Chapter XII

NEUROLOGICAL ASSESSMENT

1. Introduction

Neurological abnormalities have long been recognized as acute toxic effects following the exposure of humans to phenoxy herbicides and dioxin (Goldstein, 1959; Wallis, 1970; Berkley, 1963; Boeri, 1978). Signs and symptoms, such as hyporeflexia, a decrease in nerve conduction velocity, general muscular weakness and decreased sensation in the extremities have been noted. One study documented demyelination as a result of 2,4-D exposure (Dudley, 1972). While these effects have only been demonstrated acutely following heavy exposures, complaints of peripheral neuropathy are prominent among Vietnam veterans who have participated in the Veterans Administration Agent Orange Registry Program. Twelve percent of the 110,000 patients in the Registry had complaints compatible with symptoms of peripheral neuropathy. The recognized acute neurotoxicity of these chemicals and the prevalence of neurological complaints among veterans were primary factors in the decision to place a major emphasis on the neurological evaluation of participants in this study.

During the administration of the questionnaire, each subject was asked to provide information on any major health conditions he may have experienced. All reported neurological conditions were coded using the ICD-9-CM and group analysis of the distribution of the conditions was performed. As revealed in Table XII-1, there were no statistically significant differences in reported neurological diseases between the Ranch Hand and comparison groups.

Table XII-1

DISTRIBUTION OF REPORTED NEUROLOGICAL DISEASES BY GROUP MEMBERSHIP

Disease Category	Original Comparisons	Ranch Hand	All Comparisons
Inflammatory Diseases	2	3	3
Hereditary and Degenerative Diseases	2	1	3
Peripheral Disorders	7	7	11
Disorders of the Eye	15	14	21
Disorders of the Ear and Mastoid	14	23	21
	P = 0.73		P = 0.69

There were 1045 Ranch Handers, and 773 originally selected comparisons included in the analyses in this chapter. Where analyses were accomplished using the total comparison group, the data from 1194 comparisons were used. Some variation in numbers did occur due to missing data. In the analyses of the data obtained from the neurological evaluation, only those participants with a negative serological test for syphilis were included since chronic neurological disease can result from inadequately treated syphilis (5 Ranch Handers and no comparisons were found to have positive serological tests for syphilis.) In addition, data from 15 individuals found to have edema of the extremities on physical examination (8 Ranch Handers and 7 comparisons) were deleted from the analyses of the peripheral sensory nerve evaluation and nerve conduction velocities since edema can interfere with these clinical evaluations. Several covariables were considered in the analysis. The use of alcohol (dichotomized to ever/never); years of unprotected exposure to industrial chemicals (yes, no), insecticides (yes, no), and degreasing chemicals (yes, no); and 2-hour postprandial glucose levels equal to or greater than 120 mg/dl were used as covariates.

2. Cranial Nerve Status

The functional integrity of all 12 cranial nerves was assessed during the neurological examination. The specific cranial nerves and the examination parameters used in their evaluation are listed in Table XII-2.

Table XII-2

CRANIAL NERVE EVALUATION

Cranial Nerve		Parameter
I	Olfactory	Sense of smell
II	Optic	Visual fields
III	Oculomotor	Pupillary reaction to light Ocular movement
IV	Trochlear	Ocular movement
V	Trigeminal	Facial sensation Corneal reflex Clenching jaw
VI	Abducens	Ocular movement
VII	Facial	Smile Palpebral fissure
VIII	Acoustic	Balance (Romberg Sign)
IX	Glossopharyngeal	Gag reflex
X	Vagus	Speech Tongue position
XI	Spinal Accessory	Palate and uvula movement Neck movement
XII	Hypoglossal	Neck range of motion

Analysis of the examination data revealed no statistically significant differences in cranial nerve function between the Ranch Hand and comparison groups. No significant three-way interactions between the examination parameters, group membership and the covariables of glucose and alcohol were noted. These results are summarized in Table XII-3. Data from the entire comparison group are also presented.

