vietnam Veterans and Odds Ratios[a], by Tone Frequency and Ear

		Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[b]		Multivariate Results: Model 2[c]	
Tone Frequency and Ear		%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
500 Hz	Left										
<31[d]		94.6	2355	94.7	1865	1.0	Referent	1.0	Referent	1.0	Referent
31-50		4.3	108	4.4	87						
≥51		1.0	26	0.9	17	1.2	0.7-2.2	1.1	0.6-2.2	1.2	0.6-2.3
500 Hz	Right										
<31		96.1	2394	96.7	1906	1.0	Referent	1.0	Referent	1.0	Referent
31-50		2.9	71	2.6	52						
≥51		1.0	25	0.7	14	1.4	0.7-2.7	1.3	0.7-2.6	1.4	0.7-2.7
1000 Hz	Left										
<31		97.5	2428	97.4	1921	1.0	Referent	1.0	Referent	1.0	Referent
31-50		1.9	46	1.8	36						
≥51		0.6	16	0.8	15	0.8	0.4-1.7	0.8	0.4-1.7	0.9	0.4-1.8
1000 Hz	Right										
<31		97.3	2423	98.2	1936	1.0	Referent	1.0	Referent	1.0	Referent
31-50		1.7	43	1.3	25						
≥51		1.0	24	0.6	11	1.7	0.8-3.6	1.9	0.9-4.0	2.0	0.9-4.2
2000 Hz	Left										
<31		92.3	2297	95.5	1883	1.0	Referent	1.0	Referent	1.0	Referent
31-50		5.3	131	3.3	64						
≥51		2.5	62	1.3	25	2.0	1.2-3.2	1.8[e]	1.1-3.0	2.0[e]	1.2-3.2
2000 Hz	Right										
<31		94.3	2348	96.2	1896	1.0	Referent	1.0	Referent	1.0	Referent
31-50		3.8	94	2.6	51						
≥51		1.9	48	1.3	25	1.5	0.9-2.5	1.5	0.9-2.5	1.6	1.0-2.7
3000 Hz	Left										
<31		73.7	1836	80.4	1585	1.0	Referent	1.0	Referent	1.0	Referent
31-50		14.3	356	11.4	225						
≥51		12.0	298	8.2	162	1.5	1.2-1.9	1.4[e]	1.1-1.7	1.4[e]	1.2-1.8
3000 Hz	Right										
<31		79.7	1985	84.6	1668	1.0	Referent	1.0	Referent	1.0	Referent
31-50		11.6	289	9.3	183						
≥51		8.7	216	6.1	121	1.5	1.2-1.8	1.4	1.1-1.7	1.4	1.1-1.8
4000 Hz	Left										
<31		60.0	1493	67.7	1335	1.0	Referent	1.0	Referent	1.0	Referent
31-50		20.5	510	18.0	354						
≥51		19.6	487	14.4	283	1.5	1.2-1.7	1.3	1.1-1.6	1.4[e]	1.2-1.6

Table 7.13 Distribution of Hearing Level Thresholds, in Decibels, Among Vietnam and Non-Vietnam Veterans and Odds Ratios[a], by Tone Frequency and Ear — Continued

		Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[b]		Multivariate Results: Model 2[c]	
Tone Frequency and Ear		%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
4000 Hz	Right										
<31		67.0	1668	75.3	1485	1.0	Referent	1.0	Referent	1.0	Referent
31-50		17.0	424	13.6	269						
≥51		16.0	398	11.0	218	1.5	1.3-1.8	1.4	1.2-1.7	1.5	1.2-1.8
6000 Hz	Left										
<31		47.2	1176	55.5	1095	1.0	Referent	1.0	Referent	1.0	Referent
31-50		27.1	675	24.9	491						
≥51		25.7	639	19.6	386	1.4	1.2-1.6	1.3	1.1-1.6	1.4	1.2-1.6
6000 Hz	Right										
<31		55.3	1378	63.5	1252	1.0	Referent	1.0	Referent	1.0	Referent
31-50		21.8	543	19.9	393						
≥51		22.9	569	16.5	326	1.5	1.3-1.7	1.4	1.2-1.7	1.4	1.2-1.7
8000 Hz	Left										
<31		64.4	1603	70.8	1397	1.0	Referent	1.0	Referent	1.0	Referent
31-50		17.1	426	16.1	318						
≥51		18.5	461	13.0	257	1.5	1.3-1.8	1.4	1.2-1.7	1.5	1.2-1.8
8000 Hz	Right										
<31		69.0	1717	74.2	1464	1.0	Referent	1.0	Referent	1.0	Referent
31-50		14.6	363	14.4	283						
≥51		16.5	410	11.4	225	1.5	1.3-1.8	1.4	1.2-1.7	1.5	1.2-1.8

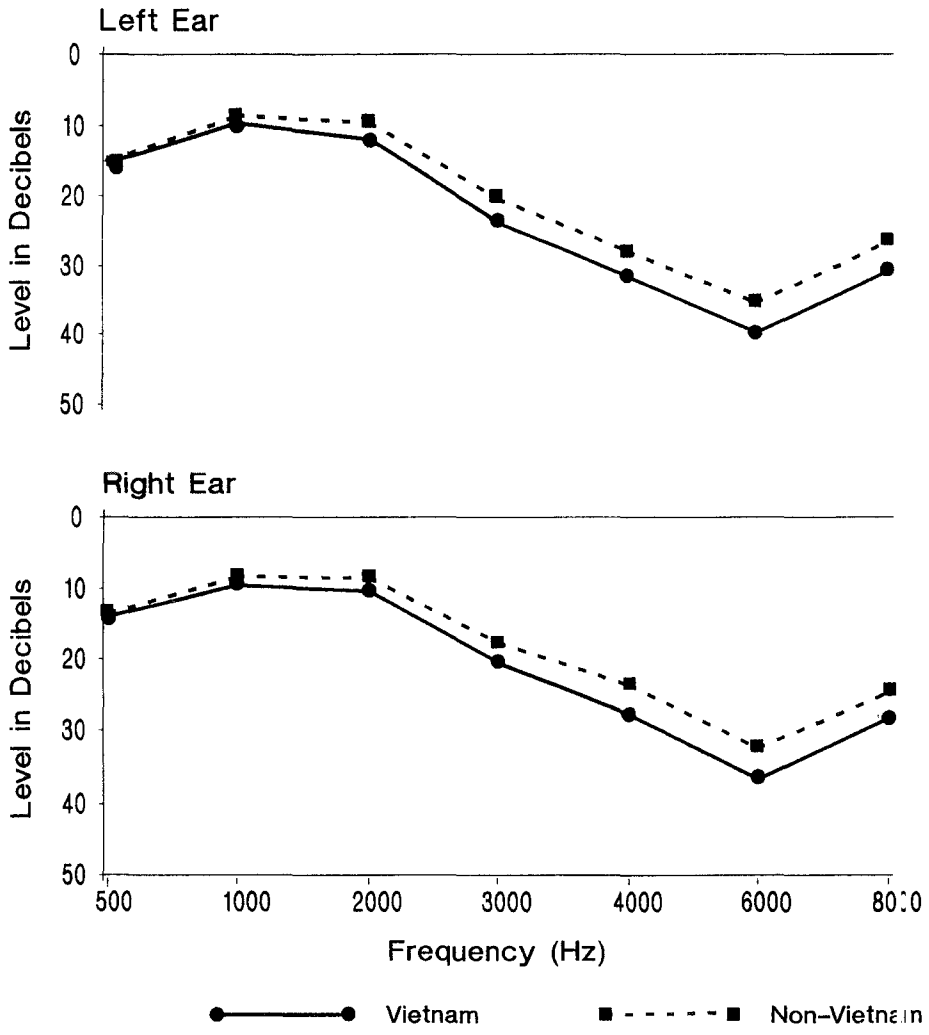
[a] Participants with thresholds <51 decibels form the referent category for computing odds ratios.
[b] Model 1 contains the six entry characteristics.
[c] Model 2 contains the six entry characteristics and preservice auditory acuity.
[d] Thresholds in decibels.
[e] Standardized for military occupational specialty.

