Table 3.10 Medical Examination Participation Rates Among Vietnam and Non-Vietnam Veterans Who Had Telephone Interviews, by Selected Neurological and Muscular Symptoms[a]

	Vietnam		Non-Vietnam	
Symptom[b]	Rate (%)[c]	No.[d]	Rate (%)[c]	No.[d]
Headaches				
No	74	1949	62	1683
Yes	79	540	70	288
Ringing in Ears				
No	74	1798	62	1596
Yes	78	692	67	375
Dizziness				
No	74	2044	62	1751
Yes	80	443	71	220
Muscle Twitching				
No	74	2078	62	1789
Yes	80	411	70	182
Numbness				
No	74	1705	61	1546
Yes	78	784	70	425
Weakness				
No	73	1903	62	1666
Yes	82	586	69	306
Muscle Soreness				
No	74	1612	62	1424
Yes	78	875	67	548

[a] Information obtained from telephone interview.
[b] Occurring during the 4 weeks preceding telephone interview.
[c] Percent of eligible veterans interviewed by telephone who underwent examination.
[d] Number of veterans with a particular symptom who participated in the medical examinations.

Table 3.11 Comparison of Self-Reported Neurological and Muscular Symptoms[a] Among Vietnam and Non-Vietnam Veterans Selected for Medical Examination and Interviewed by Telephone With Those Among Veterans Undergoing Examination

	Proportion (%) With Symptom				Prevalence Ratio	
	Vietnam		Non-Vietnam		Vietnam/Non-Vietnam	
Symptom[b]	Interviewed (N=3317)	Examined (N=2490)	Interviewed (N=3126)	Examined (N=1972)	Interviewed	Examined
Headaches	21	22	13	15	1.5	1.5
Ringing in ears	27	28	18	19	1.5	1.5
Dizziness	17	18	10	11	1.7	1.6
Muscle twitching	16	17	8	9	2.0	1.9
Numbness	30	31	20	22	1.5	1.4
Weakness	21	24	14	16	1.5	1.5
Muscle Soreness	34	35	26	28	1.3	1.3

[a] Information obtained from telephone interview.
[b] Occurring during the 4 weeks preceeding telephone interview.

representation of such veterans in the examination sample was not very different from that in the interview sample (Table 3.15). For the most part, there was less than a one percentage point increase in the prevalence of participants with such feelings in either study cohort.

Table 3.12 Medical Examination Participation Rates Among Vietnam and Non-Vietnam Veterans Who Had Telephone Interviews, by Frequency of Selected Psychological Symptoms[a]

Psychological Symptom[b]	Proportion (%) With Symptom			
	Vietnam		Non-Vietnam	
	Rate (%)[c]	No.[d]	Rate (%)[c]	No.[d]
Difficulty Sleeping				
Infrequent	73	1657	61	1545
Frequent	80	830	71	424
Problems Concentrating				
Infrequent	74	1975	63	1782
Frequent	81	512	70	188
Memory Problems				
Infrequent	74	2004	63	1759
Frequent	82	485	74	212
Short-Tempered				
Infrequent	74	1608	63	1566
Frequent	77	880	65	402
Loss of Interest				
Infrequent	73	1948	62	1724
Frequent	82	538	69	245
Felt Life Meaningless				
Infrequent	75	2183	63	1830
Frequent	77	303	70	138

[a] Information obtained from telephone interview.
[b] Occurring during the 6 months preceeding telephone interview.
[c] Number of veterans with a particular symptom who participated in the medical examinations.
[d] Percent of eligible veterans interviewed by telephone who underwent medical examination.

Table 3.13 Comparison of Self-Reported Psychological Symptoms[a] Among Vietnam and Non-Vietnam Veterans Selected for Medical Examination and Interviewed by Telephone With Those Among Veterans Undergoing Examination

Psychological Symptom[b]	Proportion (%) With Symptom				Prevalence Ratio	
	Vietnam		Non-Vietnam		Vietnam/Non-Vietnam	
	Interviewed (N=3317)	Examined (N=2490)	Interviewed (N=3126)	Examined (N=1972)	Interviewed	Examined
Difficulty sleeping	31	33	19	22	1.6	1.5
Problems concentrating	19	21	9	10	2.1	2.1
Memory problems	18	20	9	11	2.0	1.8
Short-tempered	35	35	20	20	1.8	1.8
Loss of interest	20	22	11	12	1.8	1.8
Felt life meaningless	12	12	6	7	2.0	1.7

[a] Information obtained from telephone interview.
[b] Occurring frequently during the 6 months preceeding telephone interview.

Analysis of responses to questions asked only of the Vietnam veterans indicated that certain attributes and characteristics of their military service had a modest influence on participation rates (Table 3.16). The reported level of combat experienced while serving in Vietnam had a minimal influence on participation rates. There was a 6 percentage point increase in participation rates for veterans who reported that they had a health problem that might be related to exposure to Agent Orange compared with veterans who did not report

Table 3.14 Medical Examination Participation Rates Among Vietnam and Non-Vietnam Veterans Who Had Telephone Interviews, by Frequency of Selected Memories and Attitudes Concerning Prior Army Service[a]

Army Memory or Attitude	Vietnam		Non-Vietnam	
	Rate (%)[b]	No.[c]	Rate (%)[b]	No.[c]
Avoid Army Reminders				
Infrequent	74	2091	63	1876
Frequent	80	392	72	93
Painful Army Memories				
Infrequent	75	2187	63	1901
Frequent	79	295	76	69
Felt Shame About Army				
Infrequent	75	2278	63	1920
Frequent	81	202	74	50
Felt Anxious About Army				
Infrequent	75	2269	63	1909
Frequent	81	211	75	62

[a] Information obtained from telephone interview.
[b] Percent of eligible veterans interviewed by telephone who underwent medical examination.
[c] Number of veterans with a particular memory or attitude who participated in the medical examinations.

Table 3.15 Comparison of Self-Reported Memories and Attitudes[a] Concerning Prior Army Service Among Vietnam and Non-Vietnam Veterans Selected for Medical Examination and Interviewed by Telephone With Those Among Veterans Undergoing Examination

Army Memory or Attitude[b]	Proportion (%) With Memory or Attitude			
	Vietnam		Non-Vietnam	
	Interviewed (N=3317)	Examined (N=2490)	Interviewed (N=3126)	Examined (N=1972)
Avoid Army reminders	15	16	4	5
Painful Army memories	11	12	3	4
Felt shame about Army	8	8	3	3
Felt anxious about Army	8	9	3	3

[a] Information obtained from telephone interview.
[b] Occurring frequently.

such a problem. Nonetheless, among the Vietnam veterans, the distribution of men with different experiences unique to service in Vietnam was similar in the examination and interview samples (Table 3.17).

3.2 CHARACTERISTICS OF EXAMINATION PARTICIPANTS

In this section we compare the characteristics of the veterans who participated in the examinations according to cohort status. The two groups are compared on the basis of military history, demographic, and socioeconomic characteristics. In addition, we describe the distribution of these characteristics in the three non-Vietnam groups (Korea, Germany, and the continental United States (CONUS)).

The Vietnam and the non-Vietnam cohorts showed some differences for most of the military history characteristics (Table 3.18). The Vietnam veterans tended to be younger at entry into the Army, and they were more likely to have entered the service during 1967 to 1969, to have had a tactical military occupational specialty (MOS), and to have volunteered for military service. The biggest differences between the two cohorts were, however, in

Table 3.16 Medical Examination Participation Rates Among Vietnam Veterans Who Had Telephone Interviews, by Selected Army Service Experiences[a]

Army Service Experience	Vietnam	
	Rate (%)[b]	No.[c]
Volunteered for Vietnam		
No	74	1923
Yes	78	551
Reported Combat Experience		
Minimal	72	601
Low	76	622
Moderate	76	581
High	75	618
Wounded		
No	75	2257
Yes	77	213
Perceived Herbicide Exposure[d]		
None	73	1051
Indirect	75	762
Direct	79	670
Health Problems Believed To Be Agent Orange-Related		
No	74	2042
Yes	80	437

[a] Information obtained from telephone interview.
[b] Percent of eligible veterans interviewed by telephone who underwent medical examination.
[c] Number of veterans with a particular service experience who participated in the medical examinations.
[d] Indirect—walked through defoliated area; direct—got herbicide on skin, was present while spraying was in progress, or handled herbicide equipment.

Table 3.17 Comparison of Selected Army Service Experiences[a] Among Vietnam Veterans Selected for Medical Examination and Interviewed by Telephone With Those Among Vietnam Veterans Undergoing Examination

Army Service Experience	Proportion (%) With Service Experience	
	Vietnam	
	Interviewed (N=3317)	Examined (N=2490)
Volunteered for Vietnam	21	22
Reported Combat Experience		
Minimal	25	24
Low	25	25
Moderate	23	23
High	25	25
Wounded	8	9
Perceived Herbicide Exposure		
None	44	42
Indirect	31	31
Direct	26	27
Health Problems Believed To Be Agent Orange-Related	16	18

[a] Information obtained from telephone interview.

discharge rank (pay grade) and type of discharge, with more non-Vietnam veterans having been discharged at lower ranks and having had other than honorable discharges.

The distributions of the military history characteristics among the three non-Vietnam groups differ somewhat (Table 3.18). The differences are mainly associated with the CONUS

Table 3.18 Comparison of Selected Army Service Characteristics[a] Among Vietnam and Non-Vietnam Veterans Undergoing Medical Examination, by Place of Service

	Proportion (%) With Characteristic				
	Total	Non-Vietnam			
Army Service Characteristic	Vietnam (N=2490)	Total (N=1972)	Korea (N=322)	Germany (N=816)	CONUS (N=834)
Age at Entry					
16-19	52.3	45.4	47.5	49.5	40.6
20-33	47.8	54.6	52.5	50.5	59.4
Year of Entry					
1965-66	33.3	36.8	39.1	35.9	36.8
1967-69	56.2	37.7	43.8	38.0	35.1
1970-71	10.5	25.5	17.1	26.1	28.1
Enlistment General Technical (GT) Test Score					
40-89	23.2	21.3	19.9	23.3	19.8
90-109	32.4	28.7	27.0	31.0	27.0
110-129	32.4	34.2	36.3	31.3	36.3
130-160	10.3	15.3	16.2	14.1	16.1
Primary MOS					
Tactical	34.0	25.3	30.4	28.7	20.0
Other	66.0	74.7	69.6	71.3	80.0
Type of Enlistment					
Drafted	61.7	64.9	59.6	62.3	69.5
Volunteered	38.3	35.1	40.4	37.8	30.5
Pay Grade at Discharge					
E1-E3	9.4	16.4	9.3	12.6	22.8
E4-E5	90.6	83.6	90.7	87.4	77.2
Type of Discharge					
Honorable	98.2	93.5	96.6	95.3	90.4
Other	1.9	6.5	3.4	4.7	9.6

[a] Information obtained from military records completed during active duty.

group, which had a much higher proportion of veterans who had been older at entry into the service and a lower proportion with a tactical MOS. The CONUS group also had a higher proportion of men who had been drafted, who had lower discharge ranks, and who had received other-than-honorable discharges.

The current demographic and socioeconomic characteristics of the examination participants in the Vietnam cohort were similar to those of the non-Vietnam cohort (Table 3.19). The racial distribution was virtually the same. The age at examination was slightly different, with about three quarters of the Vietnam group being in the 35- to 39-year age category, whereas only 60% of the non-Vietnam cohort was in this age category. One of the larger differences was in education, with the educational level tending to be higher in the non-Vietnam group. The income categories tended to be the same in the two groups, except for a slightly higher proportion of non-Vietnam veterans in the over-$50,000-per-year category. Marital status and region of residence were virtually the same in the two cohorts. Current occupation was the same in the two cohorts, except that more non-Vietnam than Vietnam veterans were employed in executive, managerial, or administrative positions or had a professional specialty.

The demographic and socioeconomic characteristics of the Korea, Germany, and CONUS groups tended to be similar to the characteristics of the combined non-Vietnam cohort (Table

Table 3.19 Comparison of Selected Current Demographic Characteristics[a] Among Vietnam and Non-Vietnam Veterans Undergoing Medical Examination, by Place of Service

	Proportion (%) With Characteristic				
	Total	Non-Vietnam			
Demographic Characteristic	Vietnam (N=2490)	Total (N=1972)	Korea (N=322)	Germany (N=816)	CONUS (N=834)
Race					
White	82.5	81.1	81.7	80.3	81.8
Black	11.5	12.1	11.8	13.0	11.4
Other	6.0	6.8	6.5	6.7	6.8
Age at Examination					
30-34	6.5	13.1	9.9	13.6	13.9
35-39	72.4	59.4	64.0	62.5	54.6
40-48	21.1	27.5	26.1	23.9	31.5
Education (Years)					
0-11	13.7	10.1	9.9	9.7	10.6
12-15	67.4	64.9	65.2	68.5	61.2
16-18	18.9	25.0	24.5	21.8	28.2
Income ($1,000)					
<10	9.8	9.8	9.0	10.8	9.1
10-30	46.2	44.3	42.6	44.9	44.4
30-50	32.3	31.8	36.3	29.4	32.5
>50	9.8	12.2	11.2	12.1	13.6
Marital Status					
Married	73.8	73.6	75.8	73.4	73.0
Other	26.2	26.4	24.2	26.6	27.0
Current Residence					
Midwest	29.2	29.2	32.3	30.0	27.2
Northeast	16.4	15.6	12.1	16.8	15.7
South	33.4	33.3	35.7	31.7	33.8
West	19.8	20.3	19.3	20.1	21.9
Foreign	1.2	1.7	0.6	1.4	2.4
Occupation					
Executive, managerial	18.3	20.9	24.2	19.6	21.9
Professional specialty	10.7	14.3	12.7	12.9	15.2
Office, clerical, sales	7.9	7.7	9.9	7.0	7.4
Service, transportation	12.5	10.7	8.7	11.2	11.0
Precision production, craft, repair	21.9	20.9	20.8	21.9	19.9
Operators, laborers	16.2	14.5	12.1	16.7	15.2
Farming, foresters, fishermen	3.0	2.2	2.8	1.7	2.4
Unemployed	9.3	8.6	8.1	8.7	5.6

[a] Information obtained from telephone interview and medical history at examination.