Table XII-3

ANALYSIS OF CRANIAL NERVE FUNCTION

Cranial Nerve	Parameter	Group	# Normal	# Abnormal	P Values; Ranch Hand Versus Original Comparisons	P Values; Ranch Hand Versus All Comparisons
I	Smell, left	RH	1025	19	0.67	0.68
		OC	759	12		
		AC	1172	19		
	Smell, right	RH	1027	17	0.73	0.70
		OC	760	11		
		AC	1174	17		
II	Visual fields, left	RH	1037	3	0.91*	0.87*
		OC	768	2		
		AC	1186	3		
	Visual fields, right	RH	1038	2	0.43*	0.51*
		OC	768	3		
		AC	1186	4		
III	Light reaction	RH	1031	8	0.52	0.43
		OC	763	4		
		AC	1180	6		
III-IV, VI	Ocular movement	RH	655	349	0.82	0.49
		OC	486	265		
		AC	746	423		
V	Sensation, left	RH	1035	7	0.68	0.26
		OC	769	4		
		AC	1190	4		
	Sensation, right	RH	1038	4	0.99*	0.58*
		OC	770	3		
		AC	1191	3		
	Corneal reflex	RH	1043	2	0.75*	0.49*
		OC	772	1		
		AC	1193	1		
	Jaw clench	RH	1042	1	-	-
		OC	773	0		
		AC	1194	0		

Table XII-3 (Cont'd)

ANALYSIS OF CRANIAL NERVE FUNCTION

Cranial Nerve	Parameter	Group	# Normal	# Abnormal	P Values; Ranch Hand versus Original Comparisons	P Values; Ranch Hand versus All Comparisons
VII	Smile	RH	1035	4	0.65*	0.85*
		OC	767	2		
		AC	1186	4		
	Palpebral fissure	RH	986	59	0.84	0.70
		OC	731	42		
		AC	1131	63		
VIII	Balance	RH	833	207	0.69	0.26
		OC	625	148		
		AC	813	228		
IX	Gag reflex	RH	1030	15	0.67	0.58
		OC	760	13		
		AC	1180	14		
X	Speech	RH	1041	3	-	0.26*
		OC	770	0		
		AC	1190	1		
	Tongue in midline	RH	879	4	0.63*	0.51*
		OC	662	2		
		AC	1085	3		
XI	Palate and uvula movement	RH	1042	3	0.48*	0.26*
		OC	771	1		
		AC	1192	1		
XI, XII	Neck range of motion	RH	1004	41	0.44	0.24
		OC	748	25		
		AC	1158	36		

*P values are of limited validity due to small cell sizes in these analyses
RH = Ranch Hand
OC = Originally selected comparison
AC = All comparisons
- = Cells containing zeros; P values not valid

The 18 neurological parameters listed in Table XII-3 were again analyzed with regard to occupational group and exposure level. The exposure index, stratified into 3 occupational groupings and 3 levels of exposure, was applied to these cranial nerve data. These results are summarized in Table XII-4. Fully adequate cell sizes were obtained in only 13 instances. In these analyses, in which no individuals in either group had abnormalities, statistical testing for significance was invalid, and P values are not given.

Table XII-4

CRANIAL NERVE FUNCTION VERSUS EXPOSURE LEVEL WITH EACH OCCUPATIONAL CATEGORY

Cranial Nerve	Parameter	Occupational Category	P Value
I	Smell, left	O/F	0.79
		E/F	0.67
		E/G	0.16
	Smell, right	O/F	0.01
		E/F	0.84
		E/G	0.31
II	Visual fields, left	O/F	0.05
		E/F	0.40
		E/G	0.44
	Visual fields, right	O/F	0.06
		E/F	0.40
		E/G	0.11
III	Light reaction	O/F	0.32*
		E/F	-
		E/G	0.28
III, IV, VI	Ocular movement	O/F	0.21*
		E/F	0.33*
		E/G	0.47*
V	Sensation, left	O/F	0.32
		E/F	0.12
		E/G	0.72
	Sensation, right	O/F	0.64
		E/F	0.34
		E/G	0.35
	Corneal reflex	O/F	-
		E/F	-
		E/G	0.55

Table XII-4 (Cont'd)

CRANIAL NERVE FUNCTION VERSUS EXPOSURE LEVEL WITH EACH OCCUPATIONAL CATEGORY

Cranial Nerve	Parameter	Occupational Category	P Value
	Jaw clench	O/F	0.64
		E/F	-
		E/G	-
VII	Smile	O/F	0.64
		E/F	0.57
		E/G	-
	Palpebral fissure	O/F	0.97*
		E/F	0.14
		E/G	0.12*
VIII	Balance	O/F	0.89*
		E/F	0.25*
		E/G	0.44*
IX	Gag reflex	O/F	0.99
		E/F	0.84
		E/G	0.20
X	Speech	O/F	0.38
		E/F	0.34
		E/G	0.11
	Tongue in midline	O/F	0.07*
		E/F	0.30*
		E/G	0.40*
XI	Palate and uvula movement	O/F	0.64
		E/F	-
		E/G	0.43
XI, XII	Neck range of motion	O/F	0.67*
		E/F	0.78
		E/G	0.46