Table 7.14 Distribution of Mid-to-High-Frequency Hearing Level Thresholds[a], in Decibels, Among Vietnam and Non-Vietnam Veterans and Odds Ratios[b], by Ear

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results			
							Model 1[c]		Model 2[d]	
Ear	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Left										
<31[e]	59.0	1469	67.0	1322	1.0	Referent	1.0	Referent	1.0	Referent
31-50	22.7		564	20.1	396					
≥51	18.4	457	12.9	254	1.5	1.3-1.8	1.4	1.2-1.6	1.4	1.2-1.7
Right										
<31	65.3	1626	74.7	1473	1.0	Referent	1.0	Referent	1.0	Referent
31-50	20.3	506	15.4	303						
≥51	14.4	358	9.9	195	1.5	1.3-1.8	1.4	1.2-1.7	1.5	1.2-1.8
Both										
≥51	9.4	235	6.2	123	1.6	1.2-2.0	1.4	1.1-1.8	1.5	1.2-1.9

[a] Average hearing level thresholds at three combined frequencies: 3000 Hz, 4000 Hz, 6000 Hz.
[b] Participants with thresholds <51 decibels form the referent category for computing odds ratios.
[c] Model 1 contains the six entry characteristics.
[d] Model 2 contains the six entry characteristics and preservice auditory acuity.
[e] Thresholds in decibels.

Figure 7.1 Mean Hearing Level Threshold by Tone Frequency and Ear



served in Vietnam were twice as likely to have mid-to-high-frequency hearing loss than veterans with a similar MOS who served elsewhere.

7.3.6 Other Examinations

Results of all items assessed during the neurologic physical examination are presented in Appendix Table G.1. Odds ratios comparing Vietnam and non-Vietnam veterans for cranial nerve findings clustered near 1.0. In the examination of the motor system, few abnormalities were found in either cohort, and odds ratios less than 1.0 were as common as odds ratios greater than 1.0. A high percentage of veterans in each cohort had abnormal reflexes, in part

Table 7.15 **Percent and Number of Vietnam and Non-Vietnam Veterans With Mid-to-High-Frequency Hearing Loss[a] and Odds Ratios, by Ear and Military Occupational Specialty[b] (MOS)**

	Vietnam		Non-Vietnam			Multivariate Results	
Ear and MOS	%	No.	%	No.	Crude OR	Model 1 OR[c]	Model 2 OR[d]
Left							
Other	17.6	289	13.2	194	1.4	1.2	1.3
Tactical	19.8	168	12.0	60	1.8	1.8	2.0
Right							
Other	13.3	218	10.0	147	1.4	1.3	1.3
Tactical	16.5	140	9.6	48	1.9	1.9	2.0

[a] Average hearing level threshold ≥51 decibels at three combined frequencies: 3000 Hz, 4000 Hz, and 6000 Hz.
[b] Categorized as tactical versus other.
[c] Model 1 contains race, age at entry, year of entry, enlistment status, and general technical test score.
[d] Model 2 contains contains race, age at entry, year of entry, enlistment status, general technical test score, and preservice auditory acuity.

because both hypoactive and hyperactive tendon reflexes, as well as absent plantar responses, were considered abnormal. The percentage was the same, however, for both cohorts.

Test results of visual acuity and peripheral vision were similar for Vietnam and non-Vietnam veterans. These results are presented in Appendix Tables G.23-24. The results were the same even after they were adjusted for entry characteristics or preservice visual acuity.

7.4 DISCUSSION

The neurologic assessment of participants in the VES was a comprehensive evaluation that included medical histories, physical examinations, and the results of specialized neurodiagnostic tests. As noted in each of the preceding chapters that presents organ-specific results, the Vietnam veterans reported having more symptoms and past medical conditions than the non-Vietnam veterans. Yet, we found few cohort differences in the results of the physical and diagnostic test examinations. There was little objective evidence to suggest that peripheral neuropathy was currently a greater problem among Vietnam veterans than among other veterans. One notable cohort difference that we did find, however, was that the prevalence of hearing loss was higher among the Vietnam veterans.

The Vietnam veterans' current auditory acuity was worse than that of the non-Vietnam veterans in both ears and at all frequencies tested. Further, those who served in Vietnam were 40% more likely to have mid-to-high-frequency hearing loss. Results were more striking when those with a tactical military occupational specialty (MOS) were considered. Vietnam veterans with a tactical MOS (infantrymen, armored vehicle crewmen, combat engineers, and artillery crewmen) were twice as likely (after the results were adjusted for entry characteristics and preservice auditory acuity) to have mid-to-high-frequency hearing loss than non-Vietnam veterans with a similar MOS. This form of hearing loss is the type that might be observed following exposure to loud noise.

This cohort difference in auditory acuity can be explained on the basis of prior military experiences. Several studies of servicemen have shown that exposure to military noise can result in irreversible hearing impairment (Brown, 1985; Man *et al.*, 1975; Walden *et al.*, 1975). The combat arms branches (infantry, armor, and artillery) all use weapons and equipment that are capable of producing extremely high noise levels. According to one investigator, the

sound pressure of a single rifle shot, measured at the level of the ear of the marksman, ranges from about 165 to 190 decibels (dB), depending upon the type of weapon (Salmivalli, 1979). For perspective, the current Occupational Safety and Health Administration standard for occupational noise exposure permits a maximum exposure level of 90 dB for 8 hours, with higher levels, up to 115 dB, allowed for 15 minutes (Office of the Federal Register, 1986).

At examination, we found little difference between the Vietnam and non-Vietnam veterans in the prevalence of peripheral neuropathy. A similar proportion of veterans (about 5%) in each group reported that since being discharged, they had been told, by a physician, that they had this condition. When the two cohorts were compared by using operational definitions of peripheral neuropathy that combined subjective (symptoms) and objective (physical examination and neurodiagnostic tests) elements from the neurological examination, the largest relative differences were mainly on the subjective measures. Relative cohort differences (odds ratios) were smaller when more objective definitions of peripheral neuropathy were used to compare Vietnam and non-Vietnam veterans. Moreover, in the adjusted analyses, we found no interaction between place of service and either diabetes or alcohol use, suggesting that Vietnam veterans who have diabetes or are heavy users of alcohol are not at higher risk of peripheral neuropathy than veterans with similar health problems who served elsewhere.

In both cohorts, the prevalence of peripheral neuropathy defined by using only signs (Definition 4) was higher than the prevalence of neuropathy as defined by using only symptoms (Definition 1). This is a function of the numbers and types of criteria used to create these operational definitions. Definition 4, which is more objective because it is based on physical examination and neurodiagnostic test results, is somewhat less restrictive because of the large number of measurements obtained. To meet the criteria for this definition, the participant needed to have too few symptoms to meet Definition 1 and only 3 of 41 (7%) test item results that were abnormal or outside the reference range from either the physical examination or the neurodiagnostic tests. In contrast, Definition 1 is more restrictive, but less objective. To qualify under this definition, the participant needed to have too few clinical signs (or abnormal neurodiagnostic test measurements) to meet any of Definitions 2 through 4, but he had to have 2 of 6 (33%) pertinent symptoms.

The operational definition under which the fewest number of participants qualified was Definition 3 ($\geq$2 symptoms and $\geq$2 signs)—the criteria for which would identify those with a severe peripheral neuropathy. Only 39 veterans in the two cohorts combined met these criteria. This finding implies that few participants had severe peripheral neuropathy.

The overall similarity between cohorts in the prevalence of peripheral neuropathy at the time of the examination has several possible explanations. First, the question of whether exposure to Agent Orange or TCDD can cause peripheral neuropathy has not been decided. Some investigators have reported slowed nerve conduction velocities and other signs of peripheral neuropathy among former chemical plant workers (Pazderova-Vejlupkova *et al.*, 1981; Singer *et al.*, 1982), but others have not found these signs (Suskind and Hertzberg, 1984). Several cases of peripheral neuropathy and other neurologic conditions have been reported, following acute exposure to 2,4-D and 2,4,5-T (Berwick, 1970; Goldstein *et al.*, 1959; O'Reilly, 1984). Some of the studies with results suggesting an association between herbicide exposure and peripheral neuropathy have important methodologic problems, such as the absence of comparison groups and the lack of an objective measure of exposure. In other studies, investigators have not found an association between phenoxy herbicide

exposure and peripheral neuropathy. In the baseline examination in the Ranch Hand Study of Air Force personnel involved in the aerial spraying of Agent Orange in Vietnam, nerve conduction velocity measurements were similar for those who had been exposed (including those who had directly handled the herbicides) and for those who had not been exposed (Lathrop *et al.*, 1984).

