1,391 participants said that they had never had acne. The analysis of self-reported lifetime occurrence of acne showed that significantly more Ranch Hands than Comparisons reported having had at least one occurrence of acne (42.0% vs. 37.3%, p=0.026). The estimated relative risk was 1.22 (95% C.I.: [1.03,1.44]). Since the definition of lifetime includes periods of time before and after the SEA tour, this result alone does not indicate a herbicide effect. This analysis is further refined below for more direct applicability to this study; in particular, analyses relating to acne after the start of the first SEA tour were conducted.

Relative to SEA Tour

Participants with acne were further classified relative to their SEA tour(s) as determined by military records. Of the 903 participants with acne, 466 participants had all occurrences of acne prior to the start of their first SEA tour (pre-SEA), 236 participants had acne before and aftar the start of their first SEA tour (pre- and post-SEA), 177 participants reported having acne only after the start of their first SEA tour (post-SEA), and 24 participants could not be classified distinctly into one of these three categories due to incomplete information on dates of occurrence. These category names are used to assist the reader in identifying the contrasts in subsequent analyses.

To assess whether the occurrence of acne after the start of the first SEA tour was different between the two groups, analyses were conducted that contrasted participants with acne after the start of the first SEA tour with those who did not have acne after the start of the first SEA tour. Since it is difficult to determine whether the occurrence of acne could be related to dioxin exposure for the participants who had acne both before and after the start of their first SEA tour, the analysis was performed with and without the participants in the pre- and post-SEA category. The analysis of the occurrence of acne after the start of the first SEA tour was also performed after stratifying by occurrence of acne before the start of the first SEA tour. This analysis was done to determine if occurrence of acne before the start of the first SEA tour had any effect on occurrence of acne after the start of the first SEA tour. The three analyses that were conducted are listed below:

- Participants who had acne after the start of their first SEA tour, excluding those who had acne both before and after the start of their first SEA tour, varsus participants who did not have acne after the start of their first SEA tour (post-SEA category vs. no acne and pre-SEA categories)

- Participants who only had acne after the start of their first SEA tour combined with those who had acne both before and after the start of their first SEA tour versus participants who did not have acne after the start of their first SEA tour (post-SEA and pre- and post-SEA categories vs. no acne and pre-SEA categories)

- Participants who had acne after the start of their first SEA tour versus participants who did not have acne after the start of their first SEA tour, stratified by occurrence of acne prior to their first SEA tour
  - Participants without acne prior to their first SEA tour: post-SEA category versus no acne category
  - Participants with acne prior to their first SEA tour: pre- and post-SEA category versus pre-SEA category

The results of these analyses are presented below.

In the first analysis, the 177 participants who only had acne after the start of their first SEA tour were contrasted with the 1,391 participants who never had acne combined with the 466 participants who only had acne before the start of their first SEA tour. The result of this analysis showed that the Ranch Hands had a significantly higher prevalence of acne (Est. RR: 1.52, 95% C.I.: [1.12,2.07], p=0.010). Of the Ranch Hands, 10.6 percent had an occurrence of acne, as opposed to 7.3 percent of the Comparisons.

When the 236 participants who had acne before and after the start of their SEA tour were included in the analysis, a significant difference was also detected (Est. RR: 1.30, 95% C.I.: [1.05,1.61], p=0.019). The Ranch Hands had a prevalence rate of 20.4 percent, as contrasted with a prevalence rate of 16.5 percent in the Comparisons.

In the analysis stratified by the occurrence of acne prior to the first SEA tour, a significant group difference was detected for those who did not have an occurrence of acne before their first SEA tour (Est. RR: 1.56, 95% C.I.: [1.14,2.14], p=0.007). Of the Ranch Hands with no history of acne before the start of the first SEA tour, 13.9 percent had an occurrence of acne after the start of the first SEA tour. Only 9.4 percent of the Comparisons had acne for the first time after the start of the first SEA tour. However, no significant difference was found between groups for participants with an occurrence of acne before the first SEA tour (p=0.754).

Duration of Acne

Analysis of duration of acne was performed for participants in the post-SEA category and in the post-SEA and pre- and post-SEA categories combined. A square root transformation was applied to the duration data for analysis purposes. No significant differences between the Ranch Hands and the Comparisons were detected in the analysis of duration of acne (p=0.451 for participants in the post-SEA acne category and p=0.611 for participants in the post-SEA and pre- and post-SEA acne categories combined).

Location of Acne

The location of acne was analyzed for the participants in the post-SEA acne category and those in the post-SEA and pre- and post-SEA categories

combined. The spatial distributions of acne with primary emphasis on the temples, around the eyes, or on the ears are presented in Figures 14-2 and 14-3. The distributions provided in Figure 14-2 are limited to the participants in the post-SEA only category. Figure 14-3 shows the distribution of acne by location for the Ranch Hands and Comparisons in the post-SEA and pre- and post-SEA categories combined.

No differences in the spatial distributions for the two groups were detected when the analysis was limited to the post-SEA category (p=0.274 with other sites included and p=0.339 with other sites excluded).

Based on the combined post-SEA and pre- and post-SEA categories, no difference in the spatial distribution between the two groups was noted (p=0.442). There was also no significant difference when the location of other sites was eliminated from the analysis (p=0.566).

Physical Examination Variables

Eight variables from the physical examination were analyzed in the dermatologic assessment. Table 14-4 provides the results of the unadjusted analyses. The results of the adjusted analyses are presented in Table 14-5. Table K-1 of Appendix K contains the results of the dependent variable-covariate associations.

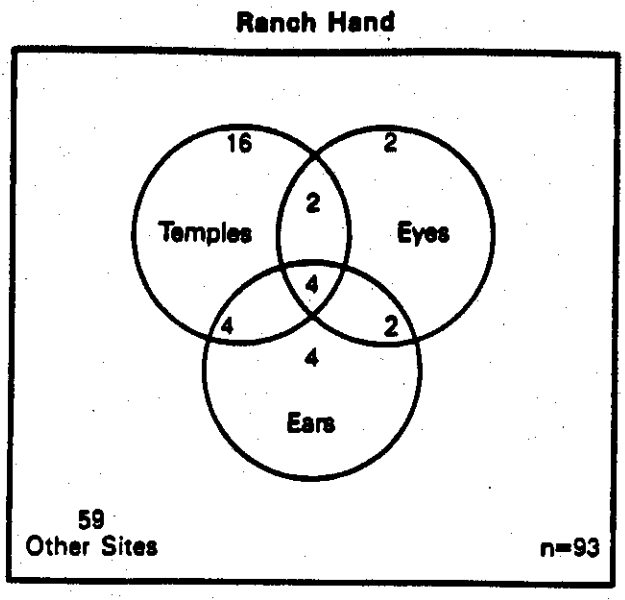
There were no cases of chloracne diagnosed at the 1987 followup.

Comedones

There was no significant difference between the percentage of Ranch Hands and Comparisons with comedones based on the unadjusted analysis (p=0.436).

As shown in Table K-1 of Appendix K, the covariate tests revealed significant associations for age and occupation ($p<0.001$ for both). The percentage of participants with comedones was highest among those born between 1923 and 1941 (25.4%), followed by those born in or before 1922 (22.6%) and those born in or after 1942 (18.1%). For occupation, 17.0 percent of the officers, 33.2 percent of the enlisted flyers, and 22.6 percent of the enlisted groundcrew had comedones.

In the adjusted analysis of comedones, there was a significant group-by-race interaction (p=0.049). Occupation and age-by-presence of pre-SEA acne were also significant terms in the model ($p<0.001$ and p=0.027, respectively). As shown in Table K-2 of Appendix K, the Black Ranch Hands had a marginally higher prevalence rate than the Black Comparisons (Adj. RR: 2.33, 95% C.I.: [0.90,6.08], p=0.083). No significant difference was detected between the nonblack Ranch Hands and Comparisons (p=0.213). Without the group-by-race interaction in the model, there was no significant difference between the two groups (p=0.396).



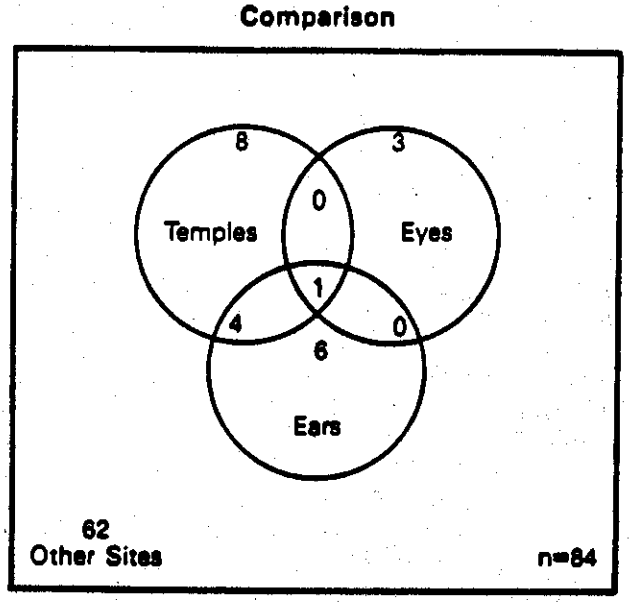
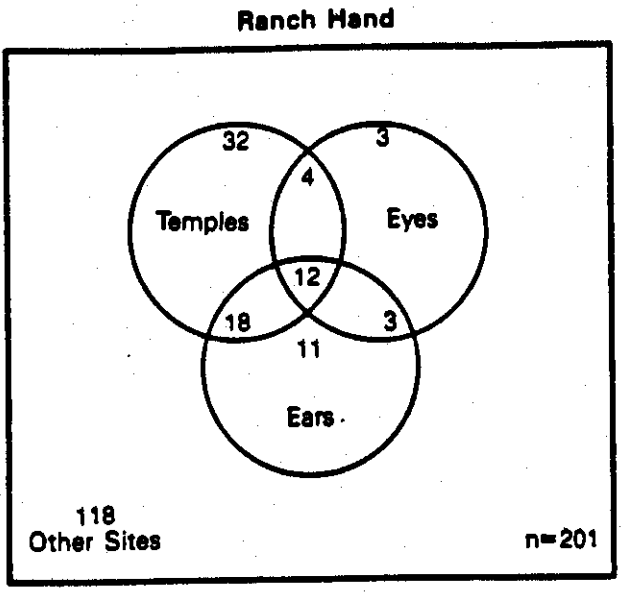