3.19). Contrary to differences noted for the military history characteristics, the CONUS veterans differed little from the other non-Vietnam veterans in terms of current socioeconomic characteristics.

3.3 DISCUSSION

Although the study met its overall goal of a 60% participation rate for the medical examinations, participation rates for the two cohorts differed (66% for Vietnam veterans versus 53% for non-Vietnam veterans). The degree of nonparticipation and the differential participation rates raise potential concerns about the representativeness of the examination participants and about selection bias. However, detailed analyses of the reasons for not participating and the personal characteristics associated with participation did not show any

markedly different characteristics or health histories for the examination participants compared with the entire sample of veterans selected for examination.

The reasons for not participating and the personal characteristics associated with participation were similar in both groups. The biggest loss to participation and the largest differential in participation rates came between the interview and examination step. For the most part, reasons for not participating in the telephone interview or the medical examinations were not health related. The nonparticipation in the examinations was mainly related to inability or unwillingness to take time away from work or having no interest in the study. Among the military history characteristics, those that had the strongest association with participation rates were type of discharge, discharge rank, and general technical test score; nonetheless, the participation rate differences did not markedly alter the distribution of these characteristics in the examination sample compared with the entire sample of men initially selected for examination.

Telephone interview information indicated that similar factors affected participation rates for both cohorts. In both groups, participation rates were higher for those with higher levels of education. Education, however, tended to have a greater relative effect on the non-Vietnam cohort.

In both groups, participation tended to be increased for veterans who reported a history of several specific health problems. The higher participation rates among these veterans did not, however, appreciably change the prevalence of these medical conditions within either examination group. For the most part, the prevalence of each condition increased only one or two percentage points in the examination sample compared with the interview sample. The presence of psychological symptoms related to stress, anxiety, depression, memory, and concentration had a similar effect upon participation. In both cohorts those who reported frequently experiencing these symptoms were more likely to participate. This, however, did not result in a large increase in the frequency of the symptoms among those examined.

Since the increased participation associated with the medical and psychological variables was similar in both groups, the prevalence ratios for these conditions in the Vietnam cohort compared with the non-Vietnam cohort remained the same in the examination sample and the interview sample. The reported medical or psychological conditions that resulted in the greatest differentials in participation rates (any malignancies, liver cirrhosis, chloracne, and use of drugs other than marijuana) involved few veterans and did not have much of an impact on the distributions of these conditions in the two cohorts. Because the number of men involved was so small, the differential participation would not be expected to have much effect on the overall examination findings.

In the two cohorts, the military history characteristics of the veterans who underwent examination differed somewhat. Most of these differences can be related to the strategic and personnel requirements of the Vietnam conflict. Therefore, it is not surprising that the Vietnam group had a higher proportion of men with a tactical MOS or that more of the Vietnam veterans entered the military in 1967-1969, a period of military buildup in Southeast Asia. Some of the cohort differences, particularly in terms of rank at discharge and type of discharge, may be attributed to the specific characteristics of the CONUS group of non-Vietnam veterans. Among non-Vietnam veterans, the proportion with discharge ranks E1 to E3 or with nonhonorable discharges was higher for the CONUS group than for those who served elsewhere. This finding suggests that the CONUS group may not have been as comparable to the Vietnam group as were the Korea and the Germany groups.

Unlike the military history characteristics, the current demographic and socioeconomic characteristics of the two cohorts were similar. The groups were essentially the same with regard to several important demographic and socioeconomic characteristics except that the non-Vietnam group tended to have a somewhat higher educational level. This may partially reflect the greater role educational level seems to have played in determining participation by non-Vietnam veterans. Interestingly, the CONUS group does not substantially differ from the two other non-Vietnam groups in current demographic and socioeconomic characteristics. This finding suggests that the dissimilarities noted in military history characteristics of the CONUS group did not result in any substantial differences in the socioeconomic status of the CONUS veterans relative to other non-Vietnam veterans.

In conclusion, we have not been able to identify any factors related to participation that would be expected to have a large influence on the health status findings for the two cohorts. Compared with those who were selected for examination, those who actually participated tended to be slightly better educated and more frequently reported certain medical or psychological conditions. Nonetheless, these increased participation rates had little influence on the prevalence rates of the conditions in the examination participants compared with the interview participants and had little effect upon the prevalence ratios for these conditions. Some of the differences in military history characteristics that were noted between the Vietnam and non-Vietnam cohorts were not unexpected. In fact, as noted in Chapter 2, it was because of anticipated differences that we selected these characteristics as primary covariates to be included as potential confounders or effect modifiers in all multivariate analyses. The similarities in current demographic and socioeconomic characteristics of the two cohorts are encouraging and indicate that these characteristics should not have much influence on the findings for one cohort compared with the other.

CHAPTER 4

General Health History

4. GENERAL HEALTH HISTORY

In this chapter, we present the general health histories of the two study groups as reported by the study participants. Our main purpose is to highlight the groups of health conditions that may have occurred more frequently among the Vietnam veterans or that are of greater concern to the Vietnam veterans than to the non-Vietnam veterans. We also compare certain lifestyle characteristics and behaviors, such as cigarette smoking and alcohol use, to determine how similar the two groups are with respect to these important health-influencing factors.

The information in this chapter comes from the medical history questionnaire that was administered as part of the medical examination battery of tests. Current medications are grouped by National Drug Code Directory class codes (U.S. Department of Health and Human Services, 1985). Medical conditions are grouped into broad categories as defined by the Ninth Revision of the International Classification of Diseases: Clinical Modification (ICD9-CM) (U.S. Department of Health and Human Services, 1980). Additional detail about the conditions making up each category can be found in the subsequent organ-specific chapters of this monograph.

4.1 CURRENT HEALTH STATUS AND HEALTH PROBLEMS

Over 80% of the veterans in both groups reported their health status to be good or excellent, but a larger proportion of Vietnam veterans (16% versus 11%) reported their health to be only fair or poor (Table 4.1).

To identify active health problems or concerns, we asked the participants to report any conditions for which they were currently receiving treatment or which they would like to discuss with a physician. A slightly larger proportion of Vietnam veterans reported having current health problems, but the two groups reported similar types of medical problems (Table 4.2). In both groups, the problems reported most frequently involved the musculoskeletal system, circulatory system, and skin and a group of symptoms, signs, and ill-defined conditions. Reporting differences were greatest for neurologic conditions; skin problems; and symptoms, signs, and ill-defined conditions. These conditions were more commonly reported by Vietnam veterans. Except for symptoms, signs, and ill-defined conditions, for which the reporting difference was 5%, the difference for all other conditions was less than 2%.

4.2 HOSPITALIZATIONS AND TREATMENTS

About half of the veterans in each group reported having been hospitalized at least once since being discharged from the military (Table 4.3). The proportion of veterans reporting at least one hospitalization, however, was slightly higher in the Vietnam veteran group. The Vietnam veterans also reported a slightly greater number of total hospitalizations.

Table 4.1 Self-Perceived General Health Status of Vietnam and Non-Vietnam Veterans

	Vietnam		Non-Vietnam	
Perceived Health	**%**	**No.**	**%**	**No.**
Excellent	27.2	676	33.3	657
Good	56.5	1407	55.7	1099
Fair	14.8	369	10.2	201
Poor	1.5	37	0.7	14

Table 4.2 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Health Problems[a], by Medical Condition

Medical Condition (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Infectious diseases (001-139)	1.7	42	1.6	31
Neoplasms (140-239)	1.7	42	1.5	29
Endocrine diseases (240-279)	2.9	71	2.0	40
Diseases of blood (280-289)	0.1	2	0.3	6
Mental disorders (290-319)	3.1	77	2.3	46
Diseases of nervous system (320-389)	4.1	102	3.1	61
Circulatory diseases (390-459)	9.0	225	9.6	189
Respiratory diseases (460-519)	5.4	135	6.2	123
Digestive system diseases (520-579)	5.8	145	5.4	106
Diseases of genitourinary system (580-629)	2.7	68	2.2	43
Diseases of skin (680-709)	8.0	198	6.1	120
Musculoskeletal diseases (710-739)	14.8	368	14.5	285
Congenital anomalies (740-759)	0.2	4	0.1	1
Symptoms, signs, and ill-defined conditions (780-799)	19.1	476	14.2	280
Injuries and poisonings (800-999)	2.3	56	2.2	43
Any condition (001-999)	54.5	1356	49.7	979

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

Table 4.3 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Hospitalizations Since Discharge, by Number of Hospitalizations

Number of Hospitalizations	Vietnam		Non-Vietnam	
	%	No.	%	No
0	47.1	1172	50.9	1003
1	29.3	729	27.2	537
2	12.4	308	13.3	263
3	5.7	142	4.7	93
4	2.6	64	1.8	35
≥5	3.0	75	2.0	41
Total[a]	100.0	2490	100.0	1972

[a] Sum of percent values in table may not equal totals because of rounding.

The reasons for hospitalization tended to be similar in the two groups, although hospitalization rates for all conditions were slightly higher among the Vietnam veterans (Table 4.4). The most common reasons for hospitalizations were the same in the two groups. These reasons were related to injuries or poisonings and diseases of the digestive system. The absolute magnitude of the differences was less than 2.0% for all conditions. For conditions commonly reported as a reason for hospitalization, relative differences between Vietnam and other veterans were largest for infectious diseases, neoplasms, nervous system conditions, respiratory diseases, and diseases of the skin.

About one-third of the veterans in both groups, with a slightly greater proportion in the Vietnam group, reported having had at least one surgical procedure after discharge from the Army (Table 4.5). The distribution of anatomical sites of the various surgical procedures was similar in the two groups, although the Vietnam veteran group reported slightly more procedures for nearly all sites. The most prevalent surgical procedures in both groups involved the musculoskeletal system and the digestive system. Except for surgery involving the skin or digestive system, which had absolute differences of 1.3% and 1.4%, respectively, between the cohorts, the absolute magnitude of the differences was less than 1.0%.

Table 4.4 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Hospitalizations Since Discharge, by Medical Condition

Medical Condition (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Infectious diseases (001-139)	2.2	54	1.7	33
Neoplasms (140-239)	1.9	48	1.3	26
Endocrine diseases (240-279)	1.4	34	1.3	26
Diseases of blood (280-289)	0.3	7	0.1	2
Mental disorders (290-319)	4.6	114	3.9	76
Diseases of nervous system (320-389)	2.1	53	1.5	29
Circulatory diseases (390-459)	5.3	132	5.0	98
Respiratory diseases (460-519)	6.6	165	5.1	100
Digestive system diseases (520-579)	12.7	315	11.5	227
Diseases of genitourinary system (580-629)	5.7	143	5.5	109
Diseases of skin (680-709)	3.5	87	2.7	54
Musculoskeletal diseases (710-739)	6.5	161	6.4	126
Congenital anomalies (740-759)	0.2	4	0.1	2
Symptoms, signs, and ill-defined conditions (780-799)	7.4	184	7.0	138
Injuries and poisonings (800-999)	21.0	522	19.2	378
Supplementary factors (V01-V82)	2.3	58	1.8	35
Any condition (001-999, V01-V82)	52.9	1318	49.1	969

Table 4.5 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Surgical Procedures Since Discharge, by Site of Procedure

Site of Procedure (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Nervous system (01-05)	2.1	53	2.0	39
Endocrine system (06-07)	0.1	2	0.1	2
Eye (08-16)	0.5	13	0.5	9
Ear (18-20)	0.7	18	0.4	8
Nose, mouth, or pharynx (21-29)	4.3	108	3.5	69
Respiratory system (30-34)	1.0	24	1.1	22
Cardiovascular system (35-39)	1.0	25	0.9	18
Hemic and lymphatic system (40-41)	0.8	19	0.4	7
Digestive system (42-54)	10.8	269	9.4	185
Urinary system (55-59)	1.6	39	1.3	26
Genital system (60-64)	2.3	58	2.1	42
Musculoskeletal system (76-84)	12.3	307	11.5	227
Skin (85-86)	5.0	124	3.7	72
Any site (01-86)	34.4	856	30.0	591

About one-fifth of the veterans in each group reported taking some form of prescription or nonprescription medication at the time of the examination (Table 4.6). The medication-use patterns were generally similar in the two groups, with a slight increase in the proportion of Vietnam veterans reporting use of nearly every category of medication. In both groups, the most commonly used medications were cardiovascular and renal medications and medications taken for the relief of pain. Relative to the non-Vietnam veterans, the Vietnam veterans reported an absolute increased use of more than 0.5% only for central nervous system medications (0.9% increase) and medications used for the relief of pain (1.4% increase). Vietnam veterans reported using respiratory medications relatively less frequently than did non-Vietnam veterans.

Table 4.6 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Use of Medications, by Drug Class

Drug Class	NDC Codes[a]	Vietnam		Non-Vietnam	
		%	No.	%	No
Anesthetics/adjuncts	100	0.0	0	0.2	3
Antidotes	200	<0.1	1	0.1	·
Antimicrobials	300	1.4	35	1.4	27
Hematologics	400	0.1	3	0.1	·
Cardiovascular/renal	500	5.5	136	5.1	100
Central nervous system	600	3.9	98	3.0	59
Gastrointestinals	800	2.5	61	2.2	43
Metabolic/nutrients	900	1.2	29	0.7	14
Hormones/hormonal mechanisms	1000	2.0	49	1.7	33
Skin/mucous membrane	1200	1.6	39	1.4	27
Neurologics	1300	1.2	31	1.2	24
Oncolytics	1400	0.2	5	0.0	0
Ophthalmics	1500	0.4	11	0.2	4
Otics	1600	0.1	2	0.1	2
Relief of pain	1700	6.0	150	4.6	91
Antiparasitics	1800	0.0	0	0.1	2
Respiratory	1900	2.6	65	3.8	75
Unclassified/miscellaneous	2000	0.1	2	0.1	·
Any medication	100-2000	20.0	498	19.8	390

[a] National Drug Code Directory class codes.