Alternatively, the observed similarity between Vietnam and non-Vietnam veterans may be related to the time that has elapsed since the possible exposure. Examinations were performed 10 to 20 years after the veterans had been in the Army. In that time, any peripheral neuropathies that resulted from exposures during military service may have resolved to the extent that they can no longer be detected. Such recoveries following acute exposure to phenoxyherbicides have been described in several case reports (Goldstein *et al.*, 1959; O'Reilly, 1984).

Further, the two groups of veterans may not differ because few of the study participants were heavily exposed to herbicides in the past. An objective measure of herbicide exposure, such as a serum TCDD level, was not available at the time of the Vietnam Experience Study. In a recent study of enlisted Vietnam veterans, however, we found that few Army ground troops had been heavily exposed to dioxin-containing herbicides in Vietnam or elsewhere (Centers for Disease Control Veterans Health Studies, in press).

Finally, the two cohorts could appear to be similar because the tests used in the examination of the peripheral nervous system were insensitive or incapable of detecting differences. This explanation is unlikely. The measurement of nerve conduction velocities is a standard and objective component of peripheral nerve assessment (He, 1985). Tests of nerve conduction amplitude are considered even more sensitive than those of nerve conduction velocity for detecting toxic distal axonopathies (Dyck, 1982). In addition, both the vibratory and thermal sensation tests were specifically designed to screen for early signs of peripheral neuropathy (Arezzo *et al.*, 1983; Arezzo and Schaumburg, 1980; Arezzo *et al.*, 1986).

Overall, nerve conduction velocities fell within the expected ranges of values for middle-aged American males (Kimura, 1983). When we examined the results of individual neurodiagnostic tests (including tests for nerve conduction amplitude and for vibration and thermal thresholds), we found few differences between cohorts. These differences tended to be small and did not follow any consistent pattern that would suggest that one group was at higher risk for a particular peripheral neuropathy than the other. Further, even those few differences in group means that are statistically significant after being adjusted for potential confounding factors are so small that they would have little clinical significance for an individual. The positive association between military service in Vietnam and these few individual test differences cannot be easily explained. Furthermore, the large number of tests we performed complicates our interpretation of these differences. Including so many health outcome variables increased the probability of spurious (chance) associations.

In this epidemiologic study, the possibility that biases in design or conduct may have affected the findings needs to be considered. Information or detection bias is one possible concern. Certainly, some of the increased prevalence of self-reported symptoms among Vietnam veterans could have been caused by their enhanced recall compared with that of the non-Vietnam veterans. Such bias, however, should have had little effect on the

examination findings. The examiners and study technicians did not know the participants' cohort status, nor were they permitted to take any "history" from the participants as they conducted the examinations.

The possibility that selection or participation bias has influenced the neurologic findings is another concern. Participation rates in the medical examinations were higher for the Vietnam group than for the non-Vietnam group. As noted in Chapter 3, veterans in both cohorts who reported having neuromuscular symptoms during the 4 weeks before the telephone interview were more likely to participate in the medical examinations. In both cohorts, however, this resulted in only a small increase in the prevalence of men with such symptoms among the examination participants compared with the telephone interview participants. More importantly, the increased participation by symptomatic veterans did not affect our comparison of the cohorts, since the prevalence ratios for symptoms among examined veterans were similar to those among all interviewed veterans. Thus, differences in participation between the Vietnam and non-Vietnam cohorts should not have introduced any substantial bias into our examination of relative cohort differences in current neurologic status.

The findings reported in this chapter are also not likely to be explained on the basis of confounding by other factors. The two cohorts were similar in most important characteristics—such as age, race, and certain personal habits that are known to influence health. The prevalences of diabetes (Chapter 11) and alcohol consumption (Chapter 4), two important causes of peripheral neuropathy in the U.S. population (Brown and Asbury, 1984; Juntunen, 1980), were similar for the two groups. A similar proportion (<1%) of Vietnam and non-Vietnan veterans reported current use of medications with known neurotoxic effects. In addition, in our analysis of peripheral neuropathy, we could adjust for diabetes and alcohol consumption, and, in general, our results were similar after they had been adjusted. Similarly, in our analysis of current audiometric results, we adjusted for any differences between the two cohorts in preservice auditory acuity.

Except for peripheral neuropathy and increased hearing loss, we did not expect to find other current neurologic conditions more frequently among the Vietnam veterans than among the non-Vietnam veterans, and we found few differences between the two groups. In the neurologic physical examination, findings for the two cohorts were similar. The current visual acuity of Vietnam veterans was the same as that of non-Vietnam veterans. In addition, as reported in Volume IV (Psychological and Neuropsychological Evaluation), the two groups performed comparably during neuropsychological testing. The Vietnam and non-Vietnam veterans demonstrated similar levels of concept-formation and problem-solving abilities, memory functioning, manual dexterity, verbal abilities, visual-perceptual-motor functioning, and mental control and attention.

In conclusion, for almost all conditions examined, the current neurologic status of Vietnam veterans was comparable to that of non-Vietnam veterans 10 to 20 years after their military service. However, the Vietnam veterans, particularly those who served in tactical military specialties, have greater hearing losses than veterans who served elsewhere.

REFERENCES

Agresti, A. Analysis of ordinal categorical data. New York: John Wiley and Sons, 1984;112-5,124-7.

Arezzo JC, Schaumburg HH, Landadio C. The thermal sensitivity tester: a device for quantitative assessment for thermal sense in diabetic neuropathy. Diabetes 1986;35:590-2.

Arezzo JC, Schaumburg HH, Petersen CA. Rapid screening for peripheral neuropathy: a field study with the Optacon. Neurology 1983;33:626-9.

Arezzo JC, Schaumburg HH. The use of the Optacon as a screening device. J Occup Med 1980;22:461-4

Bender DR, Mueller HG. Military noise induced hearing loss: incidence and management. Milit Med 1981;146:434-7.

Berkley MC, Magee KR. Neuropathy following exposure to a dimethylamine salt of 2,4-D. Arch Intern Med 1963;111:351-2.

Berwick P. 2,4-Dichlorophenoxyacetic acid poisoning in man: some interesting clinical and laboratory findings. JAMA 1970;214:1114-7.

Brown JR. Noise-induced hearing loss sustained during land operations in the Falkland Islands Campaign, 1982. J Soc Occup Med 1985;35:44-54.

Brown MJ, Asbury AK. Diabetic neuropathy. Ann Neurol 1984;15:2-12.

Centers for Disease Control Veterans Health Studies. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in U.S. Army Vietnam-era veterans. JAMA (in press).

Connolly M, Liang KY. Conditional logistic regression models for correlated binary data. Biometrika (in press).

Coombe, DH. The implications of the Army's audiometric screening programme, part 1 - Acoustic trauma amongst serving infantry personnel. Journal of the Royal Army Medical Corps 1980;126:18-24.

Draper NR, Smith H. Applied regression analysis. New York: John Wiley & Sons, 1981;225-36.

Dyck PJ. The causes, classification, and treatment of peripheral neuropathy. N Engl J Med 1982;307:283-6.

Filippini G, Bordo B, Crenna P, Massetto N, Musicco M, Boeri R. Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzo-dioxin. Scand J Work Environ - ealth 1981;7:257-62.

Goldstein NP, Jones PH, Brown JR. Peripheral neuropathy after exposure to an ester of dichlorophenoxyacetic acid. JAMA 1959;171:1306-9.

He F. Occupational toxic neuropathies - an update. Scand J Work Environ Health 1985;11:321-30.

Hoffman RE, Stehr-Green PA, Webb KB, *et al.* Health effects of long-term exposure to 2,3,7,8-Tetrachlorodibenzo-p-Dioxin. JAMA 1986;255:2031-8.

Jirasek L, Kalensky J, Kubec J. Acne chlorina and porphyria cutanea tarda during the manufacture of herbicides. Ceskoslovenska Dermatologie 1973;48:306-17.

Juntunen J. Alcoholic polyneuropathy. Acta Med Scand [Suppl] 1980;703:265-72.

Kimura J. Electrodiagnosis in diseases of nerve and muscle: principles and practice. Philadelphia: F. A. Davis, 1983.

Krarup C, Buchthal F. Conduction studies in peripheral nerve. Neurobehav Toxicol Teratol 1985;7:319-23.

Lathrop GD, Wolfe WH, Albanese RA, Moynahan PM. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: baseline morbidity study results. Brooks Air Force Base, TX: U.S. Air Force School of Aerospace Medicine, 1984.

Lathrop GD, Wolfe WH, Machado SG, *et al.* An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: first follow-up examination results. Brooks Air Force Base, TX: U.S. Air Force School of Aerospace Medicine, 1987.