Figure 14-2.
Location of Post-SEA Acne by Group



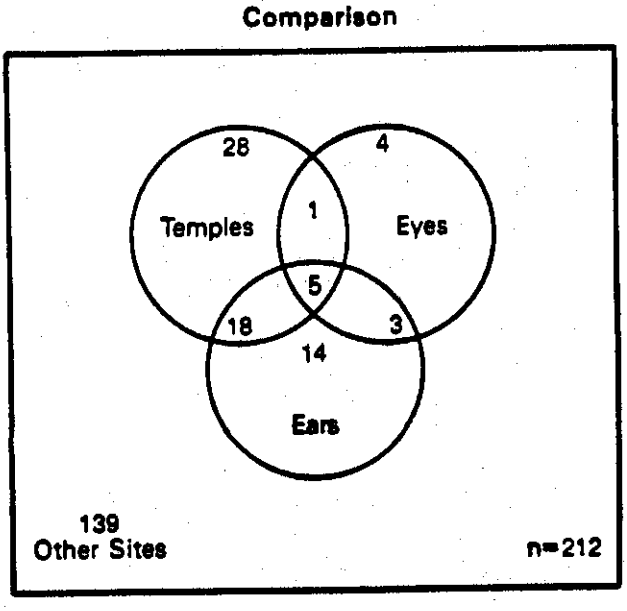


Figure 14-3.
Location of Post-SEA and Pre- and Post-SEA Acne by Group

TABLE 14-4.

Unadjusted Analysis for Dermatology Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Comedones	n	995		1,299				
	Number/%							
	Yes	213	21.4%	297	22.9%		0.92 (0.75,1.12)	0.436
	No	782	78.6%	1,002	77.1%			
Acneiform Lesions	n	995		1,299				
	Number/%							
	Yes	101	10.2%	145	11.2%		0.90 (0.69,1.18)	0.480
	No	894	89.8%	1,154	88.8%			
Acneiform Scars	n	995		1,299				
	Number/%							
	Yes	118	11.9%	139	10.7%		1.12 (0.87,1.46)	0.420
	No	877	88.1%	1,160	89.3%			
Depigmentation	n	995		1,299				
	Number/%							
	Yes	66	6.6%	83	6.4%		1.04 (0.75,1.45)	0.878
	No	929	93.4%	1,216	93.6%			

TABLE 14-4. (continued)

Unadjusted Analysis for Dermatology Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Inclusion Cysts	n	995		1,299				
	Number/%							
	Yes	105	10.6%	136	10.5%		1.01 (0.77,1.32)	0.999
	No	890	89.4%	1,163	89.5%			
Hyperpig-mentation	n	995		1,299				
	Number/%							
	Yes	146	14.7%	218	16.8%		0.85 (0.68,1.07)	0.189
	No	849	85.3%	1,081	83.2%			
Other Abnormalities	n	995		1,299				
	Number/%							
	Abnormal	759	76.3%	969	74.6%		1.10 (0.90,1.33)	0.380
	Normal	236	23.7%	330	25.4%			
Dermatology Index	n	995		1,299				
	Number/%							
	0	609	61.2%	800	61.6%	Overall		0.636
	1	273	27.4%	334	25.7%	1 vs. 0	1.07 (0.89,1.30)	0.496
	2	84	8.4%	121	9.3%	2 vs. 0	0.91 (0.68,1.23)	0.596
	3	20	2.0%	35	2.7%	3 vs. 0	0.75 (0.43,1.31)	0.386
	4	9	0.9%	9	0.7%	4 vs. 0	1.31 (0.52,3.33)	0.730

TABLE 14-5.

Adjusted Analysis for Dermatology Variables by Group

Variable	Statistic	Group		Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
		Ranch Hand	Comparison				
Comedones	n	987	1,289		0.92 (0.75,1.12)**	0.396**	GRP*RACE (p=0.049) OCC (p<0.001) AGE*SEAACNE (p=0.027)
Acneiform Lesions	n	987	1,289		0.90 (0.68,1.18)	0.426	AGE (p<0.001) SEAACNE (p<0.001)
Acneiform Scars	n	987	1,289		1.10 (0.84,1.43)	0.510	AGE (p=0.010) SEAACNE (p<0.001)
Depigmen-tation	n	995	1,299		1.04 (0.74,1.45)	0.838	AGE (p=0.010)
Inclusion Cysts	n	987	1,289		1.00 (0.76,1.31)	0.965	AGE (p=0.032) RACE*SEAACNE (p=0.035)
Hyperpig-mentation	n	987	1,289		0.86 (0.68,1.09)	0.206	RACE (p<0.001) OCC (p<0.001) SEAACNE (p=0.006)

TABLE 14-5. (continued)

Adjusted Analysis for Dermatology Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Other Abnormalities	n	995	1,299		1.08 (0.89,1.32)	0.445	RACE (p<0.001) AGE (p<0.001)
Dermatology Index	n	987	1,289	Overall		0.679	OCC (p<0.001)
				1 vs. 0	1.06 (0.88,1.28)	0.532	AGE*SEAACNE (p=0.029)
				2 vs. 0	0.91 (0.67,1.23)	0.524	
				3 vs. 0	0.76 (0.44,1.32)	0.332	
				4 vs. 0	1.28 (0.55,3.01)	0.569	

GRP: Group (Ranch Hand, Comparison).

**Group-by-covariate interaction (0.01<p<0.05)—adjusted relative risk, confidence interval, and p-value presented derived from a model fitted after deletion of this interaction.

Acneiform Lesions

In the unadjusted analysis of acneiform lesions, no significant difference was detected between the two groups ($p=0.480$).

Using pooled group data, the covariate associations with acneiform lesions showed that age, occupation, and presence of pre-SEA acne were significant ($p<0.001$, $p=0.001$, and $p<0.001$, respectively). The presence of acneiform lesions was found to be decreasing with age (15.1% for those born in or after 1942, 7.8% for those born between 1923 and 1941, and 4.8% for those born in or before 1922). The highest percentage of participants with acneiform lesions was among the enlisted groundcrew (13.1%), followed by the enlisted flyers (10.7%) and the officers (7.9%). The percentage of participants with acneiform lesions was higher for those with pre-SEA acne than those who did not have pre-SEA acne (15.3% vs. 8.7%).

Based on the adjusted analysis of acneiform lesions, there was no significant difference between the Ranch Hands and the Comparisons ($p=0.426$). Age and presence of pre-SEA acne were significant covariates in the adjusted model ($p<0.001$ for both).

Acneiform Scars

The results of unadjusted analyses of acneiform scars did not reveal a significant difference between the Ranch Hands and the Comparisons ($p=0.420$).

The significant covariate relationships with acneiform scars were age and presence of pre-SEA acne ($p=0.005$ and $p<0.001$, respectively). The association between acneiform scars and occupation was marginally significant ($p=0.051$). The percentage of participants with acneiform scars decreased with age (13.6% for those born in or after 1942, 9.7% for those born between 1923 and 1941, and 6.0% for those born in or before 1922). For occupation, 9.2 percent of the officers had acneiform scars, as compared to 12.5 percent of the enlisted flyers and 12.4 percent of the enlisted groundcrew. The participants with pre-SEA acne had a higher prevalence rate than those without pre-SEA acne (22.5% vs. 6.2%).

In the adjusted analysis of acneiform scars, there was no significant difference between the two groups ($p=0.510$). The significant covariates in the model were age and presence of pre-SEA acne ($p=0.010$ and $p<0.001$, respectively).

Depigmentation

No significant difference between the two groups was identified based on the unadjusted analysis of depigmentation ($p=0.878$).

Only the depigmentation-age association was found to be significant ($p=0.034$). The prevalence rate increased with age. Of the participants born in or after 1942, 5.3 percent had depigmentation, as compared to 7.0 percent of those born between 1923 and 1941 and 11.9 percent of those born in or before 1922.

The results of the adjusted analysis of depigmentation did not reveal a significant group difference (p=0.838). Age was a significant covariate in the model (p=0.010).

Inclusion Cysts

The unadjusted analysis of inclusion cysts did not reveal a significant difference between the Ranch Hands and the Comparisons (p=0.999).

The covariate tests for inclusion cysts showed that the relationship with race was significant (p=0.035), and the associations with age, occupation, and presence of pre-SEA acne were borderline significant (p=0.096, p=0.063, and p=0.092, respectively). For age, the highest percentage of participants with inclusion cysts was among those born between 1923 and 1941 (11.7%), followed by those born in or before 1922 (10.7%) and those born in or after 1942 (8.9%). The prevalence rate was higher for nonblacks than Blacks (10.8% vs. 5.1%). For occupation, 10.1 percent of the officers, 13.8 percent of the enlisted flyers, and 9.6 percent of the enlisted groundcrew had inclusion cysts. A higher percentage of the participants with pre-SEA acne had inclusion cysts than those without pre-SEA acne (12.3% vs. 9.8%).

Based on the adjusted analysis of inclusion cysts, there was no significant difference between the two groups (p=0.965). Age and race-by-presence of pre-SEA acne were significant terms in the model (p=0.032 and p=0.035, respectively).

Hyperpigmentation

Based on the analysis of hyperpigmentation without adjustments for covariates, no difference was found between the two groups (p=0.189).

Significant relationships were found between hyperpigmentation and race, occupation, and presence of pre-SEA acne (p<0.001, p<0.001, and p=0.003, respectively). The prevalence rate for Blacks was higher than for nonblacks (35.8% vs. 14.6%). For occupation, the prevalence rate was highest for the enlisted groundcrew (19.8%), followed by the enlisted flyers (19.6%) and the officers (9.6%). A higher percentage of the participants without pre-SEA acne had hyperpigmentation than those with pre-SEA acne (17.3% vs. 12.4%).

The results of the adjusted analysis of hyperpigmentation did not reveal a significant difference between the two groups (p=0.206). The significant terms in the model were race, occupation, and presence of pre-SEA acne (p<0.001, p<0.001, and p=0.006, respectively).