O/F = Officer, flying E/F = Enlisted, flying E/G = Enlisted, ground
* = Cell sizes of 5 or less
- = Cells containing zeros; P values not valid

3. Peripheral Nerve Status

The variables used in the assessment of peripheral nerve function were analyzed with the covariates of 2-hour postprandial glucose in excess of 120 mg%, history of alcohol use and unprotected exposure to industrial chemicals, insecticides and degreasing chemicals. There were statistical interactions between group membership (Ranch Hand and comparison) and insecticide exposure, and between insecticide exposure and the other covariables. Since these relationships have no impact on the primary question being addressed by this study, further statistical analyses of these interactions will not be undertaken at this time.

Analysis of the data pertaining to the peripheral nervous system is summarized in Table XII-5. Data from the entire comparison group are also presented. With the exception of a borderline association between group and Babinski reflex in the originals and a significant association in the entire comparison group, these analyses did not demonstrate statistically significant differences in neurological functions between the 2 groups. Matched pair analyses were performed on the Babinski reflex and the vibration sense data, using the Breslow matched logistic regression technique. A P value of 0.18 was found for the Babinski reflex and a nonsignificant P value of 0.47 was found for vibration sense. Significant interactions were, however, detected between postprandial glucose levels and several of the examination parameters. The association between abnormal glucose metabolism and peripheral neurological disease is well recognized (Scientific American, 1983) and its demonstration in this study reflects a degree of confidence in the quality of the neurological data collection process. These glucose by neurological disease associations are shown in Table XII-6. A positive history of alcohol use had borderline significance with pin prick ($P = 0.07$). In this analysis, a continuing effect of abnormal glucose is seen for vibration ($P = 0.0005$), patellar reflex ($P = 0.03$), Achilles reflex ($P = 0.04$), and light touch ($P = 0.03$). Alcohol use also had a borderline significant effect on pin prick ($P = 0.07$).

Table XII-5

ANALYSIS OF THE PERIPHERAL NERVOUS SYSTEM

Parameter	Group	# Normal	# Abnormal	P value; Ranch Hand versus Original Comparisons	P value; Ranch Hand versus All Comparisons
Pin prick	RH	934	97	0.94	0.76
	OC	691	73		
	AC	930	101		
Light touch	RH	958	73	0.78	0.67
	OC	707	57		
	AC	953	78		
Muscle Status (strength, bulk)	RH	1003	37	0.94	0.62
	OC	745	28		
	AC	1009	32		
Vibration	RH	954	78	0.38	0.30
	OC	698	67		
	AC	941	91		
Patellar Reflex	RH	1034	4	0.45	0.74
	OC	766	5		
	AC	1003	5		
Achilles Reflex	RH	995	39	0.62	0.62
	OC	746	26		
	AC	1005	35		
Biceps Reflex	RH	1030	8	0.53	1.00
	OC	767	4		
	AC	1032	8		
Babinski Reflex	RH	1024	9	0.10	0.03
	OC	770	2		
	AC	1039	2		

RH = Ranch Hand
OC = Original comparisons
AC = All comparisons

Table XII-6

POSTPRANDIAL GLUCOSE ABNORMALITIES VERSUS NEUROLOGICAL FINDINGS
(RANCH HANDERS VERSUS ORIGINAL COMPARISONS)

Parameter	Examination Status	Glucose Status # Normal	Glucose Status # Abnormal	P Value
Light Touch	Normal	1406	259	0.03
	Abnormal	100	30	
Vibration	Normal	1402	250	0.0005
	Abnormal	106	39	
Patellar Reflex	Normal	1514	286	0.03
	Abnormal	5	4	
Achilles Reflex	Normal	1463	273	0.04
	Abnormal	48	17	
Pin prick	Normal	1369	256	0.23
	Abnormal	137	33	

The data from the Ranch Hand group were also analyzed against the exposure index. As shown in Table XII-7, there were no three-way interactions between occupational group, herbicide exposure and the neurological parameters evaluated. No statistically significant results were found in the analysis of exposure versus examination parameters. Borderline associations were noted for vibration in the enlisted flying group (P = 0.10) and for Babinski Reflex in the enlisted ground personnel (P = 0.09). The relevance of these findings, in the face of the other negative results, is unclear at this time. There were no distinct patterns of increasing abnormality with increasing exposure.