LeQuesne PM. Toxic neuropathies. In: Asbury AK, Gilliatt RW, eds. Peripheral nerve disorders. London: Butterworths, 1984:184-204.

Man AL, Naggan L, Swet DV. Bilateral hearing loss as a sequel to unilateral acoustic trauma. Isr J Med Sci 1975;11:5-9.

Office of the Federal Register. Code of federal regulations: labor. Washington, DC: Office of the Federal Register, National Archives and Records Administration, 1986. (29 CFR 1910.95).

Oliver RM. Toxic effects of 2,3,7,8-tetrachlorodibenzo 1,4-dioxin in laboratory workers. Br J Ind Med 1975;32:49-53.

O'Reilly JF. Prolonged coma and delayed peripheral neuropathy after ingestion of phenoxyacetic acid weedkillers. Postgrad Med J 1984;60:76-7.

Pazderova-Vejlupkova J, Nemcova M, Pickova J, Jirasek L, Lukas E. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch Environ Health 1981;36:5-11.

Pocchiari F, Silano V, Zampieri A. Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. Ann NY Acad Sci 1979;320:311-20.

Poland AP, Smith D, Metter G, Possick P. A health survey of workers in a 2,4-D and 2,4,5-T plant. Arch Environ Health 1971;22:316-27.

Rosner, B. Multivariate methods in ophthalmology with application to other paired-data situations. Biometrics 1984;40:1025-35.

Salmivalli A. Military audiological aspects in noise-induced hearing losses. Acta Otolaryngol [Suppl] 1979;360:96-7.

Sare WM. The weedicide 2,4-D as a cause of headaches and diplopia. NZ Med J 1972;75:73-4.

Seabury JH. Toxicity of 2,4-dichlorophenoxyacetic acid for man and dog. Arch Environ Health 1963;7:202-9.

Singer R, Moses M, Valciukas J, Lilis R, Selikoff IJ. Nerve conduction velocity studies of workers employed in the manufacture of phenoxy herbicides. Environ Res 1982;29:297-311.

Stead AG. A macro for estimating the Box-Cox power transformation. In: Smith PH, ed. Proceedings of the Twelfth Annual SAS Users Group International Conference. Cary, NC: SAS Institute, 1987:942-6.

Suskind RR, Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 1984;251:2372-80.

Todd RL. A case of 2,4-D intoxication. J Iowa Med Soc 1962;52:663-4.

U.S. Department of the Army. Physical profiling, Chapter 9 in Medical services standards of medical fitness, Army Regulations C32, AR 40-501, 1980.

Walden BE, Prosek RA, Worthington DW. The prevalence of hearing loss within selected U.S. Army branches. Washington, D.C.: Army Audiology and Speech Center, Walter Reed Army Medical Center, 1975.

Wallis WE, Van Poznak A, Plum F. Generalized muscular stiffness, fasciculations, and myokymia of peripheral nerve origin. Arch Neurol 1970;22:430-9.

Ziv M, Leventon G, Philipsohn NC, Man A. Blast injury of the ear: treatment and evaluation. Milit Med 1973;138:811-3.

CHAPTER 8

Immunologic System and Infectious Diseases

8. IMMUNOLOGIC SYSTEM AND INFECTIOUS DISEASES

8.1 INTRODUCTION

In this chapter we summarize the results of laboratory assays associated with the immune system and describe the infectious conditions reported by Vietnam and other veterans. During their military service, many Vietnam veterans were exposed to combat, stress, and infectious diseases. Some may have been exposed to Agent Orange and its contaminant 2,4,7,8-tetrachlorodibenzo-p-dioxin (TCDD), to other herbicides, and to drugs, both prescribed and not prescribed. Moreover, participation in the medical examinations could have been more stressful to Vietnam veterans than to other veterans. Each of these experiences might, conceivably, have affected the immune system.

Before beginning our analyses, we postulated that certain conditions would be more prevalent among Vietnam veterans than among non-Vietnam veterans. We chose these conditions after reviewing published reports on the potential health effects of military service in Vietnam and of exposure to phenoxyherbicides or dioxin. We hypothesized that the Vietnam veterans might be at increased risk for having (1) immunosuppression (both humoral and cell-mediated); (2) enhanced susceptibility to infections; and (3) a more frequent history of certain infectious diseases, such as dengue, melioidosis, malaria, dermatophytoses, hepatitis B, and tuberculosis.

A normal immune response involves both nonspecific and specific mechanisms (Katz, 1985). The nonspecific responses are directed against many organisms, do not require prior sensitization, and are carried out by mononuclear phagocytes, polymorphonuclear neutrophils, and the complement system (Katz, 1985; Stites *et al.*, 1987). The white blood cell count, the differential, and blood smear morphology may indicate abnormalities in nonspecific responses. Acquired defects in nonspecific responses may be seen in persons with diabetes, alcoholism, renal disease, and connective tissue diseases.

The specific responses are directed against specific antigens and display memory. Two limbs of this specific response system have been delineated; they are the humoral system and the cell-mediated system. Defects in the humoral system may be screened for by measuring levels of immunoglobulins IgG, IgM, IgA and, perhaps, IgD and IgE (Katz, 1985). The humoral system may be further evaluated by measuring absolute B-cell levels in peripheral blood or in lymph nodes, serum antibody titers to specific antigens (such as diphtheria, for which the person has been vaccinated), and cellular functions, such as proliferation and antibody production *in vitro*.

The cell-mediated system involves a large number of cells, including T cells, T-cell products, antigen-presenting cells, and K (killer) cells. Defects in cell-mediated immunity may be manifested by abnormal test results or by the occurrence of certain medical conditions. Laboratory assays may reveal abnormalities in the number of lymphocytes or T lymphocytes or in delayed cutaneous hypersensitivity. Other tests that may reveal abnormalities in the cell-mediated immune system are those in which the following are evaluated: (1) T-cell subsets such as T4 (helper/inducer) and T8 (cytotoxic/suppressor), (2) proliferative responses to mitogen or specific antigens, (3) lymphokine production, and (4) cytotoxic T-lymphocyte activity (Katz, 1985; Miller, 1985; Vos, 1981). In addition, a person's medical history may suggest disseminated viral or fungal infections (Lawton and Cooper, 1983).

Results of previous studies have suggested that exposure to TCDD may suppress the immune system. In animals, exposure to TCDD has caused: thymic atrophy, especially if the

exposure occurs during ontogenesis of the immune system; lymph node atrophy; bone marrow hypocellularity; and increased susceptibility to salmonella and listeria infections (Dean and Lauer, 1984; Thigpen *et al.*, 1975). Reported effects of TCDD on humoral immunity in animals include reductions in specific antibody titers and in the number of plaque-forming cells produced after a challenge with antigen (Dean and Lauer, 1984). Reported effects on cell-mediated immunity in animals include decreased graft rejection, anergy, reduced T-cell cytotoxicity, and reduced blastogenesis following stimulation with phytohemagglutinin, concanavalin A, or lipopolysaccharide (Clark *et al.*, 1983; Dean and Lauer, 1984; Faith and Moore, 1977; Veterans Administration, 1984). Immunologic measures generally seem to return to or towards normal with time. Few data are available on the immunological effects of the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the two components of Agent Orange (Veterans Administration, 1981, 1984, 1985).

Few studies of the effects of TCDD on the human immune system have been done, but the sparse data available suggest that exposure to TCDD may produce immunologic effects, presumably immunosuppression, and that these effects may occur in the absence of chloracne (Falk *et al.*, 1984; Hoffman *et al.*, 1986; Veterans Administration, 1985). In studies of Air Force veterans involved in spraying Agent Orange in Vietnam, researchers have not found significant evidence of immunosuppression among exposed men, although the measures have not been correlated with TCDD levels (Lathrop *et al.*, 1984, 1987). Thus, data for humans are sparse and provide little information about possible associations, such as those found in animal studies, between exposure to TCDD and immunosuppression.

Psychological factors, such as stress, are known to affect the immune system, which implies that exposure to combat and other aspects of the Vietnam experience could have affected the immune system (Glaser *et al.*, 1985; Schleifer *et al.*, 1983; Tecoma and Huey, 1985). In addition, the acute stress associated with participating in the medical examinations could have influenced the results of several of the immmunologic assays performed.