4.3 TRAUMA AND INJURIES

The information on trauma and injuries obtained in the medical history questionnaire showed few differences between the two groups (Table 4.7). At the time of the medical examinations, the proportion of Vietnam veterans who reported having been in a motor vehicle crash or having had a fracture or dislocation was only slightly higher than the corresponding proportion of non-Vietnam veterans. The proportion that reported having sustained a head injury leading to loss of consciousness was the same in the two groups.

4.4 HEALTH-INFLUENCING BEHAVIORS

There were no large differences between the two groups for most of the important health-influencing behaviors (Table 4.8). Over 40% of the men in both groups were current cigarette smokers, with only a slightly higher proportion of smokers in the Vietnam group. Both groups reported similar alcohol use, with a slightly higher proportion of Vietnam veterans reporting an average of three or more drinks per day or five or more drinks on at least one occasion in the previous month (binge drinking). For both groups, the proportions who reported having driven during the previous month after having had too much to drink were about the same. Illicit drug use during the year before the examination was similar in the two groups, with about one-quarter of the men in each group reporting any drug use during this period. Furthermore, a similar proportion of men in each group reported having

Table 4.7 History of Trauma and Injuries of Vietnam and Non-Vietnam Veterans

	Vietnam		Non-Vietnam	
	%	No.	%	No.
Motor vehicle crash	23.1	574	20.4	403
Fractures or dislocations	33.3	828	30.6	603
Head injury with loss of consciousness	6.2	155	6.2	123

Table 4.8 Health-Influencing Behaviors of Vietnam and Non-Vietnam Veterans

Behavior	Vietnam		Non-Vietnam	
	%	No.	%	No.
Cigarette Smoking				
Never	24.9	619	27.5	543
Ex-smoker	28.7	715	29.3	577
Current	46.4	1156	43.2	852
Alcohol Use				
Drinks per month				
0-29	60.9	1516	62.6	1235
30-89	25.5	634	26.1	514
≥90	13.2	328	10.5	207
Binge drinking[a]	43.3	1079	40.4	797
Drink and drive[b]	14.3	356	13.8	273
Illicit Drug Use, Past Year				
None	74.0	1843	72.9	1438
Marijuana only	14.1	351	16.4	324
Other	11.7	292	10.5	207
Counseling or Treatment For Drug or Alcohol Problem	11.0	273	9.5	187
Body Mass Index (kg/m^2)				
16-24	20.6	513	21.9	432
24-28	49.2	1224	49.2	971
>28	30.2	752	28.9	569
Special Diet				
Weight loss	1.7	42	2.3	45
Diabetic	0.8	21	0.5	9
Low salt	2.3	58	2.0	39
Low fat	0.7	18	1.0	20
Vegetarian	0.2	6	0.4	7
Other	2.1	51	3.0	60

[a] Had five or more drinks on at least one occasion in the previous month.
[b] Drove after having had too much to drink on at least one occasion in the previous month.

received counseling or treatment for a drug or alcohol problem. The nutritional status of the two groups, as reflected by the body mass index, was also quite similar. Similar proportions of men in each group reported being on various dietary restrictions or special diets.

4.5 DISCUSSION

Although most of the veterans in both groups reported their health to be good or excellent, the Vietnam veterans as a group did not perceive their current general health status to be as good as the non-Vietnam veterans perceived theirs to be. The general health histories, however, did not reveal many striking differences between the two groups in terms of specific health problems that might explain these differences in self-perceived health. The most prevalent types of conditions tended to be the same in the two groups and were reported with similar frequency. These types included musculoskeletal conditions, trauma and injuries, and circulatory and digestive system problems. The Vietnam veteran group reported more hospitalizations and treatments for skin problems and nervous system disorders. Among current health problems, the categories that were most increased for the Vietnam veteran group included disorders of the skin and nervous system. The Vietnam veterans also reported relatively more frequently a group of symptoms, signs, and ill-defined conditions that could not be categorized to a definite organ system. Taken together, these

medical history findings suggest that skin disorders and nervous system problems are the medical conditions that are likely to be increased in the Vietnam veteran group.

In the mortality component of the Vietnam Experience Study (VES), we found excess mortality among the Vietnam veterans in the first 5 years after discharge from the service; this excess was primarily due to motor vehicle collisions and other injuries (Centers for Disease Control Vietnam Experience Study, 1987). These findings raise the possibility that past injuries may be affecting the current health status of the Vietnam veteran group. The information from the medical history, however, indicates that, as of the time of the VES examinations, the Vietnam veterans had experienced only slightly more trauma and injuries than had the non-Vietnam veterans.

Certain behaviors, such as smoking, alcohol use, and drug use, can influence many of the health conditions evaluated as part of the medical examinations. For the most part, the two groups did not differ markedly in the important health-influencing behaviors. For the Vietnam veteran group, the prevalence of current cigarette smoking and heavy alcohol use was slightly higher than for the non-Vietnam veteran group. The prevalence of illicit drug use in the past year and assessments of current nutritional status were, however, similar for the two groups. These small differences in health-influencing behaviors should have little impact, in terms of confounding, on the relative findings for the two cohorts.

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CHAPTER 5

Dermatology

5. DERMATOLOGY

5.1 INTRODUCTION

In the Vietnam Experience Study (VES) we emphasized the evaluation of skin conditions. During the Vietnam conflict, diseases of the skin were one of the leading causes of out-patient visits, hospitalizations, and temporary disability among U.S. Army personnel (Allen, 1977). Furthermore, skin abnormalities are among the health effects that have been most consistently associated with dioxin exposure in humans. As noted in the medical history findings from the VES (Chapter 4), Vietnam veterans reported having had more skin problems than non-Vietnam veterans; they also reported more current concern about skin problems.

Before the analysis began, we specified six skin conditions for more detailed evaluation. We selected these conditions on the basis of the results of previous studies of human exposures to dioxin or phenoxyherbicides and other studies of skin problems among personnel who served in Vietnam. The six conditions are chloracne, hyperpigmentation, hypertrichosis, porphyria cutanea tarda (PCT), skin cancer, and infection-related conditions.

Chloracne is the health condition that has been most strongly associated with dioxin exposure. Practically all investigators agree that exposure to dioxin can cause chloracne. In fact, some investigators have proposed that chloracne is the most sensitive indicator of dioxin toxicity and that it is rare to have other toxic manifestations of dioxin exposure without chloracne (Crow, 1982; Suskind, 1985).

Chloracne is an acneiform skin abnormality caused by exposure to certain chemicals. Dioxin is the most potent known chloracnegen, but several other chemicals also cause chloracne. Although several investigators of human exposures to dioxin have found chloracne, there is no uniform or standard set of clinical criteria used for diagnosing chloracne. In general, investigators agree that chloracne typically begins with comedones (blackheads), usually in the area lateral to the eyes ("crows foot" or "malar crescent") and in the ear and the area behind it. Some investigators have considered other types of lesions and other locations to be important. Ultimately, the diagnosis rests upon epidemiologic features, particularly a history of exposure to a chloracnegen, and the skin lesions. In isolated cases, chloracne may be impossible to distinguish from acne vulgaris (common acne) on the basis of the type and distribution of the lesions alone (Crow, 1982; Taylor, 1979).

In a typical case of chloracne, the onset is usually several days to months after exposure to a chloracnegen (Tindal, 1985). The lesions are typically noninflammatory, although they may become inflamed as the chloracne becomes more severe (Jirasek *et al.*, 1973 Dunagin, 1984). Mild cases resolve in several months to a few years after exposure, but severe cases may persist for up to 30 years (May, 1982; Pazderova-Vejlupkova *et al.*, 1981).

Chloracne in U.S. military personnel in Vietnam has not been documented in published reports. The condition is not mentioned in reports of dermatologic surveys conducted among U.S. Army troops during the Vietnam conflict (Allen, 1977).

Hyperpigmentation is often cited as a possible effect of exposure to dioxin and other chloracnegens. The condition may occur along with PCT, but hyperpigmentation has also been noted in dioxin-exposed persons who did not have PCT (Jirasek *et al.*, 1973). Typically, the face is affected, but other skin sites can also be involved (Crow, 1982).

Hypertrichosis, patchy areas of coarse, dark hair growth, is also often cited as a possible effect of dioxin exposure. Hypertrichosis, however, has been mentioned in only a few of the

studies of human exposure to dioxin. This condition has usually been observed after acute exposures, followed by eventual resolution (Suskind and Hertzberg, 1984; Moses *et al.*, 1984; Poland *et al.*, 1971). Hypertrichosis can occur as a cutaneous manifestation of PCT, but it has also been noted in persons with no porphyrin abnormalities (Crow, 1982; Jirasek *et al.*, 1973). It usually appears in the area of the temples (Crow, 1982).

Porphyria cutanea tarda (PCT), a disorder of hepatic heme synthesis, can have associated dermatologic manifestations, including hyperpigmentation, hypertrichosis, bullae, milia, ulcerations, and erosions. Although PCT is often cited as a possible effect of dioxin exposure, investigators have found it in humans in only two studies (Pazderova-Vejlupkova *et al.*, 1981; Poland *et al.*, 1971). There is a controversy about whether the PCT found in these two studies was due to dioxin exposure or to concomitant exposure to hexachlorobenzene, which may also cause PCT (Jones and Chelsky, 1986).

We included skin cancer as one of the six conditions to be evaluated in detail because of its potential clinical importance and because of findings in the Air Force Ranch Hand Study. In most studies of human dioxin exposure, investigators have not found skin cancer. However, in the Ranch Hand Study of Air Force personnel who serviced and flew the planes that sprayed Agent Orange in Vietnam, investigators found skin cancer to be significantly more common in the Ranch Hand group than in the comparison group (Lathrop *et al.*, 1984). Most of these skin cancers were basal cell carcinomas.

We chose infection-related skin conditions for detailed analysis because skin infections were important health problems among U.S. Army personnel serving in Vietnam (Allen, 1977). Of the various conditions, superficial fungal and bacterial skin infections were most important in terms of incidence and disability. These infections occurred most frequently among infantrymen operating in wet, lowland terrain during the rainy season. The most common skin infection was caused by *Trichophyton mentagrophytes*. This fungal infection can persist or recur over a long period. Because most of the other prevalent bacterial and fungal skin infections were not chronic, they would not be expected to have long-term sequelae; a few, however, could have left postinflammatory scars.

The other skin conditions reported among U.S. Army personnel in Vietnam would not be expected to have long-term sequelae. Next to the bacterial and fungal infections, diseases of the sebaceous glands, sweat glands, and hair follicles were most common. These diseases included miliaria (prickly heat), dyshidrosis, acne, and pseudofolliculitis barbae. Other skin diseases that occurred with reasonable frequency were contact dermatitis and skin conditions associated with immersion injuries of the feet. Exotic or distinctly tropical skin diseases such as cutaneous leishmaniasis, tropical acne, and tropical cutaneous ulcer were either rare or nonexistent (Allen, 1977).

5.2 METHODS

The information on skin conditions among the study participants is of two types: 1) self-reported medical histories and 2) diagnoses made by board-certified dermatologists who examined the participants. The history of skin conditions comes from questions asked during the telephone interview and from questions asked during the medical history portion of the examination.

Six board-certified dermatologists performed the dermatology examinations. As described in Chapter 2, all were trained to conduct a systematic and standardized examination. To prevent knowledge of cohort status or differential reporting of symptoms from influencing

their findings, the dermatologists did not obtain any history from the participants. Further, they relied on inspection only; they did not take any biopsies or examine any scrapings. The findings were recorded on standardized data collection forms that required the dermatologists to record the presence or absence of 68 skin conditions. The form also contained spaces in which the dermatologists could specify conditions that were not listed. The dermatologists also recorded the location of detected skin abnormalities, using specific location codes.

Most of the 68 conditions that were evaluated in the examination are standard dermatologic diagnoses (Fitzpatrick *et al.*, 1979). Hypertrichosis was included in the category of hirsutism. Because of the importance of evaluating acne lesions in terms of chloracne, a special scheme for grading acne lesions was developed:

Comedones only—no inflammatory lesions associated.
Grade I—comedones and few pustules.
Grade II—pustules and small papules.
Grade III—papules and small cysts.
Grade IV—cystic or acne conglobata.
Atypical acne—unusual features or location, including acne of the forearms, ears, etc., which suggested chloracne.

For analytical purposes, we also developed a definition of skin lesions that are compatible with chloracne. We modified the definition of chloracne proposed by the Veterans Administration Chloracne Task Force (Veterans Administration Chloracne Task Force, 1985). Chloracne-like lesions were defined as consisting of one of the following:

1. Comedones (comedones only or Grade I acne) occurring simultaneously on the forehead and cheek (to approximate a malar crescent distribution) or in or behind the ears, and sparing the nose.
2. Postinflammatory scars in the above chloracne-prone locations with a history of chloracne.

The analyses of skin conditions focused on the prevalence of current dermatologic abnormalities in the two groups. We also evaluated the history of dermatologic abnormalities, particularly to determine the types of skin problems that may have occurred more frequently among Vietnam veterans or which are of more concern to Vietnam veterans.

We used the analytical methods described in detail in Chapter 2. The Model 2 analyses included some covariates that were not commonly used in most other organ-system analyses, but which may be important factors in the development of certain skin conditions. These covariates included season of the year when examined, current occupation, and region of residence. In addition, since the quality control analyses (Supplement B) showed substantial variability in the prevalence of most skin conditions according to the dermatologist performing the examination, examiner was also included as a covariate in the Model 2 analyses.