Other Abnormalities

After combining all other dermatologic abnormalities to create a composite variable, there was no significant difference between the Ranch Hands and the Comparisons based on the unadjusted analysis (p=0.380).

The results of the covariate tests did not detect a significant association for presence of pre-SEA acne; however, significant relationships were found for age, race, and occupation ($p<0.001$ for all). The prevalence rate of other abnormalities increased with age (65.2% for those born in or after 1942, 82.0% for those born between 1923 and 1941, and 90.5% for those born in or before 1922). A higher percentage of nonblacks than Blacks had a dermatologic abnormality, other than the six conditions analyzed previously (76.8% vs. 51.8%). The highest percentage of other abnormalities was in the officers (79.2%), followed by the enlisted flyers (78.3%) and the enlisted groundcrew (71.0%).

No significant difference between the Ranch Hands and the Comparisons was identified in the adjusted analysis of other abnormalities ($p=0.445$). Age and race were significant covariates in the model ($p<0.001$ for both).

Dermatology Index

There was no significant difference between the two groups based on the overall unadjusted analysis of the dermatology index ($p=0.636$), which was based on the number of abnormalities present for the following conditions: comedones, acneiform lesions, acneiform scars, and inclusion cysts. The results of the four individual contrasts of one, two, three, and four abnormalities versus zero abnormalities also did not detect any significant differences between the Ranch Hands and the Comparisons ($p=0.496$ for 1 vs. 0, $p=0.596$ for 2 vs. 0, $p=0.386$ for 3 vs. 0, and $p=0.730$ for 4 vs. 0).

The covariate tests for the dermatology index revealed significant associations with occupation and presence of pre-SEA acne ($p<0.001$ for both). These results are presented in tabular form in Table K-1 of Appendix K.

Overall, the officers had the highest percentage of participants with no abnormalities on the dermatology index (67.4% with zero abnormalities), followed by the enlisted groundcrew (59.8% with zero abnormalities), and the enlisted flyers (52.2% with zero abnormalities). The enlisted flyers had the highest percentage of abnormalities in the one and two abnormality classes of the index, and the officers had the lowest percentages (one abnormality: 30.0% for enlisted flyers, 27.0% for enlisted groundcrew, and 24.3% for officers; two abnormalities: 14.1% for enlisted flyers, 9.5% for enlisted groundcrew, and 6.1% for officers). For three abnormalities, the percentages were 3.2 for enlisted groundcrew, 2.6 for enlisted flyers, and 1.4 for officers. For four abnormalities, the highest percentage was among the enlisted flyers (1.0%), followed by the officers (0.9%) and the enlisted groundcrew (0.6%).

A greater percentage of participants with pre-SEA acne than those without pre-SEA acne had abnormalities based on the dermatology index. Only 53.7 percent of those with pre-SEA acne had no abnormalities, as compared to 64.9 percent of those without pre-SEA acne. Of those with pre-SEA acne, 27.0 percent had one abnormality, 13.7 percent had two abnormalities, 4.4 percent had three abnormalities, and 1.3 percent had four abnormalities. For the participants without pre-SEA acne, 26.2 percent had one abnormality, 6.8 percent had two abnormalities, 1.5 percent had three abnormalities, and 0.6 percent had four abnormalities.

No significant difference was found in the adjusted analysis of the dermatology index (p=0.679). This finding was supported by the results of the four individual contrasts (p=0.532 for 1 vs. 0, p=0.524 for 2 vs. 0, p=0.332 for 3 vs. 0, and p=0.569 for 4 vs. 0). Occupation and age-by-presence of pre-SEA acne were significant terms in the adjusted model ($p<0.001$ and p=0.029, respectively).

Biopsy Results

Dermatologists were instructed to request skin biopsies of any lesions suspected of being malignant. The histologic classifications of the 39 skin biopsies performed in the 1987 followup are summarized in Table 14-6. Of these biopsies, 27 were classified as basal cell carcinoma. There was no significant difference in the number of men in each group who had biopsies (Est. RR: 1.03, 95% C.I.: [0.52,2.04] p=0.930) or in the number of biopsied participants who had a basal cell carcinoma (Est. RR: 2.0, 95% C.I.: [0.46,8.63] p=0.350). A more complete discussion of the post-SEA lifetime occurrence of basal cell carcinoma can be found in Chapter 10, Malignancy.

Exposure Index Analysis

Unadjusted and adjusted exposure index analyses were conducted on the physical examination variables of the dermatologic assessment; the results of these analyses are presented in Tables 14-7 and 14-8, respectively. A summary of the exposure index-by-covariate interactions is provided in Table 14-9. The detailed stratified results for the exposure index-by-covariate interactions are listed in Table K-3 of Appendix K.

The final interpretation of the exposure index data must await the reanalysis of the clinical data using the results of the serum dioxin assay. This report is expected in 1991.

Physical Examination Variables

Comedones

No significant differences among the exposure categories were detected in the unadjusted analyses. These findings were supported by the results of the adjusted analyses for the enlisted flyer and enlisted groundcrew cohorts.

In the adjusted analysis of the officer cohort, there was a significant exposure index-by-presence of pre-SEA acne interaction (p=0.014). Of the officers with pre-SEA acne, 21.4 percent in the low exposure category had comedones as compared to 14.6 percent in the medium exposure category and 4.7 percent in the high exposure category. The high versus low exposure contrast for the pre-SEA acne stratum was significant (p=0.046), although the result was not supportive of an increasing dose-response relationship. For the officers without pre-SEA acne, the percentages with comedones were 9.9, 13.3, and 21.0 for the low, medium, and high exposure categories, respectively. The high versus low exposure contrast for those without pre-SEA acne was marginally significant (p=0.080). Without this exposure index-by-presence of pre-SEA interaction in the model, no significant differences were found among the exposure level categories.

TABLE 14-6.

Histologic Classification of Skin Biopsies at the 1987 Followup

Histologic Type	Group	
	Ranch Hand	Comparison
Basal Cell Carcinoma	15[a]	12[b]
Melanoma	1	0
Suspected Squamous Cell Carcinoma	0	1[c]
Keratosis, Actinic	1	2
Keratosis, Seborrheic	1	1
Papilloma, Benign	0	1
Nevus, Compound	1	2
Cyst, Epidermal	0	1
	19	20

[a]Two individuals had basal cell carcinomas at two separate sites, and one individual had basal cell carcinomas at three separate sites.

[b]One individual had basal cell carcinomas at two separate sites.

[c]Squamous cell carcinoma could not be equivocally excluded on submarginal tissue.

TABLE 14-7.

Unadjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low		Exposure Index: Medium		Exposure Index: High		Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Comedones	Officer	n	130		124		125		Overall		0.798
		Number/%									
		Yes	16	12.3%	17	13.7%	19	15.2%	M vs. L	1.13 (0.54,2.35)	0.884
		No	114	87.7%	107	86.3%	106	84.8%	H vs. L	1.28 (0.62,2.61)	0.624
	Enlisted Flyer	n	55		63		53		Overall		0.352
		Number/%									
		Yes	18	32.7%	17	27.0%	21	39.6%	M vs. L	0.76 (0.34,1.68)	0.632
		No	37	67.3%	46	73.0%	32	60.4%	H vs. L	1.35 (0.61,2.97)	0.586
	Enlisted Groundcrew	n	147		158		140		Overall		0.860
		Number/%									
		Yes	37	25.2%	36	22.8%	32	22.9%	M vs. L	0.88 (0.52,1.49)	0.724
		No	110	74.8%	122	77.2%	108	77.1%	H vs. L	0.88 (0.51,1.52)	0.750
Acneiform Lesions	Officer	n	130		124		125		Overall		0.378
		Number/%									
		Yes	10	7.7%	7	5.6%	13	10.4%	M vs. L	0.72 (0.26,1.95)	0.690
		No	120	92.3%	117	94.4%	112	89.6%	H vs. L	1.39 (0.59,3.30)	0.592
	Enlisted Flyer	n	55		63		53		Overall		0.483
		Number/%									
		Yes	3	5.5%	7	11.1%	6	11.3%	M vs. L	2.17 (0.53,8.82)	0.446
		No	52	94.5%	56	88.9%	47	88.7%	H vs. L	2.21 (0.52,9.35)	0.452
	Enlisted Groundcrew	n	147		158		140		Overall		0.571
		Number/%									
		Yes	19	12.9%	22	13.9%	14	10.0%	M vs. L	1.09 (0.56,2.11)	0.932
		No	128	87.1%	136	86.1%	126	90.0%	H vs. L	0.75 (0.36,1.56)	0.556

TABLE 14-7. (continued)

Unadjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low		Exposure Index: Medium		Exposure Index: High		Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Acneiform Scars	Officer	n	130		124		125		Overall		0.600
		Number/%									
		Yes	10	7.7%	14	11.3%	11	8.8%	M vs. L	1.53 (0.65,3.58)	0.444
		No	120	92.3%	110	88.7%	114	91.2%	H vs. L	1.16 (0.47,2.83)	0.924
	Enlisted Flyer	n	55		63		53		Overall		0.333
		Number/%									
		Yes	7	12.7%	5	7.9%	9	17.0%	M vs. L	0.59 (0.18,1.98)	0.578
		No	48	87.3%	58	92.1%	44	83.0%	H vs. L	1.40 (0.48,4.09)	0.726
	Enlisted Groundcrew	n	147		158		140		Overall		0.879
		Number/%									
		Yes	19	12.9%	22	13.9%	21	15.0%	M vs. L	1.09 (0.56,2.11)	0.932
		No	128	87.1%	136	86.1%	119	85.0%	H vs. L	1.19 (0.61,2.32)	0.736
Depigmentation	Officer	n	130		124		125		Overall		0.610
		Number/%									
		Yes	6	4.6%	6	4.8%	9	7.2%	M vs. L	1.05 (0.33,3.35)	0.999
		No	124	95.4%	118	95.2%	116	92.8%	H vs. L	1.60 (0.55,4.65)	0.542
	Enlisted Flyer	n	55		63		53		Overall		0.253
		Number/%									
		Yes	8	14.5%	5	7.9%	3	5.7%	M vs. L	0.51 (0.16,1.65)	0.396
		No	47	85.5%	58	92.1%	50	94.3%	H vs. L	0.35 (0.09,1.41)	0.226
	Enlisted Groundcrew	n	147		158		140		Overall		0.074
		Number/%									
		Yes	4	2.7%	13	8.2%	12	8.6%	M vs. L	3.21 (1.02,10.06)	0.061
		No	143	97.3%	145	91.8%	128	91.4%	H vs. L	3.35 (1.05,10.65)	0.055