Table XII-7

PERIPHERAL NEUROPATHY BY EXPOSURE ANALYSES: SUMMARY OF P VALUES

Parameter	Occupational Group Officer	Occupational Group Enlisted Flying	Occupational Group Enlisted Ground
Pin prick	0.78	0.99	0.47
Light Touch	0.40	0.83	0.81
Muscle Status	0.43	0.96	0.65
Vibration	0.94	0.10	0.96
Patellar Reflex	0.50	0.57	1.00
Achilles Reflex	0.35	0.53	0.60
Biceps Reflex	0.49	0.57	0.91
Babinski Reflex	0.57	0.53	0.09

4. Evaluation of Central Functioning

A brief evaluation of central nervous system coordination processes was accomplished, focusing on the presence of muscle tremor, finger-to-nose coordination, gait and balance as assessed by the modified Romberg Sign. These analyses are shown in Table XII-8. As in the analysis of the peripheral nerves, there were no significant interactions of these findings with chemical exposures or group membership; however, abnormal glucose metabolism was associated with abnormal balance (P = 0.0002) and the presence of tremor (P = 0.004). Alcohol also had a significant effect on the presence of tremor (P = 0.05) and a borderline effect on balance (P = 0.09). Breslow matched pair analysis of the tremor and coordination data revealed nonsignificant P values of 0.21 and 0.31 respectively.

Table XII-8

ANALYSIS OF CENTRAL FUNCTION

				P values; Ranch Hand versus	
				Original	All
Parameter	Group	# Normal	# Abnormal	Comparisons	Comparisons
Tremor	RH	985	55	0.19	0.36
	OC	742	31		
	AC	995	46		
Coordination	RH	992	48	0.44	0.59
	OC	743	30		
	AC	998	43		
Romberg Sign	RH	833	207	0.64	0.26
	OC	625	148		
	AC	813	228		
Gait	RH	1014	24	0.47	0.76
	OC	758	14		
	AC	1018	22		

RH = Ranch Hand
OC = Original comparisons
AC = All comparisons

Exposure analysis was performed on these parameters as well. Three-factor analysis of parameter by exposure level by occupational group again demonstrated no significant interactions. In these analyses, the herbicide exposure/coordination analysis yielded a suggestive association (P = 0.10). Again, there was a statistically significant association between an abnormal Romberg Sign and abnormal glucose metabolism (P = 0.002). Two-way analysis results are shown in Table XII-9.

Table XII-9

HERBICIDE EXPOSURE VERSUS ABNORMALITY OF CENTRAL FUNCTIONING
SUMMARY OF P VALUES

Parameter	P Values		
	Officers	Enlisted Flying	Enlisted Ground
Tremor	0.50	0.76	0.20
Coordination	0.07	0.16	0.63
Romberg Sign	0.89	0.25	0.44
Gait	0.54	0.38	0.11

5. Nerve Conduction Velocity

Nerve conduction was evaluated using a continuous measurement and analyzed using a general linear model technique for maximal statistical power. Velocities were measured from 2 locations in the ulnar nerve and from 1 position in the peroneal nerve. Covariables in these analyses included history of alcohol use (measured in drink-years), abnormalities in postprandial glucose levels (equal to or greater than 120 mg/dl), and unprotected exposure to industrial chemicals, insecticides and degreasing chemicals. No associations between the chemical exposures and conduction velocities were identified on covariate analysis; however, highly statistically significant associations were noted in both the Ranch Hand and comparison groups between alcohol use and glucose and conduction velocity. This association held for both measurements of the ulnar nerve ($P \leq 0.01$) with the velocity decreasing as the drink-years of alcohol increased. Glucose was found to be associated with conduction velocity in the peroneal nerve ($P = 0.002$) and both ulnar velocities ($P = 0.001$) with velocity decreasing as glucose level increased. These analyses did not demonstrate any significant intergroup differences in velocities in either nerve. The unadjusted and adjusted means and their respective P values are presented in Table XII-10. Similar analyses, using data from the entire comparison group, were performed with similar means and results.