5.3 RESULTS

5.3.1 General Dermatologic History

In general, Vietnam veterans reported more skin problems with onset either during or after active military service than did non-Vietnam veterans (Table 5.1). The Vietnam veterans

Table 5.1 Skin Conditions, With Onset During or After Active Duty, Reported by Medical Examination Participants During Telephone Interview

Skin Condition (ICD9 Codes)[a]	Vietnam		Non-Vietnam	
	%	No.	%	No.
Skin Infection (020-139.8,680-686.9)	8.8	218	6.2	123
Viral warts (078.1)	1.4	34	1.4	23
Fungal (110-111.9,112.9, 117.9)	5.5	138	3.0	53
Skin Neoplasm (171-239.9)	2.0	50	2.0	33
Cancer (172-173.9,232-232.2)	0.6	15	0.6	12
Skin Inflammation (690-698.6)	4.1	103	3.1	62
Contact dermatitis(692-692.9)	2.3	56	2.5	49
Psoriasis (696.1)	1.2	29	0.4	8
Other Skin Disorders (700-709.9)	10.0	249	5.5	109
Hirsutism (704.1)	0.0	0	0.0	0
Acne (706.1)	0.8	19	0.8	16
Dyschromia (709.0)	1.3	33	0.8	15
Unspecified skin disorder (709.9)	2.9	72	0.8	16
Unspecified Rash (782.1)	10.4	260	6.0	118
Injury to Skin (>800)	1.3	33	0.5	10

[a] Limited to skin conditions with ICD9 codes within these numerical ranges.

reported more skin infections, particularly fungal infections, and other less well specified skin conditions, and more injuries to the skin. Although during the telephone interview the Vietnam veterans spontaneously reported over twice as many conditions that were coded as psoriasis (1.2% versus 0.4% for non-Vietnam veterans), when the participants were specifically asked during the medical examination if a physician had ever told them that they had psoriasis, the prevalence was similar in the two groups (1.8% versus 1.6% for non-Vietnam veterans).

Regarding treatments, skin problems, as would be expected, led to few hospitalizations in either group, although Vietnam veterans did report more hospitalizations for a miscellaneous group of skin disorders (Table 5.2). Vietnam veterans also reported having undergone more surgical procedures on the skin than did non-Vietnam veterans (5.0% versus 3.6%). Few

Table 5.2 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Hospitalizations for Skin Conditions Since Discharge

Reason for Hospitalization (ICD9-CM Codes)[a]	Vietnam		Non-Vietnam	
	%	No.	%	No.
Skin Infection (078.1,110-111.9, 112.9,117.9,680-686.9)	2.1	53	2.1	41
Fungal (110-111.9,112.9,117.9)	0.0	0	0.0	0
Pilonidal cysts (685.1)	1.1	28	1.2	23
Skin Neoplasms (172-239.2)	0.6	15	0.4	7
Cancer (172-173.9,232-232.9)	0.2	5	0.1	1
Lipoma (214-214.9)	0.3	7	0.1	2
Benign (216-216.9)	<0.1	1	0.2	3
Uncertain behavior (238.2,239.2)	0.1	2	0.1	1
Skin Inflammation (690-698.6)	<0.1	2	0.1	1
Other Skin Disorders (700-709.9)	1.5	36	0.7	14
Sebaceous cysts (706.2)	0.9	23	0.3	6
Unspecified Rash (782.1)	<0.1	1	0.0	0

[a] Limited to skin conditions with ICD9-CM codes within these numerical ranges.

veterans in either group were using medications for the skin at the time they were examined—1.6% of the Vietnam veterans and 1.4% of the non-Vietnam veterans.

Among conditions that are currently problems for the veterans, skin infections and a miscellaneous group of conditions, including unspecified rashes, were reported more frequently by the Vietnam veterans than by the non-Vietnam veterans (Table 5.3). The skin conditions that were specified before analysis as being possibly related to Agent Orange or dioxin exposure (hyperpigmentation or dyschromia, acneiform lesions, and hypertrichosis or hirsutism) were reported rarely in either group and did not appear to be of any greater current concern to the Vietnam veterans than to the non-Vietnam veterans.

5.3.2 Chloracne

In response to the medical history questionnaire administered at the examinations, 19 Vietnam veterans and only 1 non-Vietnam veteran reported that they had ever been told by a doctor that they had chloracne. Since the same question had been asked during both telephone and medical examination interviews, the responses to the two interviews were combined to increase the specificity of the self-reported chloracne history. Eleven Vietnam veterans and one non-Vietnam veteran consistently reported a history of chloracne in both the telephone interview and the medical examination interview, resulting in an odds ratio of 8.7 (95% CI = 1.1-67.8).

Results of the dermatologic examination showed that chloracne-like skin lesions were rare and that they occurred with a similar frequency in Vietnam and non-Vietnam veterans (Table 5.4). Only one of the participants who reported a history of chloracne, a Vietnam veteran, was found to have chloracne-like skin lesions when he was examined. Analyses of the prevalence of acne lesions according to various other grading schemes showed similar results among Vietnam and non-Vietnam veterans, with the exception of a doubling in the prevalence of

Table 5.3 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Skin Problems[a]

	Vietnam		Non-Vietnam	
Current Problem (ICD9-CM Codes)[b]	%	No.	%	No.
Skin Infection (078.1,110-111.9, 112.9,117.9,680-686.9)	1.5	37	1.1	22
Viral warts (078.1)	0.4	9	0.2	3
Fungal(110-111.9,112.9,117.9)	0.6	15	0.6	12
Skin Neoplasms (172-239.2)	0.8	20	0.9	17
Cancer (172-173.9,232-232.9)	0.2	4	0.1	2
Lipoma (214-214.9)	0.2	6	0.2	3
Benign (216-216.9)	0.4	9	0.6	11
Uncertain behavior (238.2,239.2)	<0.1	1	0.1	1
Skin Inflammation (690-698.6)	1.0	24	1.0	20
Contact dermatitis (692-692.9)	0.4	9	0.4	7
Psoriasis (696.1)	0.4	9	0.2	3
Other Skin Disorders (700-709.9)	6.4	158	4.4	87
Hirsutism (704.1)	0.0	0	0.0	0
Acne (706.1)	0.4	11	0.3	6
Dyschromia (709.0)	<0.1	1	0.2	3
Unspecified skin disorder (709.9)	3.7	91	2.4	47
Unspecified Rash (782.1)	6.1	151	3.6	70

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

[b] Limited to skin conditions with ICD9-CM codes within these numerical ranges.

Table 5.4 Percent and Number of Vietnam and Non-Vietnam Veterans With Chloracne-Like Lesions and Other Acneiform Lesions at Dermatologic Examination

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[a]		Model 2[b]	
Condition	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Chloracne-Like Lesions	0.9	22	0.8	15	1.2	0.6-2.2	1.2	0.6-2.5	–	–
Any Acne	15.6	388	16.8	332	0.9	0.8-1.1	0.9[c]	0.8-1.1	0.9	0.8-1.1
Comedones only	4.3	107	4.6	91	0.9	0.7-1.2	0.9	0.7-1.2	0.8	0.6-1.1
Acne, Grade I	8.2	205	10.1	200	0.8	0.6-1.0	0.8	0.6-1.0	0.8[d]	0.6-1.0
Acne, Grade II	5.3	133	5.1	100	1.0	0.8-1.4	1.1[e]	0.8-1.5	1.1[e]	0.8-1.5
Acne, Grade III	1.7	42	1.8	35	0.9	0.6-1.5	1.0	0.6-1.6	0.9	0.6-1.5
Acne, Grade IV	1.0	24	0.5	10	1.9	0.9-4.0	2.0	0.9-4.2	–	–
Atypical acne	0.1	3	0.1	2	–	–	–	–	–	–

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and examiner, season of examination, region of residence, occupation, occupational exposure to herbicides, smoking status, alcohol consumption, illicit drug use, and body mass index.
[c] Standardized for race.
[d] Standardized for region of residence.
[e] Standardized for year of entry.

Grade IV acne in the Vietnam group. The number of veterans with Grade IV acne was, however, small and there was no evident trend, as the odds ratios were near unity for acne Grades I-III.

5.3.3 Hypertrichosis and Hyperpigmentation

Vietnam veterans did not report hypertrichosis or hyperpigmentation as conditions of current concern or as currently active skin problems more frequently than non-Vietnam veterans. When asked specifically during the interview if they had ever had such conditions, however, Vietnam veterans did report them more frequently. Regarding abnormal hair growth (hypertrichosis), 6.8% of Vietnam veterans compared with 2.5% of non-Vietnam veterans reported having had this condition, whereas 3.6% of Vietnam veterans compared with 2.5% of non-Vietnam veterans reported having had an unusual darkening of their skin (hyperpigmentation) during the previous year. In the examination, however, both hypertrichosis and hyperpigmentation were found at a similar low frequency in the two groups (Table 5.5).

5.3.4 Porphyria Cutanea Tarda (PCT)

None of the examination participants in either group reported a history of porphyria. The urinary porphyrin pattern for only one veteran, a Vietnam veteran, was consistent with PCT (see Chapter 6), but he had no dermatologic manifestations. The urinary porphyrin patterns

Table 5.5 Percent and Number of Vietnam and Non-Vietnam Veterans With Hypertrichosis or Hyperpigmentation at Dermatologic Examination

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[a]		Model 2[b]	
Condition	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Hypertrichosis	0.2	5	0.3	5	0.8	0.2-2.7	–	–	–	–
Hyperpigmentation	4.0	99	3.2	63	1.3	0.9-1.7	1.2	0.9-1.7	1.2	0.8-1.7

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and examiner, season of examination, region of residence, occupation, occupational exposure to herbicides, smoking status, alcohol consumption, illicit drug use, and body mass index.

for 10 veterans—6 Vietnam and 4 non-Vietnam—were consistent with chronic hepatic porphyria, but none of the veterans had any dermatologic manifestations of PCT.

5.3.5 Skin Cancer

Skin cancer, as determined by the history or the examination, occurred with similar frequency in the two groups (Table 5.6). Many of the veterans who reported a history of skin cancer did not specify the type. Most of the skin cancers detected during the dermatology examination appeared to be basal cell carcinomas.

5.3.6 Skin Infections

The medical history findings suggested that the Vietnam veterans may have had, or now have, more skin infections than non-Vietnam veterans. The examination, however, showed that infections or infection-related conditions of the skin were present with similar frequency in the two groups; the only exception was a slight excess of *Tinea versicolor* among Vietnam veterans (Table 5.7). The more common fungal infections (Tinea of the nails and other Tinea) were present with nearly identical frequencies in the two cohorts. The frequency of postinflammatory scarring, as possible evidence of past skin infections, was also similar in the two groups.

5.3.7 Other Skin Conditions

All of the 68 conditions evaluated in the dermatology examination, their prevalences by place of service, and the odds ratios are shown in Appendix B. Most of the conditions were noted with similar frequency in the two groups. There were 22 conditions with an odds ratio of >1.0, and 23 with an odds ratio of <1.0. Most of the odds ratios did not deviate substantially from 1.0, with 81% (55/68) in the 0.8 to 1.3 range.

The conditions with odds ratios of ≥1.3 included hyperpigmentation, Grade IV acne, candida infections, *T. versicolor* infections, epidermal inclusion cysts, actinic keratosis, milia, poikiloderma of Civatte, dyshidrosis, lichen simplex chronicus, and psoriasis. Of these, only epidermal inclusion cysts (OR=1.3) and milia (OR=2.0) had odds ratios with 95% confidence intervals that did not include 1.0. The associations with these two conditions were not materially altered by the results of multivariate analyses that included either the six primary covariates or other secondary covariates.

5.4 DISCUSSION

Neither Vietnam nor non-Vietnam veterans frequently reported skin abnormalities that could have been related to Agent Orange or dioxin exposure, but Vietnam veterans did

Table 5.6 Percent and Number of Vietnam and Non-Vietnam Veterans With Skin Cancer, by Source of Diagnosis

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results			
							Model 1[a]		Model 2[b]	
Source of Diagnosis	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Medical history	1.0	24	0.9	18	1.1	0.6-2.0	1.1	0.6-2.1	–	–
Dermatology exam	0.6	15	0.7	14	0.8	0.4-1.8	0.8	0.4-1.7	–	–
Either	1.5	37	1.6	31	0.9	0.6-1.5	0.9	0.6-1.6	0.9	0.6-1.6

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and examiner, season of examination, region of residence, occupation, occupational exposure to herbicides, smoking status, alcohol consumption, illicit drug use, and body mass index.

Table 5.7 **Percent and Number of Vietnam and Non-Vietnam Veterans With Infection-Related Skin Conditions at Dermatologic Examination**

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results			
							Model 1[a]		Model 2[b]	
Condition	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Any Infection	59.1	1471	59.3	1169	1.0	0.9-1.1	1.0	0.8-1.1	1.0	0.8-1.1
Folliculitis	21.0	524	21.8	430	1.0	0.8-1.1	0.9[c]	0.8-1.1	0.9[d]	0.7-1.0
Hidradenitis suppurativa	0.1	3	0.2	4	–	–	–	–	–	–
Cancer case	0.5	12	0.4	7	1.4	0.5-3.5	–	–	–	–
Tinea, nails	15.2	379	14.7	290	1.0	0.9-1.2	1.0	0.9-1.2	1.0	0.8-1.2
Tinea versicolor	3.6	89	2.7	53	1.3	1.0-1.9	1.3	0.9-1.8	1.3	0.8-1.9
Tinea, other	33.1	823	33.7	664	1.0	0.9-1.1	1.0	0.8-1.1	1.0	0.8-1.1
Other infection	0.9	23	0.8	15	1.2	0.6-2.3	1.1	0.5-2.1	–	–
Postinflammatory Scars	17.8	444	18.0	355	1.0	0.8-1.2	1.0	0.9-1.2	1.0	0.8-1.2

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and examiner, season of examination, region of residence, occupation, occupational exposure to herbicides, smoking status, alcohol consumption, illicit drug use, and body mass index.
[c] Standardized for military occupational specialty and general technical test score.
[d] Standardized for military occupational specialty and occupation.

report more of these abnormalities. However, current dermatologic manifestations of such conditions—particularly chloracne-like lesions, hypertrichosis, and hyperpigmentation—occurred with similar frequency in the two groups. The only veteran with PCT—according to urinary porphyrin profiles—did not have any dermatologic manifestations. No evidence for an increased risk of skin cancer was found among the Vietnam veterans. Skin infections were reported more frequently by, and appear to be of greater concern to, the Vietnam veterans, but, on examination, no evidence of a current increase in infectious dermatologic conditions was found among the Vietnam veterans.