TABLE 14-7. (continued)

Unadjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low		Exposure Index: Medium		Exposure Index: High		Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Inclusion Cysts	Officer	n	130		124		125		Overall		0.587
		Number/%									
		Yes	13	10.0%	8	6.5%	11	8.8%	M vs. L	0.62 (0.25,1.55)	0.426
		No	117	90.0%	116	93.5%	114	91.2%	H vs. L	0.87 (0.37,2.02)	0.999
	Enlisted Flyer	n	55		63		53		Overall		0.774
		Number/%									
		Yes	8	14.5%	10	15.9%	6	11.3%	M vs. L	1.11 (0.40,3.04)	0.999
		No	47	85.5%	53	84.1%	47	88.7%	H vs. L	0.75 (0.24,2.33)	0.834
	Enlisted Groundcrew	n	147		158		140		Overall		0.650
		Number/%									
		Yes	16	10.9%	15	9.5%	18	12.9%	M vs. L	0.86 (0.41,1.81)	0.832
		No	131	89.1%	143	90.5%	122	87.1%	H vs. L	1.21 (0.59,2.48)	0.738
Hyperpigmentation	Officer	n	130		124		125		Overall		0.359
		Number/%									
		Yes	10	7.7%	13	10.5%	7	5.6%	M vs. L	1.41 (0.59,3.33)	0.578
		No	120	92.3%	111	89.5%	118	94.4%	H vs. L	0.71 (0.26,1.93)	0.678
	Enlisted Flyer	n	55		63		53		Overall		0.907
		Number/%									
		Yes	11	20.0%	11	17.5%	9	17.0%	M vs. L	0.85 (0.34,2.14)	0.904
		No	44	80.0%	52	82.5%	44	83.0%	H vs. L	0.82 (0.31,2.17)	0.878
	Enlisted Groundcrew	n	147		158		140		Overall		0.341
		Number/%									
		Yes	25	17.0%	36	22.8%	24	17.1%	M vs. L	1.44 (0.82,2.54)	0.264
		No	122	83.0%	122	77.2%	116	82.9%	H vs. L	1.01 (0.55,1.87)	0.999

TABLE 14-7. (continued)

Unadjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low		Exposure Index: Medium		Exposure Index: High		Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Other Abnormalities	Officer	n	130		124		125		Overall		0.042
		Number/%									
		Abnormal	101	77.7%	110	88.7%	98	78.4%	M vs. L	2.26 (1.13,4.51)	0.029
		Normal	29	22.3%	14	11.3%	27	21.6%	H vs. L	1.04 (0.58,1.89)	0.999
	Enlisted Flyer	n	55		63		53		Overall		0.036
		Number/%									
		Abnormal	47	85.5%	44	69.8%	46	86.8%	M vs. L	0.39 (0.16,0.99)	0.071
		Normal	8	14.5%	19	30.2%	7	13.2%	H vs. L	1.12 (0.38,3.34)	0.999
	Enlisted Groundcrew	n	147		158		140		Overall		0.272
		Number/%									
		Abnormal	103	70.1%	105	66.5%	105	75.0%	M vs. L	0.85 (0.52,1.37)	0.580
		Normal	44	29.9%	53	33.5%	35	25.0%	H vs. L	1.28 (0.76,2.16)	0.422
Dermatology Index	Officer	n	130		124		125		Overall		0.625
		Number/%									
		Abnormal	38	29.2%	37	29.8%	43	34.4%	M vs. L	1.03 (0.60,1.77)	0.999
		Normal	92	70.8%	87	70.2%	82	65.6%	H vs. L	1.27 (0.75,2.15)	0.452
	Enlisted Flyer	n	55		63		53		Overall		0.434
		Number/%									
		Abnormal	24	43.6%	28	44.4%	29	54.7%	M vs. L	1.03 (0.50,2.14)	0.999
		Normal	31	56.4%	35	55.6%	24	45.3%	H vs. L	1.56 (0.73,3.34)	0.338
	Enlisted Groundcrew	n	147		158		140		Overall		0.481
		Number/%									
		Abnormal	65	44.2%	69	43.7%	53	37.9%	M vs. L	0.98 (0.62,1.54)	0.999
		Normal	82	55.8%	89	56.3%	87	62.1%	H vs. L	0.77 (0.48,1.23)	0.330

TABLE 14-8.

Adjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Comedones	Officer	n	129	123	124	Overall		0.908**
						M vs. L	1.14 (0.53,2.43)**	0.742**
						H vs. L	1.18 (0.56,2.48)**	0.673**
	Enlisted Flyer	n	55	63	52	Overall		0.407
						M vs. L	0.91 (0.40,2.05)	0.815
						H vs. L	1.52 (0.68,3.41)	0.308
	Enlisted Groundcrew	n	146	157	138	Overall		0.623
						M vs. L	1.13 (0.65,1.96)	0.669
						H vs. L	0.85 (0.48,1.50)	0.574
Acneiform Lesions	Officer	n	129	123	124	Overall		0.180
						M vs. L	0.57 (0.19,1.71)	0.314
						H vs. L	1.45 (0.57,3.69)	0.437
	Enlisted Flyer	n	55	63	52	Overall		0.412
						M vs. L	2.16 (0.52,9.01)	0.290
						H vs. L	2.44 (0.57,10.49)	0.230
	Enlisted Groundcrew	n	146	157	138	Overall		****
						M vs. L	****	****
						H vs. L	****	****

TABLE 14-8. (continued)

Adjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
Acneiform Scars	Officer	n	129	123	124	Overall		0.874**
						M vs. L	1.16 (0.46,2.89)**	0.751**
						H vs. L	0.93 (0.36,2.39)**	0.874**
	Enlisted Flyer	n	55	63	52	Overall		0.273
						M vs. L	0.59 (0.17,2.09)	0.416
						H vs. L	1.58 (0.52,4.82)	0.421
	Enlisted Groundcrew	n	146	157	138	Overall		0.526**
						M vs. L	1.05 (0.53,2.11)**	0.882**
						H vs. L	1.46 (0.72,2.94)**	0.297**
Depigmentation	Officer	n	129	123	124	Overall		0.469
						M vs. L	0.69 (0.21,2.31)	0.547
						H vs. L	1.37 (0.46,4.07)	0.570
	Enlisted Flyer	n	55	63	52	Overall		0.264
						M vs. L	0.51 (0.15,1.68)	0.266
						H vs. L	0.35 (0.09,1.40)	0.138
	Enlisted Groundcrew	n	146	157	138	Overall		0.040**
						M vs. L	3.34 (1.05,10.59)**	0.040**
						H vs. L	3.54 (1.11,11.34)**	0.033**

TABLE 14-8. (continued)

Adjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Inclusion Cysts	Officer	n	129	123	124	Overall		0.606
						M vs. L	0.62 (0.24,1.61)	0.331
						H vs. L	0.87 (0.37,2.05)	0.745
	Enlisted Flyer	n	55	63	52	Overall		0.687
						M vs. L	1.30 (0.46,3.64)	0.620
						H vs. L	0.80 (0.26,2.53)	0.709
	Enlisted Groundcrew	n	146	157	138	Overall		****
						M vs. L	****	****
						H vs. L	****	****
Hyperpig-mentation	Officer	n	129	123	124	Overall		0.421
						M vs. L	1.12 (0.46,2.75)	0.801
						H vs. L	0.61 (0.22,1.68)	0.340
	Enlisted Flyer	n	55	63	52	Overall		0.852
						M vs. L	0.81 (0.31,2.08)	0.660
						H vs. L	0.76 (0.28,2.07)	0.597
	Enlisted Groundcrew	n	146	157	138	Overall		0.247
						M vs. L	1.53 (0.85,2.77)	0.157
						H vs. L	0.99 (0.52,1.86)	0.966

TABLE 14-8. (continued)

Adjusted Exposure Index for Dermatology Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Other Abnormalities	Officer	n	129	123	124	Overall		0.040
						M vs. L	2.12 (1.00,4.47)	0.049
						H vs. L	0.89 (0.47,1.68)	0.714
	Enlisted Flyer	n	55	63	52	Overall		0.069
						M vs. L	0.42 (0.16,1.06)	0.067
						H vs. L	1.08 (0.36,3.26)	0.888
	Enlisted Groundcrew	n	146	157	138	Overall		0.512
						M vs. L	0.93 (0.56,1.53)	0.777
						H vs. L	1.26 (0.73,2.16)	0.405
Dermatology Index	Officer	n	129	123	124	Overall		0.568
						M vs. L	1.17 (0.66,2.07)	0.589
						H vs. L	0.87 (0.50,1.50)	0.619
	Enlisted Flyer	n	55	63	52	Overall		0.335
						M vs. L	0.83 (0.39,1.77)	0.634
						H vs. L	0.56 (0.26,1.23)	0.149
	Enlisted Groundcrew	n	146	157	138	Overall		0.383**
						M vs. L	0.96 (0.61,1.52)**	0.870**
						H vs. L	1.31 (0.81,2.12)**	0.263**

****Exposure index-by-covariate interaction ($p<0.01$)—relative risk, confidence interval, and p-value not presented.

**Exposure index-by-covariate interaction ($0.01<p<0.05$)—relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

TABLE 14-9.

Summary of Exposure Index-by-Covariate Interactions
From Adjusted Analyses for Dermatology Variables*

Variable	Occupation	Covariate	p-Value
Comedones	Officer	Presence of Pre-SEA Acne	0.014
Acneiform Lesions	Enlisted Groundcrew	Presence of Pre-SEA Acne	0.009
Acneiform Scars	Officer	Age	0.021
Acneiform Scars	Enlisted Groundcrew	Race	0.045
Depigmentation	Enlisted Groundcrew	Race	0.023
Inclusion Cysts	Enlisted Groundcrew	Presence of Pre-SEA Acne	0.005
Dermatology Index	Enlisted Groundcrew	Presence or Pre-SEA Acne	0.025

*Refer to Table K-3 for a further investigation of these interactions.