Table XII-10

NERVE CONDUCTION VELOCITY (M/SEC) AND GROUP MEMBERSHIP

Nerve	Group (N)	Unadjusted Mean	P Value	Adjusted Mean	P Value
Ulnar (above the elbow)	R (1035)	55.88	0.30	55.89	0.38
	C (769)	56.15		56.12	
Ulnar (below the elbow)	R (1042)	60.50	0.39	60.52	0.48
	C (771)	60.73		60.71	
Peroneal	R (1041)	48.22	0.74	48.23	0.66
	C (769)	48.14		48.93	

Herbicide exposure analyses were performed using the covariates of occupational group serum glucose and history of alcohol use. These results are shown in Table XII-11.

Table XII-11

ADJUSTED MEAN NERVE CONDUCTION VELOCITY (M/SEC) AND EXPOSURE

Nerve	Exposure			
	Low	Med-High	High	P Value
Officers				
Ulnar (above elbow)	55.77	55.66	55.97	0.90
Ulnar (below elbow)	60.54	60.60	61.10	0.70
Peroneal	47.69	47.76	47.87	0.96
Enlisted Flying				
Ulnar (above elbow)	54.54	55.72	55.35	0.53
Ulnar (below elbow)	58.31	60.68	60.83	0.03
Peroneal	48.22	48.28	48.29	0.99
Enlisted Ground				
Ulnar (above elbow)	55.53	56.60	56.33	0.24
Ulnar (below elbow)	59.96	60.74	60.69	0.96
Peroneal	48.34	48.31	49.00	0.14

These exposure analyses have not demonstrated any consistent trends in conduction velocity and increasing exposure either within or between occupational categories. A single significant result ($P = 0.03$) was found in the distal ulnar nerve velocity in flying enlisted personnel, but there was no corresponding finding in the same nerve when measured over a larger distance above the elbow ($P = 0.53$). The borderline significance in the peroneal nerve velocity of ground enlisted personnel ($P = 0.14$) was not evident in the other occupational categories. Again, significant associations with glucose were noted, with P values falling between 0.06 and 0.005.

6. Summary

As summarized in Table XII-12, detailed analyses of the neurological examination data pertaining to the status of the cranial nerves, peripheral nerves and central functioning were performed.

Table XII-12

SUMMARY OF NEUROLOGICAL STATUS

	Analysis (P Values)			
		Exposure		
Parameter	Group	Off	Enl Fly	Enl Gnd
Cranial Nerves				
1	NS	0.01	NS	0.16
2	NS	0.05	NS	0.11
3	NS	NS	NS	NS
4	NS	NS	NS	NS
5	NS	NS	0.12	NS
6	NS	NS	NS	NS
7	NS	NS	0.14	0.12
8	NS	NS	NS	NS
9	NS	NS	NS	NS
10	NS	0.07	NS	0.11
11	NS	NS	NS	NS
12	NS	NS	NS	NS
Peripheral Nerves				
Pin Prick	NS	NS	NS	NS
Light Touch	NS	NS	NS	NS
Muscle Status	NS	NS	NS	NS
Vibration	NS	NS	0.10	NS
Patellar Reflex	NS	NS	NS	NS
Achilles Reflex	NS	NS	NS	NS
Biceps Reflex	NS	NS	NS	NS
Babinski Reflex	0.10	NS	NS	0.09
Control Function				
Tremor	0.19	NS	NS	NS
Coordination	NS	0.07	0.16	NS
Romberg	NS	NS	NS	NS
Gait	NS	NS	NS	0.11
Conduction Velocity				
Proximal Ulnar	NS	NS	NS	NS
Distal Ulnar	NS	NS	0.03	NS
Peroneal	NS	NS	NS	0.14

NS = Nonsignificant

With the exception of a borderline increase in the proportion of Ranch Handers with a positive Babinski reflex, there were no significant differences detected between the Ranch Hand and comparison groups with respect to neurological parameters. The Babinski reflex, however, did not show a significant relationship to past herbicide exposure. There were no consistent findings of increasing abnormality with increasing herbicide (dioxin) exposure. The relative risks and confidence intervals for the dependent variables analyzed in this chapter are included in Appendix XVIII. Thus, it appears at this time, that there are no neurological abnormalities in the Ranch Hand group that can be attributed to herbicide exposure in Vietnam.

The evaluation of neurological status among the participants in this study has demonstrated the ability to identify classical interactions between abnormal glucose metabolism and alcohol use and evidence of neurological abnormalities. These findings lend confidence to the validity of the negative findings of a chronic herbicide (dioxin) effect on the neurological system.