Many infectious diseases are more common in Vietnam than in other areas. These diseases include tuberculosis, malaria, dengue, hepatitis B, dermatophytoses, and melioidosis (Dashefsky and Teele, 1983; Greenberg, 1969; Ognibene and Barrett, 1982; Shaefer *et al.*, 1983), which may affect the immune system (Rouse and Horohov, 1986; Stites *et al.*, 1987; Weidanz, 1982). Details on dermatologic conditions and results of hepatitis B serologic tests are in Chapters 5 and 6, respectively, and details on tuberculosis are in Chapter 10.

8.2 METHODS

The information in this chapter is from three sources: (1) self-reported medical histories; (2) general physical examinations; and (3) laboratory assays. During the study, the interviewers, physicians, and laboratory technicians did not know which cohort the participants were in.

8.2.1 Medical History and Physical Examination

Physician's assistants administered standardized medical history questionnaires and board-certified internists conducted physical examinations (see Chapter 2), including examination of lymph nodes.

8.2.2 Laboratory Tests

Laboratory studies, conducted by personnel at Lovelace Medical Foundation, included: serum immunoglobulins IgA, IgM, and IgG; relative and absolute T-, B-, T4- and T8-lymphocyte counts; and an intradermal skin test for anergy (CMI Multitest). Absolute T, B, T4, and T8 counts, but not relative counts, are reported here. Results of the white blood cell count, differential cell count, and leukocyte morphology are reported in Chapter 12. Results for the corresponding relative (percentage) counts are reported in Appendix D.

All laboratory procedures are described in detail in Supplement A (Laboratory Methods and Quality Control) of the monograph. Lymphocyte subpopulations were characterized in the following manner. Peripheral blood mononuclear cells were stained with fluorescein-tagged monoclonal antibodies, and the percentages of mononuclear cells that were fluorescent were determined by analysis in a flow cytometer. Antibodies used were OKT3 for T lymphocytes, OKT4A for T4 lymphocytes (helper/inducer subset), OKT8 for T8 lymphocytes (cytotoxic/suppressor subset), and CCB1 for B lymphocytes (Kung *et al.*, 1979; Patrick *et al.*, 1984; Terhorst *et al.*, 1980). Absolute counts were calculated from the proportion of mononuclear cells in a given subset (*e.g.*, relative T4 count) and the total lymphocytes per milliliter of blood, as determined by microscopic differential counts performed on whole blood smears. Immunoglobulin levels were measured by nephelometry after an immunoprecipitin reaction using anti-IgG, anti-IgA, or anti-IgM antibodies.

Laboratory tests were monitored by using bench and "blind" repeat quality control procedures, as described in Chapter 2. Judged on the basis of specified quality control criteria, all assays remained in control throughout the study period; bench control data for each test are in Supplement A. For blind repeat controls, veterans were randomly selected throughout the study period, and assays on the selected men were repeated "blindly". Results, summarized in Supplement B (Medical and Psychological Data Quality) generally show good correlation between the initial and repeat assays, indicating the reliability of the assay procedures.

The absence of delayed cutaneous hypersensitivity, or anergy, was assessed with the CMI Multitest, which consists of an applicator preloaded with seven antigens (tetanus, diphtheria, streptococcus group C, old tuberculin, *Candida albicans*, trichophyton, *Proteus mirabilis*) and a glycerine control (Clark *et al.*, 1983; Kniker *et al.*, 1984). Trained technicians applied the antigens to each participant's volar forearm. Trained readers recorded the induration (in millimeters), at 48 hours, for each antigen. Study participants were classified as anergic if their reaction to each antigen was <2 millimeters.

For the CMI skin test, reliability may not have been as high as for the laboratory assays. Since anergy, the endpoint used here, is uncommon, interpretation of blind repeat results is difficult. Overall, the intraclass correlation between the first and the blind repeat readings was high (see Supplement B). However, none of the three veterans whose first readings indicated anergy and who had a blind repeat reading was anergic when the test was read again. Moreover, the correlation between total induration on the first reading and that on the blind repeat reading was relatively low (Supplement B), suggesting interreader variability. Therefore, we adjusted some analyses of skin test results for the technician (reader) factor, so that differences, if any, in the distribution of readers between the Vietnam and non-Vietnam cohorts should not confound the results. Nevertheless, results of the skin tests are to be interpreted cautiously, in part because the potential intrareader variability suggests imprecision.

We also measured melioidosis titers. The titers, however, varied substantially by technician; one technician reported 34% abnormal titers (among both Vietnam and other veterans) and another technician reported <1%. The titers also varied substantially from month to month (Supplement B). Moreover, when the melioidosis titers for 183 frozen serum samples were "blindly" measured again at a CDC laboratory, the agreement between the first and second titer was poor. Therefore, results for melioidosis titers are not reported.

8.2.3 Statistical Methods

Analyses of data related to the immune system are similar to those described in Chapter 2. We established reference ranges for each assay according to the 5th and the 95th percentiles of the combined group of Vietnam and non-Vietnam veterans (Table 8.1).

Multivariate modeling included the six entry characteristics (Model 1). In Model 2 analyses we used three covariates (defined in Chapter 2) as potential confounders and effect modifiers: cigarette smoking status, current alcohol consumption, and marital status. In some analyses, we considered additional covariates, but we did not use them in the final models because they did not confound or modify effects to any marked extent; these additional covariates included a history of diabetes, a history of malaria and other infectious diseases (for analyses of some laboratory assays), and anxiety or post-traumatic stress disorder (diagnosed during the past year, as indicated by results of the Diagnostic Interview Schedule). For linear regression analyses, we used a logarithmic transformation because the transformation yielded distributions that were more nearly Gaussian. Confidence intervals are approximate, since sample sizes were moderate and statistical assumptions of normality that underlie the linear regression results were only approximated.

8.3 RESULTS

8.3.1 Medical History and Physical Examination

Except for malaria, the frequency with which Vietnam veterans reported a history of each physician-diagnosed infectious disease was similar to that for non-Vietnam veterans (Table 8.2). A slightly greater proportion of Vietnam veterans reported a history of adenopathy (swollen lymph glands) during the year preceding the examination. On the other hand, the proportion of Vietnam (2.4%) and non-Vietnam (2.7%) veterans found to have adenopathy at the time of the physical examination was almost identical. The two groups of veterans also reported allergies with similar frequency (Table 8.3).

Except for malaria, results suggest little difference between Vietnam and other veterans in postservice hospitalizations for infectious diseases. Both groups infrequently reported these

Table 8.1 Reference Ranges for Assays Associated With the Immune System

Assay	5th Percentile	95th Percentile
Serum Immunoglobulin Levels, mg/dL		
IgG	734.20	1610.00
IgM	56.00	256.00
IgA	95.00	410.00
Lymphocyte Subset Populations, 10^3 cells/mm^3		
T-cell count	0.85	2.48
B-cell count	0.10	0.54
T4-cell count	0.56	1.74
T8-cell count	0.28	1.07
T4/T8 ratio	0.99	3.30

Table 8.2 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Physician-Diagnosed Infectious Conditions and Symptoms Since Discharge

	Vietnam		Non-Vietnam	
	%	No.	%	No.
Physician-Diagnosed Condition				
Pneumonia	8.0	198	7.1	140
Infectious mononucleosis	1.2	30	1.4	26
Meningitis	0.2	6	0.2	3
Urinary tract infection	10.0	250	9.9	195
Gonorrhea	7.2	179	6.4	127
Genital herpes	1.3	33	1.9	37
Syphilis	0.5	12	0.6	12
Melioidosis	0.1	2	0.1	1
Malaria	0.7	17	0.1	1
Tuberculosis	0.1	2	0.2	4
Symptom				
Enlarged lymph nodes in past year	2.2	56	1.5	30
Current "cold"	12.0	298	12.1	238
Any Condition or Symptom	32.3	805	32.9	648

Table 8.3 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Physician-Diagnosed Allergies, by Type of Allergy

	Vietnam		Non-Vietnam	
Allergy	%	No.	%	No.
Medication	6.7	167	7.9	156
Food	1.9	47	2.6	52
Pollen	8.1	201	10.0	197
Mold	1.7	42	1.8	35
Pets	1.8	46	2.5	50
Dust	3.6	89	4.1	81

diseases as reasons for postservice hospitalization (Table 8.4). Overall, however, Vietnam veterans, partly because of their more frequent hospitalizations for malaria (12 versus 0 non-Vietnam veterans), were slightly more likely to report an infectious disease as a reason for hospitalization. The histories of hospitalizations for infectious diseases with International Classification of Diseases (ICD) codes other than 001-139 are described elsewhere: dermatologic conditions (Chapter 5), pneumonia and influenza (Chapter 10), and urinary tract infections (Chapter 12).