Acneiform Lesions

For the officer and enlisted flyer cohorts, there were no significant differences among the exposure categories in either the unadjusted or adjusted analyses.

Based on the unadjusted analysis of the enlisted groundcrew cohort, there were no significant differences. In the adjusted analysis, there was a significant exposure index-by-presence of pre-SEA acne interaction (p=0.009). After stratifying by presence of pre-SEA acne, the high versus low exposure contrast for those without pre-SEA acne was significant (p=0.049) although the result was not suggestive of an increasing dose-response relationship. For the enlisted groundcrew without pre-SEA acne, the percentages with acneiform lesions were 13.4, 15.8, and 5.2 for the low, medium, and high exposure categories, respectively.

Acneiform Scars

The results of the unadjusted analyses did not reveal any significant differences among the exposure categories for the three occupational cohorts. These findings were supported by the adjusted results of the enlisted flyer cohort and the adjusted results of the officer and enlisted groundcrew cohorts without significant interactions in the models.

In the adjusted analysis of the officer cohort, there was a significant exposure index-by-age interaction (p=0.021). After stratifying by age, the results showed that the medium versus low exposure contrast for those born between 1923 and 1941 was significant (p=0.030). Of the officers born between 1923 and 1941, 3.8 percent in the low exposure category, 14.8 percent in the

medium exposure category, and 8.2 percent in the high exposure category had acneiform scars. The high versus low exposure contrast for this stratum was not significant.

In the enlisted groundcrew cohort, the exposure index-by-race interaction was significant (p=0.045). After stratifying by race, no significant differences were detected.

Depigmentation

There were no significant differences identified in either the unadjusted or adjusted analyses of the officer and enlisted flyer cohorts.

In the enlisted groundcrew cohort, the percentages with depigmentation were 2.7, 8.2, and 8.6 in the low, medium, and high exposure categories, respectively. In the unadjusted analysis, the overall, medium versus low, and high versus low contrasts were marginally significant (p=0.074, p=0.061, and p=0.055, respectively). In the adjusted analysis of the enlisted groundcrew cohort, there was a significant exposure index-by-race interaction (p=0.023). Although there were no significant results for Blacks, significant differences were detected for nonblacks. For the nonblacks, the highest percentage of abnormalities was in the medium exposure category (9.0%) followed by the high exposure category (7.1%) and the low exposure category (1.5%). The overall test and the medium versus low exposure contrast were significant (p=0.027 and p=0.011, respectively). A marginal difference was detected in the high versus low exposure contrast (p=0.055). Without the exposure index-by-race interaction in the model, significant differences were found (p=0.040 for overall, p=0.040 for medium vs. low, and p=0.033 for high vs. low).

Inclusion Cysts

Based on the adjusted and unadjusted analyses, no significant differences among the exposure categories were identified in the officer and enlisted flyer cohorts.

For the enlisted groundcrew cohort, no differences were detected among the exposure categories based on the unadjusted analysis. In the adjusted analysis, there was a significant exposure index-by-presence of pre-SEA acne interaction (p=0.005). For the enlisted groundcrew with pre-SEA acne, the percentages with inclusion cysts were 6.1, 19.6, and 19.5 for the low, medium, and high exposure categories, respectively. For this stratum, the medium versus low contrast was significant (p=0.047) and the high versus low contrast was marginally significant (p=0.088). For the enlisted groundcrew without pre-SEA acne, the medium versus low exposure contrast was significant (p=0.025), although this result did not support an increasing dose-response relationship (13.4% for low, 4.0% for medium, and 10.3% for high).

Hyperpigmentation

No significant differences were found among the exposure categories in any of the occupational cohorts based on the unadjusted and adjusted analyses.

Other Abnormalities

In the officer cohort, 77.7 percent in the low exposure category, 88.7 percent in the medium exposure category, and 78.4 percent in the high exposure category had at least one abnormality in the category of other dermatologic disorders. In the unadjusted analysis, the overall test and the medium versus low exposure contrast were significant ($p=0.042$ and $p=0.029$, respectively). These findings were supported by the adjusted results ($p=0.040$ for overall and $p=0.049$ for medium vs. low). The high versus low exposure contrast was not significant in either the unadjusted or adjusted analysis.

The percentages of other abnormalities in the enlisted flyer cohort were 85.5, 69.8, and 86.8 in the low, medium, and high exposure categories, respectively. In the unadjusted analysis, the overall test was significant ($p=0.036$) and the medium versus low exposure contrast was borderline significant ($p=0.071$). After adjustment for covariates, both the overall test and the medium versus low exposure contrast were marginally significant ($p=0.069$ and $p=0.067$, respectively). The high versus low contrast was not significant in the unadjusted and adjusted analyses.

No significant differences were detected in the enlisted groundcrew cohort in either the unadjusted or adjusted analyses.

Dermatology Index

The dermatology index was dichotomized for the exposure index analyses: zero abnormalities versus at least one abnormality. The unadjusted exposure index analyses of the dermatology index did not reveal any significant differences among the exposure categories. These findings were supported by the results of the adjusted analyses for officers and enlisted flyers.

For the enlisted groundcrew, a significant exposure index-by-presence of pre-SEA acne interaction was present ($p=0.025$). There were no significant differences among the exposure levels for participants without pre-SEA acne for the dermatology index. The percentage of participants classified as abnormal increased as exposure increased for participants with pre-SEA acne. Of the participants in the low exposure category, 36.7 percent were classified as abnormal. In the medium and high categories, the percentages of participants classified as abnormal were 46.4 and 53.7, respectively. The high versus low contrast was significant (Adj. RR: 2.10, 95% C.I.: [1.16,3.81], $p=0.014$). Without the exposure index-by-presence of pre-SEA acne interaction in the model, no significant differences among the exposure categories were identified.

Longitudinal Analysis

The dermatology index was investigated to assess longitudinal differences between the Ranch Hand and Comparison groups. For this analysis, the index was dichotomized. Scores of 1 or greater were classified as abnormal, and a score of 0 was classified as normal. Table 14-10 summarizes the percentages of abnormal and normal scores for the 1982, 1985, and 1987 examinations. Table 14-11 presents a summary of the analysis comparing 1982 results with

TABLE 14-10.

Summary Statistics for the Longitudinal Analysis of the Dermatology Index: 1982 Baseline, 1985 Followup, and 1987 Followup Examinations

Examination	Statistic	Group			
		Ranch Hand		Comparison	
1982 Baseline	Number/%				
	Abnormal	350	38.3%	390	36.3%
	Normal	565	61.7%	684	63.7%
1985 Followup	Number/%				
	Abnormal	431	48.2%	518	49.0%
	Normal	464	51.8%	540	51.0%
1987 Followup	Number/%				
	Abnormal	355	38.8%	411	38.3%
	Normal	560	61.2%	663	61.7%

Note: Summary statistics for the 1982 Baseline and the 1987 followup are based on 915 Ranch Hands and 1,074 Comparisons who participated in the 1982 Baseline and the 1987 followup examinations. Summary statistics on 895 of these Ranch Hands and 1,058 of these Comparisons who also participated in the 1985 followup are also included for reference purposes only.

TABLE 14-11.

Longitudinal Analysis of the Dermatology Index: A Contrast of 1982 Baseline and 1987 Followup Examination Abnormalities

Group	1982 Baseline Exam	1987 Followup Exam		Odds Ratio (OR)*	p-Value (OR_{RH} vs. OR_C)
		Abnormal	Normal		
Ranch Hand	Abnormal	189	161	1.03	
	Normal	166	399		0.648
Comparison	Abnormal	211	179	1.11	
	Normal	200	484		

*Odds Ratio: $\frac{\text{Number Normal Baseline, Abnormal 1987 Followup}}{\text{Number Abnormal Baseline, Normal 1987 Followup}}$

1987 results for each group. The results showed that the group difference did not change significantly over time for the dermatology index (p=0.648).

DISCUSSION

In any study of the biological effects of herbicides and their contaminants in humans, particular emphasis must be placed on the dermatologic examination. Of the organ systems subjected to analysis, only the skin has a clinical endpoint--chloracne--which has been conclusively related to dioxin exposure. Further, while the intact skin is a most effective protective barrier to even high concentrations of a wide range of industrial chemicals, it also serves, by cutaneous absorption, as a significant portal of entry through which internal organ systems are placed at risk of toxicity.

In dermatologic practice, as in all clinical disciplines, the history can be more important to accurate diagnosis than objective physical findings. This is particularly true in the case of chloracne which, apart from the characteristic cutaneous distribution, has no hallmark features that distinguish it from other more common acneiform eruptions. In the current study, examiners were strictly forbidden from taking any occupational history. Though at obvious variance with traditional practice, such restrictions were essential to the elimination of observer bias. During the examinations, dermatologists were instructed to biopsy lesions that were felt to be suspicious of skin cancer. Though blinded to the participants' herbicide exposure status, examiners performed a similar number of biopsies in the Ranch Hand (19) and Comparison (20) groups.

The rarity of chloracne is such that few dermatologists will encounter even a single case in a lifetime of practice. Experimental dose-response studies in animals and in humans have confirmed that the topical concentrations of TCDD required to produce overt lesions are far greater than that to which participants in the current study were likely to have been exposed in SEA. It is therefore not surprising that, in the three examination cycles completed to date, no active cases of chloracne have been detected. Recognizing the remote possibility that acute cases of chloracne may have occurred and resolved, several long-term complications of all forms of acne (scarring and hyperpigmentation) were included as dependent variables in comparative and longitudinal analyses. Neither of these complications of acne diseases were different in the two groups.

Most of the dependent variable-covariate associations documented in the current section would be expected in clinical practice. Though subject to considerable individual variation, age-related changes in the epidermis, stratum corneum, and corium are associated with thinning of the skin, an increase in capillary fragility, abnormalities in keratinization, dyshydrosis with wrinkling and scaling, and loss of elasticity. Hyperplasia of the epidermis is typically associated with keratoses (seborrheic and senile) and basal cell carcinomas.