Those skin conditions that were not expected to show an association with Vietnam military service were, for the most part, similarly frequent in the two cohorts. The only two conditions that had an increased prevalence in Vietnam veterans and met the usual criterion for statistical significance were milia and epidermal inclusion cysts. Given the large number of conditions evaluated, these increases may represent chance statistical associations. The two lesions, however, have similar histologic features, which suggests that the associations may be based on more than just chance. In any event, both lesions are benign and of minor clinical significance.

These findings are not surprising, since the examinations were performed 15 to 20 years after the veterans had been in military service. Most of the conditions of interest would be expected to have resolved; therefore, the differences in findings between the history and examinations are not incompatible. Any chloracne that might have occurred as a result of Vietnam military service would have had an onset 15 to 20 years before the examination. Although cases of chloracne have been reported to persist for up to 30 years (Tindal, 1985; May, 1982; Pazderova-Vejlupkova *et al.*, 1981), they usually resolve within a few months to a few years. Thus, chloracne probably would not have still been present at the time of the dermatologic examinations. The few cases of chloracne-like skin lesions that were detected in the examinations occurred with similar frequency in the two groups. Chloracne may, however, be impossible to distinguish from acne vulgaris on the basis of skin lesions alone,

and the few chloracne-like cases could well represent cases of acne vulgaris in which comedones just happened to be present in chloracne-sensitive skin sites.

Most of the other skin conditions that were of primary interest would also be expected to have resolved within a few years after exposure ceased. Two possible exceptions are hypertrichosis and infections with *Trichophyton mentagrophytes*. The findings would suggest, however, that hypertrichosis was a problem for only a small number of veterans and was not increased among the Vietnam veterans. Although *T. mentagrophytes* was not specifically evaluated, the finding that common fungal lesions, in general, occurred with similar frequency in the two groups suggests that *T. mentagrophytes* infections have not been a persistent problem for many Vietnam veterans.

The possibility that biases in study design or conduct affected the findings needs to be considered. Of greatest concern is the possibility that bias, caused by selective participation, influenced the results. The examination participation rate for the Vietnam group was higher than the rate for the non-Vietnam group (see Chapter 3). In both groups, veterans who reported having had any skin problems during or after discharge from active duty were more likely to participate in the examinations, but this increased participation was similar in both groups. As a result, the prevalence ratio of veterans with histories of dermatologic problems for Vietnam veterans compared with non-Vietnam veterans was the same, 1.5, in the telephone interview sample and the examination sample. Thus, differential participation is not likely to have influenced appreciably the relative dermatologic findings in the two cohorts.

Possible information or detection biases are also concerns. Certainly, some of the increased prevalence of self-reported dermatologic conditions among Vietnam veterans could be due to their differential or enhanced recall of these conditions. These biases, however, do not appear to have influenced findings from the dermatologic examination. If such biases were influencing our analysis of examination findings, given that we found virtually no differences in the prevalence of abnormalities, we would have to speculate that the examiners were underascertaining conditions in the Vietnam veterans compared with the non-Vietnam veterans. This is not likely, since the dermatologists did not know where the participants served. Furthermore, any ascertainment bias the examiners introduced would be expected to alter the findings in an opposite direction. It seems reasonable to assume that the examiners' general expectations would be for Vietnam veterans to have worse health than non-Vietnam veterans. Therefore, we would expect that any detection bias would have resulted in overascertainment of problems among Vietnam veterans compared with non-Vietnam veterans.

Another concern is the relatively large variability among examiners in the prevalence of specific diagnoses. Additional analyses showed no evidence that this variability introduced confounding or effect modification into the study results. Thus, although the prevalence estimates for certain conditions varied widely according to examiner, the relative risks (comparing Vietnam with non-Vietnam veterans) did not, in general, vary by examiner.

The findings are also not likely to be explained on the basis of confounding by other factors. The two cohorts were very similar on most important characteristics that could influence dermatologic conditions. Furthermore, results of additional analyses, adjusted for the effects of several important covariates, did not change the study results.

Another possibility is that the study did not have sufficient power to detect differences between the two groups or that increased risk occurred only in certain subgroups and not in Vietnam veterans in general. The size of the sample examined was sufficient to detect a

doubling of the relative risk for conditions with a prevalence of 1% to 1.5%. Most of the conditions of primary interest were present at this level or higher, except for chloracne-like lesions, PCT, and hypertrichosis. The point estimate of the relative risk for chloracne-like lesions indicates that even if chloracne did occur among some Vietnam veterans, it has not left residual lesions or scars to the extent that these lesions or scars are now more prevalent in the Vietnam veterans than in the non-Vietnam veterans. Even though only a few men were found to have hypertrichosis, the finding of an equal number in each group suggests that the condition is not a greater problem in Vietnam veterans than in non-Vietnam veterans. PCT was found in only one veteran, indicating that if PCT is a problem among Vietnam veterans, it affects only a few. The extensive analyses that were done for interactions in the multivariate models did not identify a subgroup of Vietnam veterans who were at increased risk for dermatologic problems.

In summary, skin conditions that could be associated with dioxin exposure occurred infrequently, but Vietnam veterans reported these conditions more often than non-Vietnam veterans. Current manifestations of these conditions, however, were equally present in both groups. In the past, Vietnam veterans may have had more dermatologic problems, particularly skin infections, but, for the most part, these problems have left no lasting sequelae in terms of an increased prevalence of current skin abnormalities.

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CHAPTER 6

Gastrointestinal System

6. GASTROINTESTINAL SYSTEM

6.1 INTRODUCTION

In this chapter we describe the gastrointestinal conditions found among Vietnam and non-Vietnam veterans who participated in the Vietnam Experience Study (VES). We also present the results of several serum enzyme determinations and other laboratory tests conducted during the medical examination. These assays, and their results, are included in this chapter, because most are commonly referred to as "liver function tests" (McIntyre, 1985); we recognize, however, that other organ systems can also affect the tests and their results.

As previously noted, in our evaluation we adopted a broad approach to two types of health conditions: (1) those that Vietnam veterans have expressed concerns about, and (2) those that investigators have suggested might be associated with exposure to phenoxyherbicides or dioxin. Before the analysis, we selected seven conditions for detailed study. We selected them on the basis of results of previous studies of gastrointestinal problems among military veterans and of health outcomes associated with dioxin or phenoxyherbicide exposure. These seven conditions are hepatitis B infection, elevation of serum transaminases, induction of hepatic microsomal enzymes, alterations in cholesterol and triglyceride levels, urinary porphyrin abnormalities, alcohol-related liver disease, and gastric and duodenal ulcers.

In 1964, during the early part of the Vietnam conflict, medical concern about hepatitis led to several programs in which all arriving troops were given gamma globulin as a preexposure prophylaxis (Dean and Ognibene, 1982). The following year, when the conflict escalated supplies of gamma globulin dwindled, and these programs had to be discontinued. The incidence of clinical hepatitis due to all causes among American soldiers in Vietnam between 1965 and 1971 was 6 to 10 cases per 1,000 per year (Dean and Ognibene, 1982). Hepatitis was listed as one of the main causes of death among medical patients hospitalized in Vietnam (Arnold and Cutting, 1978). In two studies of blood specimens from military personnel, investigators found that about 40% of those with clinical hepatitis were infected with hepatitis B (Neumann and Benenson, 1974; Snitbhan *et al.*, 1975). Hepatitis B infection was endemic in Southeast Asia; analyses of surface antigen subtypes suggested that hepatitis B was being transmitted from the native population to military personnel stationed in Vietnam (Dean and Ognibene, 1982; Snitbhan *et al.*, 1975).

Elevated levels of aspartate (AST) and alanine aminotransferase (ALT) have been found in blood specimens from humans after acute exposures to dioxin (Webb *et al.*, 1986). These levels may indicate hepatocellular damage (McIntyre, 1985), but because the two enzymes, particularly AST, are found in other organs, they may reflect other types of damage. Hepatocellular damage has many causes, including infectious and inflammatory diseases, circulatory disorders, and exposure to drugs, such as alcohol, and other toxins.

The results of several studies of humans have suggested that exposure to dioxin may induce the production of microsomal enzymes. Other substances that induce these enzymes include alcohol, cigarette smoke, medications, and certain illicit drugs (Hunter and Chasseaud, 1976). For humans, the induction of enzymes is difficult to measure directly, but some investigators have suggested that elevated levels of D-glucaric acid in urine and γ-glutamyl transferase (GGT) in serum may reflect the induction of microsomal enzymes (Goldberg, 1980). In a study in Seveso, Italy, investigators found that urinary D-glucaric acid

levels were higher among children living near a chemical plant 5 years after a reactor explosion than among children who had never lived near the plant (Ideo *et al.*, 1985). May (1982), studying a group of workers 10 years after an industrial explosion involving herbicide production, found higher mean levels of D-glucaric acid among employees exposed to the herbicide than among those who were not exposed. These employees also had higher mean levels of GGT. In contrast, however, in the Ranch Hand Study of U.S. Air Force personnel involved in the aerial spraying of Agent Orange in Vietnam, investigators found no significant differences in the GGT levels obtained in the baseline examination (Lathrop *et al.*, 1984) or in the first follow-up examination (Lathrop *et al.*, 1987).

Several investigators have suggested that changes in the levels of cholesterol and lipids in serum may also reflect the induction—by dioxin—of hepatic enzymes (May, 1982; Moses *et al.*, 1984; Walker and Martin, 1979). Elevated triglyceride and cholesterol levels have been found among humans exposed to dioxin (Martin, 1984; Moses *et al.*, 1984; Walker and Martin, 1979). Other investigators, however, have found no such differences in triglyceride levels (Suskind and Hertzberg, 1984). Furthermore, in three studies investigators found that total cholesterol levels were lower in the exposed groups (Hoffman *et al.*, 1986; Lathrop *et al.* 1987; May, 1982).

As noted in Chapter 5, porphyria cutanea tarda (PCT) is often cited as a possible effect of exposure to dioxin. However, only two groups of investigators have reported an association, in humans, between exposure to dioxin and PCT (Pazderova-Vejlupkova *et al.*, 1981; Poland *et al.*, 1971). Further, both studies involved workers potentially exposed to other substances during their employment, so the PCT may have been caused by exposure to a chemical other than dioxin—hexachlorobenzene, for example (Jones and Chelsky, 1986).

PCT, a heritable or acquired disorder of hepatic heme synthesis, has several dermatologic manifestations. PCT is believed to be one disorder within the larger category of chronic hepatic porphyria (Hill, 1985). Doss (1979) has postulated that chronic hepatic porphyria, regardless of its cause, develops in stages, each with its own pattern of urinary porphyrins. These porphyrin patterns have been further characterized (Strik *et al.*, 1980), and distinct types of chronic hepatic porphyria have been identified.

The ingestion of alcohol may have acute and chronic effects on liver function. Excessive alcohol use among Vietnam veterans has been previously described (Egendorf *et al.*, 1981; Yager *et al.*, 1984). In the mortality component of the VES, the proportion of Vietnam and non-Vietnam veterans dying from alcohol-related natural causes (including alcohol-related liver disease) was the same (Centers for Disease Control Vietnam Experience Study, 1987). In a study among Australian conscripts, however, the mortality rate for diseases of the digestive system was significantly higher among veterans who served in Vietnam than among veterans who served elsewhere (Fett *et al.*, 1987). Chronic abuse of alcohol was a common factor in most of these deaths.

Several investigators have noted a higher prevalence of ulcer disease among veterans with certain war experiences. Goulston *et al.* (1985) found a significantly higher prevalence of endoscopically confirmed ulcer disease among World War II veterans who were former prisoners-of-war. Others have shown a similar association between ex-prisoner status and subsequent ulcer disease (Beebe, 1975; Gill and Bell, 1981).

In addition, the results of several studies of humans have suggested an association between peptic ulcer disease and exposure to dioxin or phenoxyherbicides (Poland *et al.*, 1971; Suskind and Hertzberg, 1984). One group of investigators (Bond *et al.*, 1983) reported

a significantly higher prevalence of radiographically proven ulcer disease among workers who had been exposed to dioxin during the industrial production of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) than among workers who had not been exposed.

Within the context of the medical examination component of the VES, we are limited in evaluating the current prevalence of alcohol-related liver disease and ulcer disease. No single laboratory test or set of tests was available for readily diagnosing these two conditions. Invasive tests such as liver biopsy and gastrointestinal endoscopy, which would have provided information for diagnosing these conditions, were not included in the examination. Thus, in evaluating of these two health outcomes, we must rely primarily on historical information.

Diarrheal diseases, caused by a variety of viral, bacterial, and parasitic agents, were a major cause of disability among troops serving in Vietnam (Neel, 1973). Between 1965 and 1969 the average annual rate of hospitalization for diarrheal diseases ranged from 35 to 69 per 1,000 men. Since most of these diseases were acute, self-limited illnesses for which recovery was the general rule, we did not expect to find residual health effects from previous infections.

6.2 METHODS

The information in this chapter was obtained from three sources: (1) self-reported medical histories; (2) general physical examinations; and (3) laboratory assays. During the study, all physicians, interviewers, and technicians were unaware of the veterans' cohort status.

6.2.1 Medical History and Physical Examination

As described in Chapter 2, physician's assistants administered a standardized medical history questionnaire, and the clinic manager monitored the interviews daily. Results of an analysis of the quality of the data are given in Supplement B (Medical and Psychological Data Quality) of the monograph. In brief, we found little interobserver variability among interviewers for any of the items on the questionnaire.

Board-certified internists performed standardized physical examinations, and during the examinations, they were not permitted to elicit any historical information from participants. Results of quality control analyses showed variability in the prevalence of the physical findings. There was no indication, however, that this variability introduced either confounding or effect modification into the analysis of cohort differences. Results of these quality control analyses are also presented in Supplement B.