Other indicators of health at the time of the examination were also similar for the two groups. Less than 2% of veterans in either cohort reported having current infectious or immunologic conditions (Table 8.5). For both groups, specific conditions were rare, and the groups reported them with equal frequency. The proportion of veterans who reported taking an antibiotic medication at the time of the examination was the same for the two groups, 1.4% (Table 8.6). Fewer than 1% of veterans in either group reported taking antineoplastic or antiparasitic medications, reproductive hormones, or corticosteroids.

8.3.2 Laboratory Tests

On the basis of a comparison of geometric means, the immune status of Vietnam veterans was similar to that of other Veterans (Table 8.7). After entry characteristics were controlled for, geometric means for the Vietnam veterans' assays were similar to those for other veterans, differing by a maximum of only 1.6%.

Table 8.4 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Post-Discharge Hospitalizations for Infectious or Immunologic Conditions

Condition (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Any Infectious Disease (001-139)	2.2	54	1.7	33
Intestinal Infection (001-009)	0.2	4	0.4	8
Tuberculosis (010-018)	<0.1	1	0.0	0
Zoonotic Bacterial Disease (020-027)	0.0	0	0.0	0
Melioidosis (025)	0.0	0	0.0	0
Other Bacterial Disease (030-041,100-104)	0.3	7	0.3	5
Viral Disease (045-079)	1.0	24	0.8	16
Rickettsia and Malaria (080-088)	0.5	13	0.1	1
Malaria (084)	0.5	12	0.0	0
Venereal Disease (090-099)	0.0	0	0.0	0
Mycoses (110-118)	<0.1	1	0.1	2
Helminthiases (120-129)	<0.1	1	0.1	1
Other Infectious Conditions (130-139)	0.1	3	0.0	0
Immunologic Disorders (279)	0.0	0	0.0	0

For most of the immunologic assays, the proportion of Vietnam veterans with assay values above the reference range was similar to the corresponding proportion of non-Vietnam veterans (Table 8.8). The proportion of Vietnam veterans with T4-lymphocyte counts above the reference range was moderately greater than the corresponding proportion of non-Vietnam veterans (OR=1.5). However, controlling for entry characteristics reduced the difference (OR=1.4) and the lower confidence limit for the adjusted estimate was 1.0. Vietnam veterans with serologic evidence of prior hepatitis B infection (as evidenced by their having antibodies to hepatitis B surface or core antigens) were substantially more likely than the corresponding non-Vietnam veterans to have T4-lymphocyte counts above the reference range (OR=3.5). On the other hand, once veterans with evidence of hepatitis B infection were excluded, Vietnam and other veterans were about equally likely to have a T4-lymphocyte count above the reference range (OR=1.1). For other assays, after the entry characteristics, smoking status, alcohol consumption, and marital status were controlled for, the proportion of Vietnam veterans with assay values above the reference range was similar to the corresponding proportion of other veterans (Table 8.8).

Table 8.5 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Infectious or Immunologic Conditions[a]

Condition (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Any Infectious Disease (001-139)	1.7	42	1.6	32
Intestinal Infection (001-009)	<0.1	1	0.0	0
Tuberculosis (010-018)	<0.1	1	0.0	0
Zoonotic Bacterial Disease (020-027)	0.0	0	0.0	0
Melioidosis (025)	0.0	0	0.0	0
Other Bacterial Disease (030-041,100-104)	<0.1	1	0.0	0
Viral Disease (045-079)	0.6	16	0.7	14
Rickettsia and Malaria (080-088)	0.1	3	0.0	0
Malaria (084)	0.1	2	0.0	0
Venereal Disease (090-099)	<0.1	1	0.0	0
Mycoses (110-118)	0.8	19	0.8	15
Helminthiases (120-129)	0.0	0	0.0	0
Other Infectious Conditions (130-139)	0.1	3	0.2	3
Immunologic Disorders (279)	0.0	0	0.0	0

[a] From medical history: conditions that the veteran would like to discuss with a physician or that were currently being treated.

Table 8.6 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Use of Selected Medications, by Type of Medication

Medication	Vietnam		Non-Vietnam	
	%	No.	%	No.
Corticosteroids	0.8	21	0.6	11
Antibiotics	1.4	35	1.4	27
Antineoplastics	0.2	5	0.0	0
Antiparasitics	0.0	0	0.1	2
Reproductive hormones	<0.1	1	0.1	2

The proportion of Vietnam veterans with assay results below the reference range was similar to the corresponding proportion of non-Vietnam veterans (Table 8.9). In most analyses, the statistically most important covariate was smoking history. Similar to the findings in the Ranch Hand study (Lathrop *et al.*, 1987), smokers tended to have higher T-, T4-, and T8-lymphocyte counts than nonsmokers. The proportion of Vietnam veterans with anergy was slightly smaller than the corresponding proportion of non-Vietnam veterans, but confidence limits included unity. More detailed laboratory results are given in Appendix D.

8.4 DISCUSSION

Before we did the study, we suspected that Vietnam veterans were at greater risk of selected infectious diseases (Greenberg, 1969; Ognibene and Barrett, 1982). As we noted in Volume II (Telephone Interview), many of these *a priori* hypotheses were confirmed for infectious diseases that were diagnosed before discharge. However, Vietnam veterans reported postdischarge infectious diseases with a frequency similar to that of other veterans. Vietnam veterans reported hospitalizations since discharge for all infectious conditions combined slightly more often than other veterans, but less than 3% in either group reported being hospitalized, and the absolute difference between cohorts was <1%. Most of the excess reflected more frequent hospitalizations for malaria, a disease to which Vietnam veterans were more frequently exposed than other veterans. As shown in Appendix Table A.2, Vietnam veterans also more frequently reported having skin boils in the year preceding the examination. The proportion of Vietnam veterans who reported an infectious illness as a

Table 8.7 Means and Percent Differences Between Means for Immunologic Assays for Vietnam and Non-Vietnam Veterans

Assay	Crude Geometric Mean		Crude Results		Multivariate Results: Model 1[a]		Multivariate Results: Model 2[b]	
	Vietnam	Non-Vietnam	% Diff	95% CI	% Diff	95% CI	% Diff	95% CI
Serum Immunoglobulin Levels, mg/dL								
IgG	1077.9	1077.2	0.1	-1.4, 1.5	0.0	-1.3, 1.4	0.1	-1.3, 1.4
IgM	120.9	121.3	-0.3	-3.0, 2.5	-0.6	-3.4, 2.2	-0.7	-3.4, 2.2
IgA	206.8	202.6	2.1	-0.8, 5.1	1.2	-1.7, 4.3	1.1	-1.9, 4.1
Lymphocyte Subset Populations, 10^3 cells/mm^3								
T-cell count	1.5	1.5	1.7	-0.3, 3.7	0.5	-1.5, 2.6	0.4	-1.5, 2.3
B-cell count	0.2	0.2	2.9	-0.2, 6.1	1.6	-1.6, 4.8	1.7	-1.3, 4.9
T4-cell (helper/inducer) count	1.0	1.0	2.2	0.2, 4.4	1.0	-1.1, 3.2	0.8	-1.2, 2.8
T8-cell (cytotoxic/suppressor) count	0.6	0.6	0.9	-1.4, 3.4	0.1	-2.4, 2.6	0.1	-2.3, 2.5
T4/T8 ratio	1.8	1.8	1.2	-1.0, 3.4	0.8	-1.4, 3.1	0.6	-1.6, 2.9

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and smoking status, alcohol consumption, and marital status.