Among the dermal appendages, the sebaceous glands typically become less active with age, though an increase in comedones in selected areas (often infraorbital and nasal) may occur. Also noted and present in various forms were pigmentation disorders. In association with atrophy of the skin,

depigmentation is common whereas with epidermal hyperplasia, hyperpigmentation can occur. With the exception of typical acne, which is more common at an early age, an increase in most other forms of skin disease would be expected over time and was documented in the current study.

Consistent with established clinical patterns, a number of skin diseases were found to occur more commonly in Black participants. As nonspecific sequelae to trauma or inflammation, hypo- and, more commonly, hyperpigmentation occur more frequently in dark skinned races. Acneiform lesions and, in fact, all follicular diseases occur more commonly in Blacks and may relate to race-specific variations in the shape and orientation of the hair follicles. Finally, as a genetically determined trait, exaggerated mesenchymal responses to trauma and inflammation are common in Blacks, with keloid formation being the most familiar example.

With one exception, group comparison of the variables analyzed revealed no significant differences between the Ranch Hands and Comparisons. As noted previously, close to an equal number of biopsies was performed in each group. The Ranch Hands were found to have a statistically significant increase in the incidence of post-SEA basal cell carcinoma, a finding that is discussed in Chapter 10, Malignancy. Though Ranch Hands were found to have a slightly greater incidence of reported acne developing after SEA service, the distribution of locations of acne was similar to that of the Comparisons and not in a pattern consistent with chloracne. This difference in reported acne was not corroborated on physical examination of the participants. Finally, longitudinal analysis of all cutaneous disorders over three examination cycles failed to reveal any health detriment related to group.

SUMMARY

The 1987 dermatologic assessment was based on reported occurrence, duration, and location of acne; six dermatologic disorders: comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, and hyperpigmentation; other abnormalities; and a dermatology index based on the presence of comedones, acneiform lesions, acneiform scars, and inclusion cysts. Results of the Ranch Hand and Comparison contrasts are summarized in Table 14-12.

A significantly higher percentage of Ranch Hands than Comparisons reported that they had experienced at least one occurrence of acne during their lifetime ($p=0.026$); the occurrence of acne in this analysis included episodes before the start of the first SEA tour. Subsequent analysis indicated that, for participants with no history of acne before the start of the first SEA tour, a higher percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour ($p=0.007$). No difference in the occurrence of acne after the start of the first SEA tour was present for participants with an occurrence of acne before the start of the first SEA tour. There was also no difference between the Ranch Hands and Comparisons based on the analysis of duration or location of acne, which was limited to participants with acne after the start of the first SEA tour. These observations suggest that the increased reports of acne after service in SEA were not due to chloracne.

TABLE 14-12.

Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Dermatology Variables

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
Occurrence of Acne				
Lifetime	D	0.026	--	RH>C
Relative to SEA Tour[a]				
Post-SEA vs. Pre-SEA/None		0.010	--	
Post-SEA/Pre- and Post-SEA vs. Pre-SEA/None		0.019	--	
Post-SEA vs. None		0.007	--	
Pre- and Post-SEA vs. Pre-SEA		NS	--	
Duration of Acne	C	NS	--	
Location of Acne	D	NS	--	
Comedones	D	NS	** (NS)	
Acneiform Lesions	D	NS	NS	
Acneiform Scars	D	NS	NS	
Depigmentation	D	NS	NS	
Inclusion Cysts	D	NS	NS	
Hyperpigmentation	D	NS	NS	
Other Abnormalities	D	NS	NS	
Dermatology Index	D	NS	NS	

D: Discrete analysis performed.
--Analysis not performed.
RH>C: Higher prevalence rate in Ranch Hands than in Comparisons.
[a]The analyses of occurrence of acne relative to SEA tour are contrasts resulting from the further classification of lifetime occurrence of acne.
NS: Not significant ($p>0.10$).
C: Continuous analysis performed.
** (NS): Group-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Table K-2 for a detailed description of this interaction.

The results revealed no significant differences between the two groups based on the unadjusted and adjusted analyses of acneiform lesions, acneiform scars, depigmentation, inclusion cysts, hyperpigmentation, other abnormalities, and the dermatology index determined at the physical examination. In the unadjusted analysis of comedones, no significant difference between the Ranch Hands and Comparisons was found; however, there was a significant group-by-race interaction in the adjusted analysis ($p=0.049$). Exploration of the interaction revealed that the Black Ranch Hands had a marginally higher prevalence rate of comedones than the Black Comparisons ($p=0.083$). No difference was found for the nonblacks. Without the group-by-race interaction in the model, no significant difference between the two groups was found based on the prevalence of comedones. The fact that there were no differences in duration or location of reported acne subsequent to service in SEA and the lack of group differences in the physical examination strongly suggest that the increase in reported acne was not due to chloracne. This increase in reported skin disease could be due to differential reporting or wartime living conditions among study participants.

In the exposure index analyses, most of the results did not suggest an increasing dose-response relationship that was consistent across the three exposure levels. However, in the unadjusted analysis of depigmentation for the enlisted groundcrew cohort, borderline significant differences were identified that were consistent with an increasing dose-response relationship. In the adjusted analysis of depigmentation for this cohort, there was an exposure index-by-race interaction. Exploration of the interaction resulted in significant and marginally significant differences; however, the percentages were no longer consistently increasing with exposure level. In the officer cohort, the overall tests and medium versus low exposure contrasts were significant based on the analyses of other abnormalities; however, the high versus low contrasts were not significant. In the adjusted analysis of the dermatology index, a significant exposure index-by-presence of pre-SEA acne interaction was found in the enlisted groundcrew. The high versus low contrast was significant for participants with pre-SEA acne, and the percentage of participants classified as abnormal increased as exposure levels increased. Clarification of these exposure analyses must await the completion of the serum dioxin assays.

Based on the longitudinal analysis of the dermatology index, the difference between groups did not change significantly between the 1982 Baseline and the 1987 followup examinations.

In conclusion, no current cases of chloracne were diagnosed at the 1987 physical examination. Although more Ranch Hands reported having experienced at least one occurrence of acne in their lifetime, the remainder of the dermatologic evaluation showed that the two groups were similar.

CHAPTER 14

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CHAPTER 15

CARDIOVASCULAR EVALUATION

INTRODUCTION

Background

Cardiac disease and peripheral vascular disease are not recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin. Both bradycardia and tachycardia have been suggested following acute heavy exposure to the 2,4-D and 2,4,5-T components, but the cardiovascular effects after chronic low-dose exposure are essentially unknown.

Although a few recent studies have observed evidence of cardiac dysfunction, many investigators have concluded that the cardiovascular effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) have not been adequately assessed. A decrease in beta-adrenergic responsiveness and an increase in intracellular calcium in papillary muscle and the selective augmentation or decrease in various differential cardiac responses have been observed in guinea pigs, leading to the conclusion that TCDD causes a specific pattern of cardiac dysfunction.[1] Researchers have found a significant decrease in blood pressure and resting heart rates after the administration of TCDD to rats.[2] In guinea pigs, TCDD adversely affected the atrial muscle; in rats, it significantly decreased the positive inotropic effect of isoproterenol in papillary muscle.[2,3] In rabbits, TCDD has been shown to cause lipoprotein lipase activity reduction and other changes in the metabolic pathways and force of contraction in the aorta muscle, causing preatherosclerotic-type lesions typical of hyperlipidemia in aortic arches.[4-6] TCDD has also been shown to produce increased sensitivity of the heart to the arrhythmic effects of drugs affecting the cardiovascular system, including quinidine, reserpine, and strophanthin K in mice.[7]

Most earlier studies viewed the cardiac abnormalities as expected consequences of a moribund state, and not as indicators of primary cardiac toxicity. Following oral administration of 2,4-D and 2,4,5-T, sheep and cattle developed cardiac hemorrhages.[8] In another experiment,[9] a lethal oral dose of TCDD in young Rhesus monkeys produced increased heart weights. Horses and cats showed generalized vascular degeneration following exposure to soil contaminated with TCDD,[10] and mice and guinea pigs fed high amounts of TCDD manifested low heart weights.[11] A teratogenic experiment using 2,4,5-T in developing fish eggs showed graduated lethality and cardiovascular anomalies, which included enlarged veins and heart chambers.[12] Another study using ventricular muscle strips from chick embryos exposed to polychlorinated biphenyls (including TCDD) showed a marked decrease in contractibility.[13] This primary cardiotoxic response was presumably mediated by the Ah receptor and, as supported by another study with chick embryo hearts, was associated with increase prostaglandin synthesis.[14] Another study with rats found changes in measures of right and left atrial function, but of a stimulative nature rather than mechanical.[4]

Human case reports and epidemiologic studies have not detected significant cardiac abnormalities following exposure to herbicides or TCDD. In three case reports of acute 2,4-D poisoning, cardiac dilation and cardiac arrest were observed in the one fatal case,[15] while only transient nodal tachycardia was observed in one of the two nonfatal cases.[16,17] Three laboratory technicians with chloracne, neurological symptoms, and hypercholesterolemia following significant direct exposure to TCDD did not manifest any cardiac dysfunction;[18] however, of 10 industrial workers with chloracne, 4 complained of heart palpitations and shortness of breath.[19] In another two studies involving 128 industrial workers, no excess of cardiac complaints or findings was noted.[20-22] A case of intoxication with 2,4-D in a 51-year-old man was shown to prolong the Q-T interval in an electrocardiogram (coma was also induced).[23]

In two epidemiologic studies using similar cohorts from a Nitro, West Virginia, chemical plant, no significant cardiac impairments were detected in exposed workers.[24,25] However, one study found significantly lower levels of high density lipoprotein (HDL) cholesterol in individuals with chloracne, as contrasted to individuals without chloracne.[25] Two recent clinical-epidemiologic pilot studies of residential areas in Missouri contaminated by TCDD did not disclose any significant cardiac disease in exposed residents,[26,27] although a Times Beach study noted diminished peripheral pulses in the exposed group (as did the Baseline Air Force Health Study [AFHS]). The AFHS 1985 followup study found differences of borderline significance in verified heart disease that were not supported by other cardiac measurements.[28] Another study examined Vietnam veterans for cardiovascular lesions using chest radiographs.[29] This study found no difference in exposed and control study groups.