6.2.2 Laboratory Tests

Lovelace Clinical Laboratory, using methods described in Chapter 2, performed the laboratory tests; these assays and the values that define their reference ranges, are listed in Table 6.1. The serum tests were done with a Kodak Ektachem 700 autoanalyzer. In addition, serologic tests for hepatitis B surface antigen (HBsAg) and antibodies to core antigen (HBcAb) and surface antigen (HBsAb) in serum were measured by using commercially available radioimmunoassays.

An overnight (about 12 hours) collection of urine was tested for creatinine, D-glucaric acid, and porphyrins. D-glucaric acid was measured by using ion-exchange chromatography. Urine porphyrins were quantified by using high-performance liquid chromatography (HPLC)

Table 6.1 Reference Values for Serum Enzymes and Other Laboratory Tests Associated With Liver Function

Serum Analytes	Reference Value[a]
Alanine aminotransferase, IU/L	92.0
Aspartate aminotransferase, IU/L	56.0
Lactic dehydrogenase, IU/L	545.9
γ-glutamyl transferase, IU/L	140.9
Total bilirubin, mg/dL	1.6
Unconjugated bilirubin, mg/dL	1.1
Alkaline phosphatase, IU/L	126.0
Triglycerides, mg/dL	273.0
HDL cholesterol, mg/dL	28.6
Total cholesterol, mg/dL	282.0
Urine Analytes	
D-glucaric acid, mg/g of creatinine	29.1
Total porphyrins, (stop)m(stop)g/g of creatinine	92.0

[a] Reference values were defined as the 95th percentile for the Vietnam and non-Vietnam veteran cohorts combined, except for the reference value for HDL cholesterol, which was defined as the 5th percentile

(Hill *et al.*, 1982). Total porphyrin levels and D-glucaric acid levels are presented in units per gram of creatinine, to adjust for differences in urine volume. Stool was tested for occult blood by using Hemoccult slides (Smith Kline).

All laboratory tests were monitored by using bench and "blind" repeat quality control procedures, as described in Chapter 2. In general, for the assays described in this chapter, the correlation between the original and repeat measures was high. Throughout the study, all bench controls were maintained within the acceptable contractual performance criteria. Detailed descriptions of all analytic procedures, performance criteria, quality control methods, and bench control data for each test are in Supplement A (Laboratory Methods and Quality Control). Data on blind repeat measures and intertechnician variability are in Supplement B.

For participant samples analyzed from February 17, 1986 through July 2, 1986, a problem with a calibration standard (instability over time), which the manufacturer later identified, caused total bilirubin values to be falsely elevated. The assays could not be repeated because bilirubin is light sensitive, and thus unstable. Therefore, the determinations for 1,226 participants were lost, and the sample size for this assay was reduced from 4,462 to 3,236 (1,837 Vietnam and 1,399 non-Vietnam veterans). The problem did not affect the assay for unconjugated bilirubin because, in that assay, a different calibration standard is used.

In July 1985, about 1 month after the medical examinations had begun, porphyrin analyses were phased into the study. During the first 6 months of analyses, specimens were screened by means of a spectrophotometric test (Jones and Sweeney, 1979) that measured total urinary porphyrins. Those specimens with total porphyrin levels ≥250 ug/L (or ≥160 ug/g urine creatinine) were further tested by using HPLC to quantify five porphyrins—coproporphyrin, heptacarboxylporphyrin, hexacarboxylporphyrin, pentacarboxylporphyrin, and uroporphyrin (Hill *et al.*, 1982). Beginning in January 1986, the spectrophotometric screening test was discontinued, and HPLC was used to measure the five porphyrins in all specimens.

For analysis of the porphyrin data, we classified study participants by type of chronic hepatic porphyria (CHP) pattern, using the five porphyrins assayed by HPLC. This classification is outlined in Table 6.2 (Hill, 1985; Strik *et al.*, 1980). Since CHP could be detected by

Table 6.2 Urinary Porphyrin Chromatographic Patterns of Chronic Hepatic Porphyria (CHP)

Pattern Classification[b]	Porphyrin distribution[a]				
	URO/COP	HEP/COP	% URO	% HEP	% (URO+HEP)
Normal	.2-.5	<1	<20	<5	<25
Type A	<1	<1	<30	5-15	30-50
Type B	>1	<1	30-50	15-20	45-70
Type C	>1	>1	>50	20-30	50-80
Type D	>1	>1	>60	25-35	65-90

[a] COP = coproporphyrin, HEP = heptacarboxylporphyrin, URO = uroporphyrin; URO/COP and HEP/COP are ratios; % URO, % HEP, and % (URO+HEP) refer to percent of total porphyrin.
[b] Adapted from Strik *et al.* (1980).

using the spectrophotometric screening test, its prevalence was estimated on the basis of results from all 4,131 participants (2,289 Vietnam and 1,842 non-Vietnam veterans) tested beginning in July 1985. Total porphyrin levels were calculated as the sum of the five specific porphyrins assayed by HPLC. Because routine HPLC measurement of the porphyrins was available only during the second half of the study period, the analysis comparing total porphyrin levels between cohorts was limited to the 2,284 participants (1,241 Vietnam and 1,043 non-Vietnam veterans) whose specimens had been analyzed by means of HPLC between January and September 1986.

6.2.3 Statistical Methods

We used the analytical methods described in detail in Chapter 2. All the results of continuous laboratory assays reported in this chapter were approximately log normally distributed; thus, these results were log transformed before they were analyzed. Unless otherwise noted, the reference ranges for laboratory measures were defined by the 95th percentile of the distribution for that measure in both cohorts combined.

In the Model 2 regression analyses, we used the following three covariates (defined in Chapter 2): current alcohol consumption, current illicit drug use, and body mass index. Current alcohol dependence was defined by using Diagnostic Interview Schedule criteria for the presence of this syndrome in the month preceding the examination, as described in Volume IV (Psychological and Neuropsychological Evaluation) of the monograph. To categorize tobacco smoking status (defined as current cigarette use versus other), we combined ex-smokers with "never-smokers." We also adjusted results of these analyses for current use of medications known to affect laboratory assays (Sedman, 1984; Sherman and Finlayson, 1982; Wallach, 1986). Few veterans in either cohort used these medications (listed in Table 6.3). Results of regression analyses, which included other variables—current annual income, education, region of birth, marital status, history of diabetes, hepatitis B surface antigen status, reported occupational exposure to herbicides—suggested that these additional variables had little or no effect on the comparisons between cohorts, and so we did not include these variables in the final regression models.

6.3 RESULTS

6.3.1 General Medical History

In general, Vietnam veterans were more likely than non-Vietnam veterans to report a history of physician-diagnosed gastrointestinal conditions, with onset after military service (Table 6.4). Ulcer disease (stomach and duodenal) was the most prevalent of these

Table 6.3 Current Medications Reported by Vietnam and Non-Vietnam Veterans That Affect Selected Laboratory Test Values

A. Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Use of Medications That Affect Laboratory Assays, by Type of Assay

Assay	Vietnam		Non-Vietnam	
	%	No.	%	No.
D-glucaric acid and γ-glutamyl transferase	2.1	52	2.3	45
Total bilirubin	2.1	51	1.7	33
ALT and AST[a]	1.6	39	1.0	20
Cholesterol	4.5	111	4.0	78
Triglycerides	0.7	18	0.5	9

B. Current Medications Reported by Veterans that Affect Laboratory Assays, by Type of Assay[b]

D-glucaric acid and γ-glutamyl transferase

Isoniazid
Metronidazole
Cimetidine
Carbamezepine
Phenytoin
Griseofulvin
Meprobamate
Rifampin
Phenobarbital
Butalbital

Bilirubin

Epinephrine
Methyldopa
Phenelzine
Theophylline
Ascorbic acid
Codeine
Heroin

ALT and AST[a]

Ascorbic acid
Codeine
Heroin
Isoniazid
Hydralazine

Triglycerides

Estrogens
Cholestyramine
Ascorbic acid

Cholesterol

Phenytoin
Thiazides
Sulfonamides
Corticosteroids
Colestipol
Allopurinol
Tetracyclines
Erythromycin
Isoniazid
MAO inhibitors
Azathioprine
Neomycin
Estrogens
Cholestyramine
Thyroxine

[a] ALT = alanine aminotransferase, AST = aspartate aminotransferase.
[b] Includes only those medications reportedly used at time of examination. Other medications that may affect these laboratory assays but not used by veterans are not listed.

conditions; the absolute difference between cohorts for this diagnosis was about 2%. More Vietnam than non-Vietnam veterans reported a history of alcohol-related liver damage and pancreatitis, but few participants in either cohort reported a history of cirrhosis.

About one-tenth of the veterans in each cohort reported being hospitalized since their discharge from service because of gastrointestinal conditions (Table 6.5). Slightly more non-Vietnam veterans had been hospitalized for disorders of the esophagus, stomach, and duodenum. This category included 2.0% non-Vietnam and 1.4% Vietnam veterans who reported hospitalizations for ulcer disease. Only 0.4% Vietnam and 0.2% non-Vietnam veterans reported hospitalizations for gastritis. A similarly small proportion of veterans in either group had been hospitalized for gastrointestinal hemorrhage.

Table 6.4 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Physician-Diagnosed Gastrointestinal Conditions Since Discharge

Condition	Vietnam		Non-Vietnam	
	%	No.	%	No.
Alcohol-related liver damage	1.5	38	0.9	17
Pancreatitis	0.5	12	0.4	8
Hepatitis	3.1	74	2.6	50
Cirrhosis	0.2	5	0.3	5
Gastritis	6.2	152	5.2	102
Stomach or duodenal ulcer	8.6	210	6.7	129

Table 6.5 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Gastrointestinal Hospitalizations Since Discharge

Reason for Hospitalization (ICD9-CM Codes)	Vietnam		Non-Vietnam	
	%	No.	%	No.
Hepatitis (070)	<0.1	1	0.2	3
Malignancy (150-159)	0.1	3	0.0	0
Disorders of esophagus, stomach or duodenum (530-537)	2.5	61	2.9	57
Appendicitis (540-543)	2.2	55	2.5	49
Hernia (550-553)	4.3	107	2.8	56
Enteritis or colitis (555-558)	0.7	17	0.7	13
Other intestinal diseases (560-569)	1.3	33	0.8	15
Liver necrosis or cirrhosis (570-571)	<0.1	1	0.1	1
Other liver disorders (572-573)	1.0	26	0.9	18
Biliary disease (574-576)	0.8	19	0.9	17
Pancreatic disorders (577)	0.4	11	0.3	5
Hemorrhage (578)	0.2	5	0.2	4
Any of above (070, 150-159, 530-578)	12.1	301	11.0	217

In addition to being the most common reason for prior hospitalization, hernias were the most frequently reported condition that required surgical repair (Table 6.6). Vietnam veterans were more likely to report past hernia surgery, and in each group most of these procedures involved inguinal hernias. Operations on the anus, the next most prevalent site of surgery, primarily involved procedures for hemorrhoids. About 2% of veterans in both groups had had appendiceal surgery since being discharged. Other sites of surgical procedures involving the gastrointestinal system were rare for both cohorts.

Vietnam veterans were more likely than non-Vietnam veterans to report having gastrointestinal symptoms during the year preceding the examination (Table 6.7). Overall, 25% of Vietnam and 20% of non-Vietnam veterans reported having at least one symptom in the previous year. Symptoms included diminished appetite, weight loss, difficulty swallowing food, recurrent abdominal pain, vomiting of blood, bloody stools, and loose bowel movements. The absolute difference between cohorts in the prevalence of any particular symptom was less than 3%.

Table 6.6 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Gastrointestinal Surgical Procedures Since Discharge, by Site of Surgery

	Vietnam		Non-Vietnam	
Site of Surgery (ICD9-CM Codes)	%	No.	%	No.
Esophagus (42)	0.1	2	0.1	
Stomach (43-44)	0.6	16	0.6	
Intestine (45-46)	0.4	10	0.3	6
Appendix (47)	2.2	55	2.5	49
Anus (48-49)	3.0	74	2.6	5
Liver (50)	0.1	2	0.2	3
Biliary system (51)	0.7	17	0.9	18
Pancreas (52)	<0.1	1	0.0	0
Hernia (53)	4.0	100	2.6	52
Other (54)	0.6	15	0.5	9
Any of above (42-54)	10.8	269	9.4	185

Table 6.7 Percent and Number of Vietnam and Non-Vietnam Veterans With Self-Reported Gastrointestinal Symptoms In Past Year

	Vietnam		Non-Vietnam	
Gastrointestinal Symptom	%	No.	%	No.
Appetite loss lasting more than 2 weeks	3.6	90	2.1	41
Rapid unexplained weight loss >10 pounds	2.3	58	1.2	24
Unexplained difficulty swallowing food	2.7	68	1.6	31
Recurrent abdominal pain at same location	10.2	254	8.1	160
Vomiting blood	1.1	27	0.7	14
Having a bloody or tar-like stool	7.6	188	6.4	126
Abnormally frequent or loose stools	9.7	240	8.3	164
Any of above	25.2	627	20.2	390

Nearly a quarter of the veterans in both cohorts reported having gastrointestinal symptoms in the past year, but only about 5% of the veterans reported having currently active gastrointestinal problems (Table 6.8). Overall, current gastrointestinal problems were not much more prevalent among the Vietnam veterans than among the non-Vietnam veterans. Only 1% of the veterans in either group reported gastric or duodenal ulcers as a current health problem. Other conditions of particular interest in this study (hepatitis, alcohol-related liver diseases such as cirrhosis) were reported rarely in either group and did not appear to be of greater concern to the Vietnam veterans than to the non-Vietnam veterans.

Few veterans reported current use of gastrointestinal medications (Table 6.9). Almost all of these medications were for the treatment of ulcers, and their reported use was about the same for the two groups.