Table 8.8 Percent and Number of Vietnam and Non-Vietnam Veterans With Immunologic Assay Results That Are Above Reference Range[a], and Odds Ratios

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[b]		Model 2[c]	
Assay	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Serum Immunoglobulin Levels										
IgG	4.8	120	5.1	101	0.9	0.7-1.2	1.0	0.7-1.4	0.9	0.7-1.3
IgM	4.6	115	5.1	101	0.9	0.7-1.2	0.9	0.7-1.2	0.9	0.8-1.1
IgA	5.0	125	4.8	94	1.1	0.8-1.4	1.0[d]	0.8-1.4	1.0[d]	0.8-1.3
Lymphocyte Subset Populations										
T-cell count	5.2	129	4.7	92	1.1	0.8-1.5	1.1[e]	0.8-1.5	1.1[e]	0.8-1.5
B-cell count	5.2	130	4.1	80	1.3	1.0-1.7	1.2	0.9-1.7	1.3	0.8-1.7
T4-cell (helper/inducer) count	5.5	138	3.9	76	1.5	1.1-2.0	1.4	1.0-1.9	1.4	1.0-1.9
T8-cell (cytotoxic/suppressor) count	4.5	111	5.3	104	0.8	0.6-1.1	0.9	0.6-1.2	0.9	0.7-1.2
T4/T8 ratio	5.1	128	4.7	92	1.1	0.8-1.5	1.1	0.8-1.4	1.1	0.8-1.4

[a] Defined as values above the 95th percentile for both cohorts combined. See Table 8.1 for specific values.
[b] Model 1 contains the six entry characteristics.
[c] Model 2 contains the six entry characteristics and smoking status, alcohol consumption, and marital status.
[d] Standardized for military occupational specialty.
[e] Standardized for type of enlistment.

current health problem was, however, almost identical to the corresponding proportion of non-Vietnam veterans. This striking similarity suggests that Vietnam veterans are no more susceptible to infections than other veterans.

Before the study, we were particularly concerned that Vietnam veterans would report having had melioidosis more frequently than other veterans, because one group of investigators had found that melioidosis titers ≥1:40 were about three times more prevalent

Table 8.9 Percent and Number of Vietnam and Non-Vietnam Veterans With Immunologic Findings That Are Below Reference Range[a] or Abnormal, and Odds Ratios

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[b]		Model 2[c]	
Finding	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Serum Immunoglobulin Levels										
IgG	5.0	125	5.0	98	1.0	0.8-1.3	1.0	0.8-1.4	1.0	0.8-1.4
IgM	4.7	117	4.7	93	1.0	0.8-1.3	1.0	0.8-1.4	1.0	0.8-1.4
IgA	4.4	109	5.6	111	0.8	0.6-1.0	0.8	0.6-1.1	0.8	0.6-1.1
Lymphocyte Subset Populations										
T-cell count	4.8	120	5.1	101	0.9	0.7-1.2	1.0	0.8-1.3	1.0	0.8-1.4
B-cell count	4.4	109	4.2	83	1.0	0.8-1.4	1.1	0.8-1.5	1.1	0.8-1.5
T4-cell (helper/inducer) count	4.5	111	5.0	99	0.9	0.7-1.2	1.0	0.7-1.3	1.0	0.7-1.3
T8-cell (cytotoxic/suppressor) count	4.2	105	4.4	87	1.0	0.7-1.3	1.0	0.8-1.4	1.0	0.7-1.4
T4/T8 ratio	4.7	117	5.3	105	0.9	0.7-1.1	0.9	0.7-1.2	0.9[d]	0.7-1.2
Anergy[e]	3.5	88	3.9	76	0.9	0.7-1.2	1.0	0.7-1.4	1.0	0.7-1.4
Adenopathy, Physical Exam	2.4	60	2.7	53	0.9	0.6-1.3	0.9[f]	0.6-1.3	0.9	0.6-1.3
Positive Rapid Plasma Reagin (Syphilis)	0.5	13	0.9	18	0.6	0.3-1.2	0.6	0.3-1.3	—	--

[a] Defined as values for immunoglobulin levels or lymphocyte subset populations below the 5th percentile for both cohorts combined. See Table 8.1 for specific values.
[b] Model 1 contains the six entry characteristics.
[c] Model 2 contains the six entry characteristics and smoking status, alcohol consumption, and marital status.
[d] Standardized for cigarette smoking.
[e] <2-mm response to all seven recall antigens in the CMI test.
[f] Standardized for type of enlistment.

among Vietnam veterans than among other veterans (Clayton *et al.*, 1973). We did not analyze our melioidosis titers because of their documented lack of validity; results from the medical history were, however, reassuring in that none of the veterans reported having been hospitalized for melioidosis. Moreover, veterans in both groups rarely reported other possible manifestations of recrudescent melioidosis that might not have been correctly recognized as melioidosis, such as osteomyelitis or septicemia. Thus, although under certain clinical circumstances a high index of suspicion for the diagnosis of melioidosis may be warranted among those who lived in endemic areas (Shaefer *et al.*, 1983), our results suggest that recrudescent melioidosis has rarely occurred among Vietnam veterans.

Consistent with findings from the medical history, results from the immunologic assays for Vietnam veterans did not differ substantially from the results for non-Vietnam veterans. The results suggest that the proportion of Vietnam veterans with T4-lymphocyte counts above the reference range might be slightly higher than the corresponding proportion of non-Vietnam veterans, although the lower confidence limit was 1.0. Results of additional analyses, however, suggest that differences, if any, are restricted to the subgroup of veterans with serologic evidence of prior hepatitis B infection. The importance of the subgroup difference between Vietnam and other veterans in the prevalence of T4-lymphocyte counts above the reference range is unclear. The difference in T4 counts may reflect chance, a physiologic response to an infection associated with a hepatitis B risk factor (such as intravenous drug use), coinfection, or a response to some other immunologic challenge that occurred among those with hepatitis B infection.

Since even before the study began, we were concerned that possible exposure to dioxin and stress in Vietnam might suppress the immune system, and we were reassured to find no evidence of increased anergy, lymphocytopenia, increased numbers of suppressor T cells (T8 lymphocytes), or reduced immunoglobulin levels among the Vietnam veterans. There are, of course, assays of the immune system other than those we used. Nevertheless, the results of the tests we did use do not support the view that Vietnam veterans are more likely to be immunosuppressed than non-Vietnam veterans. The absence of immunosuppression is consistent with recent results which suggest that most veterans did not receive heavy exposure to dioxin in Vietnam (Centers for Disease Control Veterans Health Study, in press).

The possibility that biases in the design or carrying out of the study may have affected our findings needs to be considered. In Chapters 3 and 5, we discussed the possibility of selection bias and confounding, and concluded that these potential biases were probably not of major importance in this study. Information bias, also discussed in Chapter 5, may have affected results from the medical history and have produced the generally minor differences found. On the other hand, information bias should have been small for the laboratory assays, since the technicians did not know the cohort status of the veterans and since results of the "blind" repeat tests and the tests with the quality control standards suggest that reliability and validity were good.

In summary, with a few exceptions such as malaria, Vietnam and other veterans had similar histories of infectious diseases since discharge. Our results do not suggest that Vietnam veterans are at more risk for infections or immunosuppression than other veterans, as might be expected if exposure to dioxin, stress, or some other aspect of the Vietnam experience were affecting their immune system.

REFERENCES

Centers for Disease Control Veterans Health Study. Serum 2,3,7,8-tetrachlorodibenzo-para-dioxin levels in U.S. Army Vietnam-era Veterans. JAMA (in press).

Clark DA, Sweeney G, Safe S, Hancock E, Kilburn DG, Gauldie J. Cellular and genetic basis for suppression of cytotoxic T cell generation by haloaromatic hydrocarbons. Immunopharmacology 1983;6:143-53.

Clayton AJ, Lisella RS, Martin DG. Meloidosis: a serologic survey in military personnel. Milit Med 1973;138:24-6.

Dashefsky B, Teele DW. Infectious disease problems in Indochinese refugees. Pediatr Ann 1983;12:232-44.

Dean JH, Lauer LD. Immunological effects following exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin: a review. In: Lowrance WW, ed. Public health risks of the dioxins. Los Altos, CA: William Kaufmann, 1984:275-94.

Faith RE, Moore JA. Impairment of thymus-dependent immune functions by exposure of the developing immune system to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J Toxicol Environ Health 1977;3:451-65.

Falk H, Stehr PA, Stein GF, *et al.* A pilot epidemiologic study of health effects of 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) contamination in Missouri. In: Poland A, Kimbrough RD, eds. Banbury report 18: Biological mechanisms of dioxin action. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1984:447-60.

Glaser R, Kiecolt-Glaser JK, Stout JC, Tarr KL, Speicher CE, Holliday JE. Stress-related impairments in cellular immunity. Psychiatry Res 1985;16:233-9.

Greenberg JH. Public health problems relating to the Vietnam returnee. JAMA 1969;207:697-702.

Hoffman RE, Stehr-Green PA, Webb KB, *et al.* Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 1986;255:2031-8.

Katz P. Clinical and laboratory evaluation of the immune system. Med Clin North Am 1985;69:453-64.

Kniker WT, Anderson CT, McBryde JL, Roumiantzeff M, Lesourd B. Multitest CMI for standardized measurement of delayed cutaneous hypersensitivity and cell-mediated immunity. Normal values and proposed scoring system for healthy adults in the U.S.A. Ann Allergy 1984;52:75-82.