Because the herbicide literature has not identified consistent cardiovascular findings that merited a specific clinical focus, the AFHS has collected data by questionnaire, physical examination, laboratory testing, and medical record reviews that would identify group differences on a variety of cardiac endpoints.

The data collected can be classified into three major categories: central cardiac function, peripheral vascular function, and heart disease history. Central cardiac and peripheral vascular function were assessed by physical examination and laboratory procedures. Coronary heart disease (CHD) data have been gathered through questionnaire and medical records review. CHD has been of general concern in this study because both cohorts are largely within the high risk ages of 40 to 65.

Another component of the cardiovascular examination evaluates risk factors such as age, race, family history of heart disease, smoking, cholesterol, cholesterol-HDL ratio, personality type, changes in cortisol levels, body weight, and alcohol use.[30-35] Cholesterol can be viewed in two different ways. On the one hand, it is a potential confounding factor for cardiovascular disease that one would wish to adjust for in comparing groups of individuals exposed or not exposed to dioxin. However, hypercholesterolemia itself has been associated with acute exposure to chlorophenols and dioxin,[18,20,21,25,36,37] and the question arises as to whether this might have a future adverse impact on cardiovascular health. Therefore, analyses adjusting for this variable should be interpreted

carefully. Chapter 13, Gastrointestinal Assessment, presents analyses of cholesterol and cholesterol-HDL ratio viewed as dependent variables. (No significant group difference was found for either variable.)

Baseline Summary Results

The 1982 Baseline examination found no statistically significant differences between the Ranch Hand and Comparison groups in systolic or diastolic blood pressure, the frequency of abnormal electrocardiographs (ECG), heart sound abnormalities, abnormal funduscopic findings, or carotid bruits. However, a statistically significant difference emerged in the frequency of abnormal peripheral pulses: 12.8 percent of the nonblack Ranch Hands exhibited absent or diminished peripheral pulses, compared to 9.4 percent of the nonblack Original Comparisons ($p=0.05$). This difference was consistent across various pulse combinations and remained statistically significant when all Ranch Hands were contrasted with all Comparisons, adjusting for age, lifetime smoking history, and cholesterol level.

No statistically significant differences were found between the two groups in the occurrence of reported or verified heart disease or heart attacks, although a significant group-by-lifetime smoking history interaction (for heart disease) was noted in the older (40 or more years of age) subgroup; i.e., older Ranch Hands smoking more than 10 pack-years developed more heart disease than their Comparisons, whereas older Ranch Hands smoking less than 10 pack-years exhibited less heart disease. No significant dose-response relationships of any of the cardiovascular response variables with the exposure index were noted.

Over 80 percent of the cardiac conditions reported on the study questionnaire were verified by a detailed review of medical records. There was also strong correlation between the past medical history of cardiac disease and the Baseline cardiovascular examination findings, although the differences in peripheral pulse abnormalities occurred primarily in older individuals without a history of cardiovascular disease.

Finally, the well-known risk factors of age, smoking, and cholesterol were found to be highly correlated with each other and with several of the cardiovascular response variables.

1985 Followup Study Summary Results

The cardiovascular health of both cohorts was assessed by collecting reported and record-verified heart disease events; measurements of central cardiac function by systolic blood pressure, abnormal heart sounds, and ECG findings; and evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Analyses were adjusted for age, race, occupation, percent body fat, cholesterol, HDL, cholesterol-HDL ratio, smoking history (lifetime and current smoking level), alcohol history (lifetime and current drinking level), personality score, and differential cortisol.

The analysis of cardiovascular disease history did not reveal significant group differences in reported or verified hypertension, reported heart disease, or reported or verified heart attacks. A significant difference did emerge in the proportion of individuals with verified heart disease: 24 percent in the Ranch Hands versus 20 percent in the Comparisons ($p=0.054$ unadjusted, $p=0.036$ adjusted). After further review of the medical records, this observation was found to be in error. There were no group differences in verified heart disease (relative risk = 1.1, 95% C.I.: [0.9-1.4]). There was good correlation between the verified cardiovascular history and the central and peripheral cardiovascular abnormalities detected at the physical examination, supporting accuracy and validity of the cardiovascular measurements.

The adjusted analyses of central cardiac function disclosed a significant group-by-age interaction involving systolic blood pressure in the Black cohort, with a mean systolic blood pressure greater in the Ranch Hands than in the Comparisons at younger age levels, but a lower mean pressure at the older ages; the group-by-age interaction was not significant in the nonblack cohort. Additionally, there was a significant group-by-lifetime smoking history interaction for the overall ECG findings and significant group-by-lifetime smoking history and group-by-percent body fat interactions for arrhythmia, but they all generally pointed to lower adjusted relative risks in the Ranch Hands.

In the analyses of peripheral vascular function, no significant overall group differences were observed for abnormalities involving radial, femoral, popliteal, posterior tibial, dorsalis pedis, or three anatomic aggregates of these pulses, either by manual palpation or Doppler techniques. This overall finding was in distinct contrast to the 1982 Baseline examination, which, by the manual palpation method, showed significant peripheral pulse deficits in the Ranch Hands. This reversal in pulse findings over the two examinations was primarily attributed to the rigid 4-hour tobacco abstinence applied prior to Doppler testing, although other factors may have been involved.

For manually determined pulse abnormalities, there was a significant group-by-race interaction for the popliteal pulses; a significant group-by-percent body fat interaction for the leg pulses; and significant group-by-occupation interactions for the posterior tibial, dorsalis pedis, and the three pulse aggregates (leg, peripheral, and all pulses). No interactions were encountered in the adjusted analyses of the Doppler results and none showed significant group differences. Of interest was the fact that the manual and Doppler techniques differed significantly in the detection of abnormalities for all pulse or pulse combinations except radial pulses.

For the exposure index analyses, the only statistically significant effects were those pointing to less bradycardia and less reported and verified heart disease in the medium exposure level category, as contrasted to the low exposure category, among the enlisted groundcrew. In many cases, there were too few abnormalities within the occupational categories to permit formal statistical tests. Overall, the exposure analyses were deemed unsupportive of any meaningful dose-response relationships.

The longitudinal analysis of the pulse index confirmed the significant group difference in the change in results from the Baseline examination to the

1985 followup examination, largely due to a relatively greater increase of pulse abnormalities in the Comparison group than in the Ranch Hand group. There was no significant difference between the two groups in the change in overall ECG findings between the Baseline and 1985 followup examinations.

The covariates were distributed similarly in the two groups, except for a slightly higher level (statistically significant) of current Ranch Hand smoking (also observed at Baseline) and a slightly lower mean percent body fat. The general covariate effects were strong and showed expected classical associations with the cardiovascular measurements. However, unexpected effects were consistently noted for personality score, with higher proportions of various cardiovascular abnormalities associated with scores in the Type B direction. (Although smoking was positively associated with many of the cardiovascular measurements, negative associations were seen between current smoking and reported and verified essential hypertension, and between lifetime smoking and verified hypertension.)

Parameters of the 1987 Cardiovascular Examination

Dependent Variables

The analysis of the 1987 cardiovascular examination was based on data from the questionnaire and physical examination and subsequent medical records verification. No laboratory examination data were analyzed as dependent variables, although data from the laboratory examination were used to construct selected covariates.

Questionnaire Data

During the Baseline, 1985 followup, and 1987 followup questionnaire health interview, each participant was asked if he ever had a heart condition since his tour of duty in Southeast Asia (SEA). Medical records were sought on all individuals to verify the reported conditions and to determine the time of occurrence of major cardiac events (including cardiovascular death). In addition, the review-of-systems portion of the physical examination recorded the overall history of heart trouble, as well as other serious illnesses.

Based on the self-reported information and the subsequent verification, three conditions, each classified as yes or no, were analyzed: essential hypertension, heart disease (excluding essential hypertension), and myocardial infarction. These endpoints were each analyzed twice, as reported and as verified by medical records.

The heart disease endpoint includes rheumatic fever with heart involvement, chronic rheumatic heart disease, hypertensive heart disease, ischemic heart disease, disease of pulmonary circulation, and other forms of heart disease (acute pericarditis and endocarditis, other diseases of the pericardium and endocardium, cardiomyopathy, conduction disorders and dysrhythmias, heart failure, and ill-defined descriptions of heart disease).

A series of morbidity-mortality analyses based on these conditions was also conducted. These analyses focused on the full Ranch Hand cohort and the first Comparison of the randomly ordered set matched to the Ranch Hands. Because of competing mortality and possible misclassification of the cause of death, the endpoints of (1) death (any cause) or verified nonfatal heart disease, and (2) death (any cause) or verified nonfatal myocardial infarction were examined to assess group differences in the most extreme case (i.e., all deaths being associated with cardiovascular disease). The other two endpoints examined were (3) fatal or nonfatal verified heart disease, and (4) fatal or nonfatal verified myocardial infarction or fatal heart disease. Each variable was classified as yes or no. These variables were based on the history of each individual from the end of his tour of duty in SEA to the present.

Participants with a verified history of diabetes or a 2-hour postprandial glucose level of 200 mg/dl or more, as well as individuals with a pre-SEA verified history of essential hypertension or heart disease, were excluded from the analyses of reported and verified essential hypertension, heart disease, and myocardial infarction. Only individuals with pre-SEA heart disease were excluded from the morbidity-mortality analysis.

Physical Examination Data

Cardiovascular data from the physical examination at the 1987 followup were divided into two main categories: central cardiac function and peripheral vascular function. In addition, associations between data from the physical examination and data on verified cardiovascular diseases were examined.