6.3.2 Hepatitis B Infection

Few veterans in either cohort were currently infected with hepatitis B (Table 6.10), as evidenced by the small proportion who were positive for hepatitis B surface antigen (HBsAg). The tests of more Vietnam than non-Vietnam veterans were positive for antibodies to hepatitis B surface antigen (HBsAb) and core antigen (HBcAb). In both groups, the most prevalent marker for hepatitis B infection was HBcAb. The prevalence of past hepatitis B infection (defined as having antibody to either surface or core antigens while being negative

Table 6.8 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Gastrointestinal Problems[a]

	Vietnam		Non-Vietnam	
Condition (ICD9-CM Codes)	%	No.	%	No.
Hepatitis (070)	<0.1	1	0.0	0
Malignancy (150-159)	<0.1	1	0.0	0
Diseases of esophagus, stomach or duodenum (530-537)	2.6	65	2.2	44
Appendicitis (540-543)	<0.1	1	0.0	0
Hernia (550-553)	0.8	19	0.9	17
Enteritis or colitis (555-558)	0.6	15	0.5	9
Other intestinal diseases (560-569)	1.0	26	1.2	23
Liver necrosis or cirrhosis (570-571)	0.2	4	0.1	2
Other liver disorders (572-573)	0.2	4	0.1	2
Biliary disease (574-576)	0.1	2	0.0	0
Pancreatic disorders (577)	0.1	2	0.1	2
Hemorrhage (578)	0.2	5	0.1	1
Any gastrointestinal condition (070, 150-159, 530-578)	5.4	134	4.8	94

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

Table 6.9 Percent and Number of Vietnam and Non-Vietnam Veterans Reporting Current Use of Gastrointestinal Medications, by Type of Medication

	Vietnam		Non-Vietnam	
Type of Medication	%	No.	%	No.
Antiulcer	1.9	48	1.8	35
Antidiarrheals	0.2	6	0.1	2
Laxatives	0.1	2	0.2	3
Miscellaneous	0.2	6	0.2	3
Any of above	2.3	56	2.0	40

for HBsAg) was significantly higher among Vietnam veterans, even after the results were adjusted for smoking status, alcohol consumption, body mass index, and current illicit drug use.

6.3.3 Serum Transaminases

The mean values for alanine aminotransferase and aspartate aminotransferase did not differ significantly between cohorts (Table 6.11). The proportion of veterans with values above the reference range for either assay was the same in the two cohorts (Table 6.12). In addition, the groups of veterans were similar with respect to lactic dehydrogenase, a serum analyte that is usually increased, along with the serum transaminases, when there is hepatocellular damage.

6.3.4 Hepatic Microsomal Enzymes

Mean levels of D-glucaric acid were similar for Vietnam and non-Vietnam veterans (Table 6.11). The unadjusted geometric mean for γ-glutamyl transferase (GGT) was about 5%

Table 6.10 Percent and Number of Vietnam Veterans With Positive Serologic Tests for Hepatitis B and Odds Ratios, by Type of Test

	Vietnam		Non-Vietnam		Crude Results		Multivariate Results: Model 1[a]		Model 2[b]	
Laboratory Test	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Hepatitis B surface antigen	0.5	13	0.9	18	0.6	0.3-1.2	0.6	0.3-1.2	–	–
Antibody to hepatitis B surface antigen	8.9	221	6.0	119	1.5	1.2-1.9	1.5	1.2-1.9	1.5	1.2-1.9
Antibody to hepatitis B core antigen	13.7	341	11.3	223	1.2	1.0-1.5	1.3	1.0-1.5	1.2[c]	1.0-1.5
Past hepatitis B infection[d]	14.1	350	11.1	217	1.3	1.1-1.6	1.4	1.1-1.6	1.3[c]	1.0-1.6

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and smoking status, alcohol consumption, body mass index, marijuana use, and other illicit drug use.
[c] Standardized for marijuana use.
[d] Defined as having antibody to either surface or core antigens while being negative for hepatitis B surface antigen.

Table 6.11 Means and Percent Differences Between Means for Laboratory Tests Associated With Liver Function for Vietnam and Non-Vietnam Veterans

	Crude Geometric Mean		Crude Results		Multivariate Results: Model 1[a]		Model 2[b]	
Laboratory Test	Vietnam	Non-Vietnam	% Diff	95% CI	% Diff	95% CI	% Diff	95% CI
Alanine aminotransferase, IU/L	26.4	25.8	2.4	-2.0,7.0	1.7	-2.8,6.5	0.1	-4.1,4.5
Aspartate aminotransferase, IU/L	26.0	26.0	0.1	-2.6,2.9	0.2	-2.6,3.1	-0.6	-3.6,2.1
Lactic dehydrogenase, IU/L	413.2	411.3	0.4	-0.6,1.5	0.5	-0.6,1.6	0.3	-0.7,1.4
D-glucaric acid, mg/g of creatinine	10.6	10.2	3.7	0.0,7.5	2.8	-1.0,6.8	3.1	-0.7,7.0
γ-glutamyl transferase, IU/L	43.2	41.1	5.2	1.3,9.2	4.5[c]	0.6,8.5	2.4[c]	-1.1,6.0
Triglycerides, mg/dL	94.1	92.6	1.6	-2.0,5.3	0.2	-3.4,4.0	-1.0	-4.3,2.4
HDL cholesterol, mg/dL	42.9	43.3	-0.8	-2.4,0.8	-0.5	-2.1,1.2	-0.3[d]	-1.7,1.2
Total cholesterol, mg/dL	209.8	207.2	1.3	0.1,2.5	1.1	-0.1,2.3	1.0	-0.2,2.2
Total porphyrins, μg/g of creatinine	43.0	42.2	1.7	-2.5,6.1	0.7	-3.6,5.2	0.4	-3.9,4.9
Total bilirubin, mg/dL	0.8	0.8	0.0	-2.6,2.6	0.5[e]	-2.2,3.3	0.4[e]	-1.6,2.5
Unconjugated bilirubin, mg/dL	0.5	0.5	-3.0	-5.9,0.0	-2.4	-5.4,0.8	-2.2	-5.2,0.9
Alkaline phosphatase, IU/L	82.9	81.7	1.5	0.0,3.1	1.2	-0.4,2.8	1.0	-0.6,2.5

[a] Model 1 contains the six entry characteristics.
[b] Model 2 contains the six entry characteristics and smoking status, alcohol consumption, body mass index, marijuana use, other illicit drug use, and medications taken at time of exam.
[c] Standardized for race.
[d] Standardized for marijuana use.
[e] Standardized for year of entry.

higher among Vietnam veterans than among non-Vietnam veterans, a statistically significant difference. The percent difference in mean values (standardized for race) changed little after the results were adjusted for the six entry characteristics. However, after adjustment for additional covariates associated with hepatic enzyme induction, particularly alcohol consumption, the difference in means between Vietnam and non-Vietnam veterans decreased to 2%, a statistically nonsignificant result.

The findings for the proportion of veterans with microsomal enzyme levels above the reference range were in accord with the comparisons of mean values (Table 6.12). The

Table 6.12 Percent and Number of Vietnam and Non-Vietnam Veterans With Laboratory Test Results Outside[a] of the Reference Range and Odds Ratios, by Selected Laboratory Tests Associated With Liver Function

							Multivariate Results			
	Vietnam		Non-Vietnam		Crude Results		Model 1[b]		Model 2[c]	
Laboratory Test	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI
Alanine aminotransferase	5.3	132	4.4	87	1.2	0.9-1.6	1.2	0.9-1.5	1.1	0.8-1.5
Aspartate aminotransferase	5.4	134	4.4	86	1.2	0.9-1.6	1.2	0.9-1.7	1.2	0.9-1.6
Lactic dehydrogenase	4.9	121	5.2	102	0.9	0.7-1.2	0.9	0.7-1.3	0.9	0.7-1.2
D-glucaric acid	5.1	127	4.9	96	1.0	0.8-1.4	1.0	0.8-1.4	1.0	0.8-1.4
γ-glutamyl transferase	5.5	136	4.4	87	1.3	1.0-1.6	1.3[d]	1.0-1.8	1.1[e]	0.8-1.6
Triglycerides	4.7	116	5.3	105	0.9	0.7-1.1	0.9[f]	0.7-1.2	0.9[f]	0.6-1.1
HDL cholesterol	5.3	131	4.3	84	1.2	0.9-1.7	1.2	0.9-1.5	1.1	0.8-1.5
Total cholesterol	5.1	126	4.7	93	1.1	0.8-1.4	1.1	0.8-1.5	1.1	0.8-1.4
Total porphyrins	5.2	65	4.5	47	1.2	0.8-1.7	1.2	0.8-1.8	1.2	0.8-1.8
Total bilirubin	5.1	94	4.9	69	1.0	0.8-1.4	1.0	0.7-1.4	1.0	0.7-1.4
Unconjugated bilirubin	4.9	122	5.3	104	0.9	0.7-1.2	0.9[g]	0.7-1.2	0.9[g]	0.7-1.3
Alkaline phosphatase	5.2	130	4.3	84	1.2	0.9-1.6	1.3	1.0-1.7	1.3	1.0-1.8

[a] Defined as values above the 95th percentile, except for HDL it was defined as below the 5th percentile.
[b] Model 1 contains the six entry characteristics.
[c] Model 2 contains the six entry characteristics and smoking status, alcohol consumption, body mass index, marijuana use, other illicit drug use, and medications taken at time of exam.
[d] Standardized for age at entry and race.
[e] Standardized for age at entry, race, and alcohol consumption.
[f] Standardized for type of enlistment.
[g] Standardized for year of entry.

proportion of veterans with D-glucaric acid values above the reference range was the same in both cohorts. The percent of veterans with elevated GGT levels was slightly higher for Vietnam veterans (unadjusted OR=1.3). This difference between cohorts was mostly attributable to alcohol consumption (adjusted OR=1.1).

Stratifying the results by race shows that most of the cohort differences in mean GGT levels are related to differences between black Vietnam and black non-Vietnam veterans (Table 6.13). After the results were adjusted for the six entry characteristics, the mean value was 23% higher among black Vietnam veterans than among black non-Vietnam veterans, whereas among white veterans the comparable difference was only 2.4%. Even after the results were adjusted for alcohol consumption, as well as other conditions that may affect GGT levels—body mass index, history of alcohol dependence, diabetes, hepatitis B surface antigen, elevated serum bilirubin, and current use of certain medications and illicit drugs—mean GGT levels were nearly 20% higher among black Vietnam veterans than among other black veterans.

When we analyzed the proportion of veterans with GGT levels above the reference range by race, we found no differences between cohorts for whites, but we did find differences between cohorts for blacks (Table 6.13). After we adjusted the results for conditions (excluding current alcohol consumption) that alter GGT levels, we found that black Vietnam veterans were twice as likely as black non-Vietnam veterans to have values above the reference range. With further adjustment for alcohol consumption, cohort differences within this subgroup diminished, but the proportion of black Vietnam veterans with elevated values was still larger.

Table 6.13 Differences in G-Glutamyl Transferase Test Results for Vietnam and Non-Vietnam Veterans, by Race

A. Means and Percent Differences Between Means in IU/L

							Multivariate Results			
	Crude Geometric Mean		Crude Results		Model 1[a]		Model 2, No Alcohol[b]		Model 2, With Alcohol[c]	
Race	Vietnam	Non-Vietnam	% Diff	95% CI	% Diff	95% CI	% Diff	95% CI	% Diff	95% CI
All races	43.2	41.1	5.2	1.3, 9.2	4.5	0.6, 8.5	3.8	0.1, 7.6	2.4	-1.1, 6.0
White	39.8	38.3	3.7	0.0, 7.6	2.4	-1.8, 6.7	1.5	-2.5, 5.7	0.6	-3.2, 4.5
Black	71.0	57.7	23.0	5.8, 43.0	23.2	10.8, 37.0	23.7	11.6, 37.0	19.8	8.5, 32.2
Other	52.0	51.2	1.6	-12.9, 18.6	0.0	-13.5, 15.5	-0.7	-13.6, 14.2	-4.3	-16.2, 9.4

B. Percent and Number of Veteran With Results Outside of the Reference Range and Odds Ratios[d]

	Vietnam		Non-Vietnam		Crude Results		Model 1[a]		Model 2, No Alcohol[b]		Model 2, With Alcohol[c]	
	%	No.	%	No.	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All races	5.5	136	4.4	87	1.3	0.9-1.6	1.3	1.0-1.8	1.4	1.0-1.8	1.1	0.8-1.6
White	3.1	64	3.0	48	1.0	0.7-1.5	1.0	0.7-1.5	1.0	0.7-1.5	0.9	0.6-1.4
Black	19.9	57	12.1	29	1.8	1.1-2.9	1.9	1.2-3.2	2.1	1.2-3.7	1.7	0.8-3.7

[a] Model 1 contains the six entry characteristics.

[b] Model 2, no alcohol, contains the six entry characteristics and smoking status, body mass index, marijuana use, other illicit drug use, and medications taken at time of exam. Estimates given are standardized for age at entry. For the "all races" category, estimates are also standardized for race.

[c] Model 2 contains the six entry characteristics and alcohol consumption, smoking status, body mass index, marijuana use, other illicit drug use, and medications taken at time of exam. Estimates given are standardized for age at entry and alcohol consumption. For the "all races" category, estimates are also standardized for race.

[d] Estimates are not presented for "other" races because of small sample size.