Kung PC, Goldstein G, Reinherz EL, Schlossman SF. Monoclonal antibodies defining distinctive human T-cell surface antigens. Science 1979;206:347-9.

Lathrop GD, Wolfe WH, Albanese RA, Moynahan PM. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: baseline morbidity results. Brooks Air Force Base, Texas: U.S. Air Force School of Aerospace Medicine, 1984.

Lathrop GD, Wolfe WH, Machado ST, *et al.* An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: first followup examination results. Brooks Air Force Base, Texas: U.S. Air Force School of Aerospace Medicine, 1987.

Lawton AR III, Cooper MD. Immune deficiency diseases. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. Harrison's principles of internal medicine. 10th ed. New York: McGraw-Hill, 1983:354-62.

Miller K. Immunotoxicology. Clin Exp Immunol 1985;61:219-23.

Ognibene AJ, Barrett O Jr, eds. General medicine and infectious diseases (vol II): Internal medicine in Vietnam. Washington, D.C.: United States Army, Office of the Surgeon General and Center of Military History, 1982.

Patrick CW, Swartz SJ, Harrison KA, Keller RH. Collection and preparation of hematopoietic cells for cell marker analysis. Lab Med 1984;15:659-65.

Rouse BT, Horohov DW. Immunosuppression in viral infections. Rev Infect Dis 1986;8:850-73.

Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M. Suppression of lymphocyte stimulation following bereavement. JAMA 1983;250:374-7.

Shaefer CF, Trincher RC, Rissing JP. Melioidosis: recrudescence with a strain resistant to multiple antimicrobials. Am Rev Respir Dis 1983;128:173-5.

Stites DP, Stobo JD, Wells JV, eds. Basic and clinical immunology. 6th ed. Los Altos, CA: Appleton and Lange, 1987.

Tecoma ES, Huey LY. Psychic distress and the immune response. Life Sci 1985;36:1799-812.

Terhorst C, Van Agthoven A, Reinherz EL, Schlossman SF. Biochemical analysis of human T lymphocyte differentiation antigens T4 and T8. Science 1980;209:520-1.

Thigpen JE, Faith RE, McConnell EE, Moore JA. Increased susceptibility to bacterial infection as a sequela of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Infect Immun 1975;12:1319-24.

Veterans Administration. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. I. Washington, D.C.: Veterans Administration, 1981.

Veterans Administration. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. III. Washington, D.C.: Veterans Administration, 1984.

Veterans Administration. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. V. Washington, D.C.: Veterans Administration, 1985.

Vos JG. Screening and function studies in immunotoxicity testing. Vet Q 1981;3:190-5.

Weidanz WP. Malaria and alterations in immune reactivity. Br Med Bull 1982;38:167-72.

CHAPTER 9

Cardiovascular System

9. CARDIOVASCULAR SYSTEM

9.1 INTRODUCTION

In this chapter we describe the cardiovascular conditions found among participants in the Vietnam Experience Study (VES). As noted in Chapter 1, the VES was intended to assess health effects relative to the general Vietnam military experience and was not focused exclusively on the potential effects of exposure to herbicides. Nonetheless, when the study was designed (Centers for Disease Control, 1983), the major concerns about the physical health of Vietnam veterans were related to possible exposure to Agent Orange. Thus, in evaluating the diverse health concerns that Vietnam veterans have expressed and in examining the many health conditions that have been suggested as being associated with Agent Orange or dioxin exposure, we took a broad approach.

Before we began our analysis, we specified three cardiovascular conditions for more detailed evaluation. We selected these conditions on the basis of the results of previous studies of human exposures to dioxin or herbicides or because other investigators had postulated that certain psychosocial factors, which may be a consequence of prior wartime service, may increase the risk of cardiovascular disease. The three conditions are peripheral vascular disease, hypertension, and ischemic heart disease.

We included peripheral vascular disease because of findings reported in the baseline examination of the Ranch Hand Study of U.S. Air Force personnel (Lathrop *et al*, 1984). In that study, investigators found that the nonblack personnel who had been involved in the aerial spraying of Agent Orange in Vietnam were more likely than the comparison group to have abnormal peripheral pulses. Since these results were based on palpation of peripheral pulses, investigators included Doppler measurements in the first follow-up examination (Lathrop *et al.*, 1987). They found no difference between cohorts in the prevalence of pulse abnormalities. Other investigators have found no association between dioxin exposure and peripheral vascular disease (Hoffman *et al.*, 1986).

We examined hypertension in detail because we reasoned that this condition might be more prevalent among Vietnam veterans as a result of their having experienced psychological stress from their wartime service. Stress is believed to play a role in the initiation and maintenance of hypertension in some individuals (Shapiro, 1978; Syme and Torfs, 1978), although the mechanism by which it does so is unclear. Further, hypertension has been found among troops after combat (Graham, 1945). Less is known about the association between this health outcome and exposure to dioxin-containing herbicides. At present, there is no evidence to suggest that hypertension is a direct consequence of dioxin exposure (Webb *et al.*, 1986).

In our previous study of postservice mortality, we found that mortality from cardiovascular diseases was lower for Vietnam veterans than for non-Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1987). In the VES, we focused our analysis on the evaluation of ischemic heart disease morbidity for two reasons. First, some investigators have suggested that stress and other psychological factors increase the risk for this health outcome (Kasl, 1984). Anxiety and depression, which were more prevalent among Vietnam veterans who participated in the VES (see Volume IV), have been associated with several manifestations of ischemic heart disease, including angina and myocardial infarction (Jenkins, 1976). Second, several investigators have suggested that exposure to dioxin or phenoxyherbicides may be associated with atherosclerotic heart disease. England (1981)

described two persons with coronary artery anomalies among agricultural workers who used 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Walker and Martin (1979) reported that three of eight persons with chloracne from industrial exposure to 2,4,5-T had clinical signs of ischemic vascular disease. Results of the first follow-up examination in the Ranch Hand study (Lathrop *et al.*, 1987) showed that verified heart disease (excluding hypertension) was significantly more common in the cohort that worked with Agent Orange.

Finally, Vietnam veterans might be at higher risk for these three health outcomes—peripheral vascular disease, hypertension, and ischemic heart disease—because of alterations in their blood lipid and cholesterol levels, which some investigators have suggested result from exposure to dioxin. Elevated serum triglyceride and cholesterol levels have been found in humans exposed to dioxin (Martin, 1984; Moses *et al.*, 1984; Walker and Martin, 1979).

9.2 METHODS

In this chapter, we present information obtained from four sources: (1) self-reported medical histories; (2) general physical examinations; (3) Doppler measurements of peripheral pulses; and (4) electrocardiograms (ECGs). During the study all physicians, interviewers, and technicians were unaware of the veterans' cohort status.

9.2.1 Medical History and Physical Examination

As described in Chapter 2, physician's assistants administered standardized medical history questionnaires. The clinic manager monitored the interviews daily. Results of an analysis of data quality, described in detail in Supplement B (Medical and Psychological Data Quality) of the monograph, showed little variability among interviewers for any of the cardiovascular items on the questionnaire.

Standardized physical examinations were performed by board-certified internists, as described in Chapter 2. Physicians were not permitted to elicit any historical information from participants during the examinations. Results of quality control analyses showed variability in the prevalence of physical findings detected by examining physicians, but there was no indication that this variability introduced either confounding or effect modification into the analysis of cohort differences. All quality control analyses are described in detail in Supplement B.

With the participant in a sitting position, a registered nurse, using a standard mercury sphygmomanometer, took blood pressure measurements, two times consecutively, from both arms. For analysis we used an average of the values from the right arm; measurements from the left arm were used to verify individual results (NHLBI, 1984).

9.2.2 Doppler Measurement of Peripheral Pulses

For this examination, participants were requested not to smoke, drink caffeine-containing beverages, or exercise for 1 hour before being tested. Trained technicians, using a Parks Dual Frequency Bidirectional Doppler instrument, obtained Doppler measurements. Blood pressure was recorded to determine three measures of lower extremity arterial flow: the resting index, the hyperemic index, and the recovery index.

The resting index is the ratio of the ankle-to-brachial systolic blood pressure with the subject at rest. To determine this index, the technician (1) measured both brachial artery pressures consecutively with the participant lying on his back; (2) located on the right leg the dorsalis pedis and posterior tibialis arteries, using the Doppler probe; (3) selected the artery