Central Cardiac Function

The assessment of central cardiac function at the cardiovascular examination was made by measurements of systolic blood pressure, heart sounds (by auscultation), and an ECG. Systolic blood pressure was determined in a sitting position by an automated electronic monitor on the nondominant arm placed at heart level; the systolic pressure corresponding to the lowest diastolic value of three readings was recorded. Detection of abnormal heart sounds was conducted by standard auscultation with the participant placed in sitting, supine, and left lateral supine positions. Fourth heart sounds were assessed; murmurs were graded in intensity and location and were judged to be functional (normal) or organic (abnormal) in nature. All examiners and diagnosticians were retrained on the detection of fourth heart sounds and the notation of innocent murmurs without recording them as abnormal heart sounds. ECGs were obtained after adherence to a 4-hour abstinence from tobacco. A standard 12-lead ECG was performed; an additional rhythm strip in lead II was produced if any deviation from normal was found. The following items were considered to be abnormal: right bundle branch block (RBBB), left bundle branch block (LBBB), nonspecific T-wave changes, bradycardia, tachycardia, arrhythmia, and other major diagnoses (e.g., atrial-ventricular block, evidence of a prior myocardial infarction).

Thus, the variables analyzed in the evaluation of the central cardiac function include systolic blood pressure, heart sounds, and eight conditions

associated with the ECG. (An overall assessment of the ECG was analyzed, as well as the individual conditions of RBBB, LBBB, nonspecific T-wave changes, bradycardia, tachycardia, arrhythmia, and other diagnoses.) Systolic blood pressure was analyzed as a continuous variable and also as a discrete variable, classified as normal (≤140 mm Hg) or abnormal (>140 mm Hg). All other variables were dichotomized as normal/abnormal.

Participants with a verified history of diabetes or a 2-hour postprandial glucose level of 200 mg/dl or more and those with verified pre-SEA hypertension or heart disease were excluded from the analyses of the central cardiac function variables.

Peripheral Vascular Function

Peripheral vascular function was assessed during the cardiovascular examination by the diastolic blood pressure; funduscopic examination of small vessels; the presence or absence of carotid bruits; and manual palpation of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Diastolic blood pressure was measured by an automated electronic monitor. The recorded value represents the lowest diastolic value of three readings. Elevated diastolic blood pressure is an indicator of increased vascular resistance of the peripheral arterial system. The funduscopic examination was conducted with undilated pupils in a standard manner, with emphasis placed upon detection of arterio-venous nicking (a sign of chronic blood pressure elevation), hemorrhages, exudates, and papilledema. The presence or absence of carotid bruits was assessed by auscultation in both carotid arteries.

Diastolic blood pressure was analyzed as both a continuous and discrete variable, dichotomized as normal (≤90 mm Hg) or abnormal (>90 mm Hg). The funduscopic examination, carotid bruits, and the five aforementioned pulses were also dichotomized as abnormal/normal for analysis. Pulses were considered abnormal if diminished or absent on either side. In addition, three pulse indices were constructed from the radial, femoral, popliteal, dorsalis pedis, posterior tibial pulse, and carotid pulse measurements as follows:

- Leg pulses--femoral, popliteal, dorsalis pedis, and posterior tibial pulses
- Peripheral pulses--radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses
- All pulses--radial, femoral, popliteal, dorsalis pedis, posterior tibial, and carotid pulses.

Each of these indices was considered normal if all components were normal or abnormal if one or more pulses were abnormal.

Participants with a verified history of diabetes or a 2-hour postprandial glucose level of 200 mg/dl or more, or with a verified history of pre-SEA essential hypertension or heart disease were excluded from the analyses of the peripheral vascular function variables. Individuals with peripheral edema

were excluded from the analysis of the individual peripheral pulses in addition to the analysis of the peripheral pulse indices affected by that excluded pulse.

Questionnaire-Physical Examination Associations

The central and peripheral cardiovascular examination findings were analyzed together with the verified cardiovascular disease endpoints to determine the degree of association of the 1987 followup examination and the medical history. In particular, pairwise associations of systolic and diastolic pressure, the overall ECG, heart sounds, the funduscopic examination, carotid bruits, and the peripheral pulses with verified essential hypertension, verified heart disease (excluding essential hypertension), and verified myocardial infarction were investigated.

The same medical exclusions as described previously for the individual variables were made for the questionnaire-physical examination associations.

Covariates

A number of covariates were examined in the cardiovascular examination, both in pairwise associations with the dependent variable and in adjusted statistical analyses. Many of these covariates are considered to be classical risk factors for CHD. Covariates examined included age, race, occupation, lifetime cigarette smoking history, current level of cigarette smoking, lifetime alcohol history, current alcohol use, cholesterol, HDL, cholesterol-HDL ratio, percent body fat, personality type, differential cortisol response, family history of heart disease, and family history of heart disease before the age of 50. Personality type was determined from the Jenkins Activity Survey administered during the 1985 followup examination, and differential cortisol response was determined from laboratory results from the 1985 laboratory examination. Family history of heart disease was defined as "yes" if the participant's brother(s) or father died of heart disease or a heart attack and "no" otherwise. Family history of heart disease before the age of 50 was defined as "yes" if the participant's brother(s) or father died of heart disease or a heart attack before his 50th birthday and "no" otherwise.

In the discussion of the covariate effects, 0 pack-year lifetime cigarette smokers will be referred to as "nonsmokers," at most 10 pack-year lifetime cigarette smokers will be referred to as "moderate lifetime smokers," and greater than 10 pack-year lifetime cigarette smokers will be referred to as "heavy lifetime smokers." The current cigarette smoking categories will be referred to as "nonsmokers," "former smokers," "moderate current smokers" (for those currently smoking >0-20 cigarettes per day), and "heavy current smokers" (for those currently smoking >20 cigarettes per day). Similarly, the lifetime alcohol use categories will be referred to as "nondrinkers" (0 drink-years), "moderate lifetime drinkers" (>0-40 drink-years), and "heavy lifetime drinkers" (>40 drink-years); and the current alcohol use categories will be referred to as "light current drinkers" ($\leq$1 drink/day), "moderate current drinkers" (>1-4 drinks/day), and "heavy current drinkers" (>4 drinks/day). Finally, individuals with less than 10 percent body fat will be referred to as "lean," individuals with between 10 and 25 percent body fat will be referred

to as "normal," and individuals with greater than 25 percent body fat will be referred to as "obese."

Participants at the 1987 followup examination who did not attend the 1985 followup examination had missing information for personality type and differential cortisol response. Individuals on corticosteroids in 1985 were excluded from analyses adjusting for differential cortisol. Individuals with fever ($\geq 100^{\circ}F$) or a positive hepatitis B surface antigen test were excluded from analyses adjusting for cholesterol, HDL, and cholesterol-HDL ratio.

Relation to Baseline and 1985 Followup Studies

The evaluation of the 1987 cardiovascular examination was similar to the Baseline examination and the 1985 followup. The Doppler evaluation of the peripheral pulses was not conducted for the 1987 followup. Also, the two history of heart disease covariates were added for the 1987 followup.

The cardiovascular longitudinal analysis focused on the overall ECG diagnosis, where group differences in the changes from Baseline to the 1987 followup were analyzed.

Statistical Methods

Most of the basic statistical analysis methods used in the cardiovascular examination are described in Chapter 7. Due to the large number of covariates, however, adjusted Ranch Hand versus Comparison contrasts were carried out as follows: (1) Models adjusting only for age, race, and occupation were examined first; followed by (2) models incorporating group-by-age, group-by-race, and group-by-occupation interactions. Analyses were then performed adjusting for (3) all covariates; and (4) all covariates, but with only one variable selected from among each of the following sets: (a) lifetime cigarette smoking history and current cigarette smoking level; (b) lifetime alcohol history and current alcohol use; (c) cholesterol, HDL, and the cholesterol-HDL ratio; and (d) family history of heart disease and family history of heart disease before the age of 50. The first three analyses were done for preliminary investigative purposes; only results from the last analysis are reported.

Table 15-1 summarizes the statistical analyses performed for the 1987 cardiovascular examination. The first part of this table describes the dependent variables analyzed. The second part of this table provides a further description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Table 15-2 provides a list of the number of participants excluded and reasons for exclusion by group, as well as the number of participants with missing data for the dependent variables and covariates described in Table 15-1.

TABLE 15-1.

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Reported Essential Hypertension	Q-SR, PE	D	No Yes	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Verified Essential Hypertension	Q-V, PE	D	No Yes	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Reported Heart Disease (Excluding Essential Hypertension)	Q-SR, PE	D	No Yes	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Verified Heart Disease (Excluding Essential Hypertension)	Q-V, PE	D	No Yes	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR

TABLE 15-1. (continued)

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Reported Myocardial Infarction	Q-SR, PE	D	No Yes	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Verified Myocardial Infarction	Q-V, PE	D	No Yes	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Morbidity-Mortality Analysis	Q-V, PE	D	Living Deceased	--	Descriptive Only
Systolic Blood Pressure (mm Hg)	PE	D/C	Normal: <140 Abnormal: >140	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT,TT AC:LR,GLM CA:CC,TT,GLM, CS,FT UE:CS,FT, GLM,TT AE:LR,GLM

TABLE 15-1. (continued)

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Heart Sounds	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
ECG: Overall	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR L:OR
ECG: RBBB	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
ECG: LBBB	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR

TABLE 15-1. (continued)

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
ECG: Nonspecific T-Waves	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
ECG: Bradycardia	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
ECG: Tachycardia	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
ECG: Arrhythmia	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR

TABLE 15-1. (continued)

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
ECG: Other Diagnoses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Diastolic Blood Pressure (mm Hg)	PE	D/C	Normal: <90 Abnormal: >90	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT,TT AC:LR,GLM CA:CC,TT,GLM, CS,FT UE:CS,FT, GLM,TT AE:LR,GLM
Funduscopic Examination	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Carotid Bruits	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR

TABLE 15-1. (continued)

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Radial Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Femoral Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Popliteal Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Dorsalis Pedis Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR

TABLE 15-1. (continued)

Statistical Analysis for the Cardiovascular Evaluation

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Posterior Tibial Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Leg Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Peripheral Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
All Pulses	PE	D	Normal Abnormal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, CHOL,HDL, CHOL/HDL, %BFAT,PERS, DIFCORT, HRTDIS, HRTDIS50	UC:CS,FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Questionnaire-Physical Exam	PE	D	Normal Abnormal	--	UC:CS,FT