Table 6.14 Porphyrin Profiles From HPLC Chromatographs of Veterans With Chronic Hepatic Porphyria (CHP)

Place of Service and Case No.	Porphyrin Measures and Indices[a]											
	Total Porphyrin	URO	COP	HEP	HEX	PEN	URO/COP	HEP/COP	% URO	% HEP	% (URO+HEP)	Pattern Classification[b]
Vietnam												
1	1791	1389	117	175	44	66	11.9	1.5	77.6	9.8	87.3	Type D[c]
2	420	353	30	25	1	11	11.8	0.8	84.0	6.0	90.0	Type C
3	290	213	45	27	0	5	4.7	0.6	73.4	9.3	82.8	Type C
4	592	360	101	60	39	32	3.6	0.6	60.8	10.1	70.9	Type B
5	395	318	44	27	0	6	7.2	0.6	80.5	6.8	87.3	Type B
6	233	101	100	11	5	16	1.0	0.1	43.3	4.7	48.1	Type B
Non-Vietnam												
7	697	402	87	90	68	50	4.6	1.0	57.7	12.9	70.6	Type C
8	1301	773	338	80	22	88	2.3	0.2	59.4	6.1	65.6	Type B
9	390	217	130	23	0	20	1.7	0.2	55.6	5.9	61.5	Type B
10	150	82	48	10	5	5	1.7	0.2	54.7	6.7	61.3	Type B

[a] The following measures are in milligram per gram of urine creatinine: total porphyrin, COP = coproporphyrin, HEP = heptacarboxylporphyrin, HEX = hexacarboxylporphyrin, PEN = pentacarboxylporphyrin, URO = uroporphyrin; URO/COP and HEP/COP are ratios; % URO, % HEP, % (URO+HEP) refer to percent of total porphyrin.

[b] For classification criteria, see Table 6.2.

[c] Type D pattern is characteristic of porphyria cutanea tarda.

6.3.5 Cholesterol and Triglycerides

For the two cohorts, neither mean total cholesterol levels (Table 6.11) nor the proportions with values above the reference range differed (Table 6.12). Mean high density lipoprotein (HDL) cholesterol levels were similar between Vietnam and non-Vietnam veterans, as were the proportions in each cohort with low values for this assay. Measures of triglycerides were also similar for the two groups (Tables 6.11-6.12).

6.3.6 Urine Porphyrins

Mean total urinary porphyrins, and the proportion with values above the reference range, were similar between cohorts (Tables 6.11-6.12). Only 10 veterans, 6 Vietnam and 4 non-Vietnam veterans, met the criteria for chronic hepatic porphyria. Specific porphyrin patterns for these 10 veterans are presented in Table 6.14. Only one participant, a Vietnam veteran, had chronic hepatic porphyria pattern D, the type usually associated with porphyria cutanea tarda (PCT). None of the veterans with chronic hepatic porphyria had dermatologic findings, such as bullae or hypertrichosis, commonly associated with PCT. In addition none of these veterans had any history of chloracne, nor did they have any lesions compatible with chloracne noted during dermatologic examination.

6.3.7 Alcohol-Related Liver Disease

Certain physical findings may be associated with alcohol-related liver disease and cirrhosis. These findings include abdominal ascites, palpable liver, splenomegaly, scleral icterus, spider angioma, parotid gland enlargement, gynecomastia, and small testes. These signs were rarely detected during the physical examination, and the prevalence of each finding was similar in the two cohorts. Specific details on the occurrence of these findings are presented in Appendix C.

6.3.8 Other Gastrointestinal Conditions

The results of other laboratory tests that may reflect functional disturbances associated with liver disease, including bilirubin and alkaline phosphatase, were similar between cohorts (Tables 6.11-6.12). Results of additional assays, including albumin and prothrombin time, which are presented in Appendixes D and E, were also similar.

Over 30 gastrointestinal conditions were evaluated during the medical examinations, particularly during the medical history and physical examinations. These conditions are presented in Appendix Tables A.1 and C.1. For the most part, these other conditions occurred infrequently in either cohort. Differences, when detected, tended to be minor and did not follow any consistent pattern that suggested that one group was at higher risk for a particular series of adverse gastrointestinal outcomes than the other.

One noteworthy finding was that more Vietnam (1.3%) than non-Vietnam veterans (0.5%) had occult blood in their stools (OR = 2.8; 95% CI = 1.3-6.0). Among those with occult blood in their stools, 15 of 29 Vietnam veterans and 3 of 9 non-Vietnam veterans reported a past history of either peptic ulcer or gastritis or the occurrence of certain symptoms (vomiting of blood or black stools) in the year preceding the examination. In both groups, among the others whose tests were positive, there was a heterogeneous group of other conditions that can be associated with occult blood loss, including hemorrhoids, anal fissures, and the current use of certain medications (*e.g.*, aspirin and nonsteroidal antiinflammatory agents). Only 1, a Vietnam veteran, of the 38 with stool occult blood was anemic (hemoglobin <14 g/dL).

6.4 DISCUSSION

In our examination of the gastrointestinal system, we focused on several medical conditions and health measures that have been suggested as being associated with prior military service or exposure to phenoxyherbicides and dioxin. The prevalence of most gastrointestinal conditions was low in both cohorts. Although Vietnam veterans reported more past medical conditions and symptoms, we found few differences between cohorts in current measures of health.

We performed numerous serum assays and found few differences between cohorts. The mean values and the proportions of veterans with values outside the reference range were the same for both cohorts for the following assays: aspartate aminotransferase, alanine aminotransferase, bilirubin (total and unconjugated), total cholesterol, and triglycerides. Several of these assays, such as those for the transaminases and bilirubin, are commonly referred to as "liver function tests" (McIntyre, 1985), although, as stated earlier, it is well recognized that disturbances in other organ systems may also cause changes in these measures. These results suggest that the two groups do not differ in their current hepatic function.

We focused on two measures of hepatic microsomal enzyme induction, D-glucaric acid and γ-glutamyl transferase (GGT), because previous studies, both in animals (Nebert and Negishi, 1982) and humans (May, 1982), have suggested that dioxin is a potent inducer of these enzymes. Other substances, including alcohol and cigarette smoke, are also known to affect the hepatic microsomal enzyme system (Hunter and Chasseaud, 1976). Measures of D-glucaric acid showed no differences between the Vietnam and non-Vietnam veterans, but measures of GGT did show differences, which could be attributed, in part, to differences between the groups in alcohol consumption.

The GGT results also showed one noteworthy difference for a subgroup of veterans. Black Vietnam veterans had higher mean values and a larger proportion with values outside the reference range than did black non-Vietnam veterans. These subgroup differences are not likely to be a function of hepatic enzyme induction, because D-glucaric acid levels were similar between cohorts for all racial categories. Differences in Army entry or service characteristics do not seem to account for the findings because the results did not change after being adjusted for these factors. Neither are these differences between black Vietnam and non-Vietnam veterans explained by the following factors that affect this assay: age, body mass index, current alcohol use, alcohol dependence, diabetes, presence of hepatitis B surface antigen, elevated serum bilirubin, illicit drug use, and current medications. Complicating our interpretation of these results is the fact that the GGT assay lacks specificity—that is, the level of GGT rises in almost all types of liver diseases, so the assay is not specific to any one liver disease. In addition, the GGT level may also be elevated as a result of diseases in other organs, including the kidneys, pancreas, and prostate (Goldberg, 1980; Penn and Worthington, 1983). On the basis of available information, we cannot determine the reason for the elevated GGT levels among black Vietnam veterans.

Urine porphyrin assays were conducted because, in two earlier studies of industrial workers, investigators found an association between dioxin exposure and porphyria cutanea tarda (PCT) (Pazderova-Vejlupkova *et al.*, 1981; Poland *et al.*, 1971). We found few veterans in either group with porphyrin abnormalities suggestive of chronic hepatic porphyria (CHP). Most of those with CHP reported moderate-to-heavy alcohol consumption (average ≥2

drinks per day), a known risk factor for this form of porphyria (Bickers, 1982). Of the six Vietnam veterans with CHP, only one had a pattern consistent with PCT.

The observed similarity between cohorts regarding these herbicide- and dioxin-related conditions has at least two possible explanations. One is that the conditions have resolved since the exposures. Indeed, since the examinations were performed 15 to 20 years after the veterans were in the Army, most of these conditions would be expected to have resolved.

The second possible explanation is that few study participants were heavily exposed to herbicides. An objective measure of herbicide exposure, such as the level of dioxin in blood serum, was not available at the time of the VES. However, in another study of enlisted Vietnam-era veterans conducted after technologic advances made it possible to measure dioxin leavels in serum (Patterson *et al.*, 1988), we found that few Army ground troops had been heavily exposed to herbicides in Vietnam or elsewhere (Centers for Disease Control Veterans Health Study, in press).

Hepatitis B infection was selected as an outcome of interest because this viral infection may be associated with chronic liver dysfunction. Cohort differences in hepatitis B infection may be explained on the basis of prior military experience. The prevalence of past hepatitis B infection was higher among Vietnam veterans than among non-Vietnam veterans. This higher prevalence could be related to the Vietnam veterans' service in a country where hepatitis B infection is endemic (Snitbhan *et al.*, 1975)—although other possible explanations can be given. In any event, the prevalence of current hepatitis B infection in both veterans' groups is less than 1%, as measured by a serologic test for viral surface antigen. In addition, there was little evidence of current hepatic dysfunction among veterans in either cohort.

For both cohorts, the prevalence rate of hepatitis B infection based on blood-test results was higher than the rate estimated on the basis of prior physician-diagnoses of hepatitis. This discrepancy in rates is to be expected, since in a large proportion of those affected, hepatitis B infection is often asymptomatic or produces only a mild illness, without jaundice. Those veterans who had mild illnesses were not likely to recognize that their symptoms were caused by hepatitis B infection. Furthermore, with a mild illness, they were not likely to have a blood test. Consequently, rates based on clinical illness will underestimate the actual prevalence of prior infection.

The relative prevalence of peptic ulcer disease in the two cohorts is difficult to assess, since our analysis relied primarily upon self-reported historical data. No consistent pattern is evident to suggest that one group is at a much higher risk than the other for this particular health outcome. About 2% more Vietnam veterans than non-Vietnam veterans reported a history of gastric or duodenal ulcer. At the same time, however, more non-Vietnam veterans than Vietnam veterans reported having been hospitalized for ulcers since they were discharged from the Army. More Vietnam than non-Vietnam veterans reported having gastrointestinal symptoms in the year before the examination, but only 1% of veterans in either group reported gastric or duodenal ulcers as current health problems. A similar small number of Vietnam and non-Vietnam veterans reported current use of antiulcer medications. Taken together, these results do not show a strong association between Vietnam service and ulcers.

One unexpected finding was the higher prevalence of occult blood in the stools of Vietnam veterans. This test abnormality was rare, with 1.3% of the Vietnam and 0.5% of the non-Vietnam veterans having detectable stool occult blood. Results of studies of asympto-

matic persons in the general population show stool occult blood among 1% to 6% of those screened (Simon, 1985; Winawer *et al.*, 1980). Among persons age 40 to 49 years participating in comprehensive medical examinations, 1.7% tested positive for stool occult blood (Winawer *et al.*, 1980).

Occult blood in the stool can result from blood loss at any site in the gastrointestinal system, including lesions associated with gastritis and peptic ulcer disease. There is no indication that the occult blood in the stools of the VES participants was caused solely by peptic ulcer disease. Of those veterans who had stool occult blood, about half of the Vietnam veterans and one-third of the non-Vietnam veterans had either symptoms (vomiting blood or passing black, tarry stools) or prior diagnoses (peptic ulcer disease or gastritis) of upper gastrointestinal disease. The remaining veterans with stool occult blood had a variety of conditions, such as hemorrhoids, that can be associated with this finding.

In our study, we could not determine the site of blood loss among those whose tests were positive. The medical examinations were designed to be a comprehensive appraisal of the veterans' physical health, but isolated positive findings from the examinations were not further evaluated at the examination facility. However, in an exit interview the veterans were advised of the need for any additional medical follow-up.

Nonetheless, the stool occult blood results should be viewed within the context of other studies in which medical follow-up was performed (Winawer *et al.*, 1980; Winchester *et al.*, 1980). In a study of over 14,000 persons who participated in a screening program for stool occult blood, follow-up results were available for 60% of the 617 participants whose tests were positive for occult blood (Winchester *et al.*, 1980). Of those with occult blood and medical follow-up, about 40% had no detectable gastrointestinal lesions at the follow-up. Most of those with gastrointestinal lesions had either hemorhoids or diverticulosis and less than 5% had peptic ulcer disease. Similar results have been reported in other studies of occult blood screening (Simon, 1985).

Another outcome of interest concerning the Vietnam experience was alcohol-related liver disease, particularly since previous investigators have found excessive alcohol use among Vietnam veterans (Egendorf *et al.*, 1981; Yager *et al.*, 1984). For most study participants, we found few differences between Vietnam and non-Vietnam veterans in their use of alcohol, as described in Chapter 3. However, about 3% more Vietnam than non-Vietnam veterans reported current alcohol use of ≥90 drinks per month (13.2% versus 10.5%). In addition, as described in Volume IV (Psychological and Neuropsychological Evaluation) of this monograph, more Vietnam (13.7%) than non-Vietnam (9.2%) veterans met the criteria for alcohol abuse or dependence in the month preceding their examinations.

The two cohorts differed in reported heavy use of alcohol, but there was little objective evidence that the prevalence of alcohol-related liver disease was higher among the Vietnam veterans. Less than 2% in either group reported being told by a physician that they had liver damage from alcohol; even fewer had been told that they had cirrhosis. In the physical examination, the groups showed similar low prevalences of signs associated with liver disease, such as ascites and palpable liver. With γ-glutamyl transferase (GGT) as the only exception, the results of the laboratory assays that should reflect alcohol-induced liver damage were similar between cohorts. Further, these results changed little after being adjusted for current alcohol consumption. For GGT, the percent difference in mean values and odds ratios did decrease after the results were adjusted for alcohol use, but this change did not explain all of the differences between cohorts, particularly among black veterans.

In summary, we detected few differences in measures of liver or gastrointestinal function between the Vietnam and non-Vietnam groups. Vietnam veterans were more likely to have been infected with hepatitis B in the past, but they have no apparent lasting effects from this infection. More Vietnam veterans had positive tests for stool occult blood, but this abnormality affected less than 2% of the veterans in either group. Black Vietnam veterans had higher values for GGT than black non-Vietnam veterans. Otherwise, in results for laboratory tests and medical examinations related to gastrointestinal or liver function, the two cohorts were alike.

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