In the presence of relatively small sample sizes, these results demonstrated that the prevalence of abnormal urinary white cell counts in Black enlisted personnel did not vary significantly by group for either age category, although the reversal of group proportions for different ages was prominent and fully reflective of the group-by-age interaction. It is noted that the Black group-by-age interaction is opposite the nonblack group-by-age interaction (see Table 17-13), explaining the significant three-way interaction involving group, age, and race.

In summary, the unadjusted analysis of urinary WBC/HPF abnormalities showed no group differences, but the adjusted analyses showed significant effects for diabetic class and occupation for nonblack enlisted participants, and a group-by-age interaction for both Black and nonblack enlisted participants. Only for younger nonblack participants was a significant group effect seen (Ranch Hands>Comparisons).

The observations from this examination were consistent with the negative Baseline findings.

Blood Urea Nitrogen (BUN)

BUN was analyzed as a continuous variable using two sample t-tests, analysis of variance, and analysis of covariance techniques. The data were transformed to the square root scale for analysis. Adjusted analyses used the covariates of race, occupation, diabetic class, and age, as in analysis of discrete dependent variables.

As noted in Table 17-4, unadjusted group summary statistics revealed no significant differences in mean BUN levels ($p=0.554$). The groups were combined and contrasted to the covariates, and results are presented below.

These tests of covariate association showed a significant racial effect ($p=0.007$), with a higher mean BUN level for nonblacks than Blacks; a significant effect for occupation ($p<0.001$), with officers having a higher mean level than both enlisted categories; a significant age effect ($p<0.001$), with a higher mean BUN level for older than for younger participants; and a marginally significant ($p=0.059$) difference due to diabetic class, with participants in the impaired category having the highest mean BUN level.

An analysis of covariance using the above four covariates demonstrated the significant effects of age ($p<0.001$), occupation ($p=0.015$), and significant group-by-race ($p=0.022$) and race-by-diabetic class ($p=0.024$) interactions.

Table 17-16 presents mean BUN values, adjusted by the covariates and covariate interactions, stratified by race. Test results for the equality of adjusted means between groups are given in the p-value column.

As noted from this table, Black Comparisons had a significantly higher adjusted mean BUN level than Black Ranch Hands ($p=0.017$), and there was no group difference for nonblacks.

These results were analogous to the findings at the Baseline examination (although race was not used as a covariate), i.e., no detriment to the Ranch Hand group and a significant covariate effect of age.

TABLE 17-16.

Adjusted Analysis of BUN by Race and Group

Race	Group	Total	Adjusted Mean*	p-Value
Nonblack	Ranch Hand	956	14.15	0.907
	Comparison	1,206	14.17	
Black	Ranch Hand	60	12.40	0.017
	Comparison	83	13.75	

*Converted from square root scale.

Urinary Specific Gravity

The unadjusted means of the urine specific gravity disclosed a marginally significant difference between the Ranch Hand and Comparison groups ($p=0.082$). The summary statistics of the unadjusted analysis are given in Table 17-4.

By t-tests and analysis of variance, tests of association were performed on the combined groups using the covariates of race, occupation, diabetic class, and age. These tests showed a significant effect of occupation ($p<0.001$), with officers having the lowest mean urine specific gravity and the enlisted groundcrew category having the highest, and a significant effect ($p=0.018$) due to diabetic class, with the diabetic category having the highest specific gravity and the normal (nondiabetic) class having the lowest mean value. The effects of age and race were not statistically significant ($p=0.382$ and $p=0.065$, respectively).

An analysis of covariance with these four covariates showed significant effects due to diabetic class ($p=0.019$), and significant group-by-race ($p=0.017$) and group-by-occupation ($p=0.034$) interactions. Adjusted group mean specific gravities were stratified by race and by occupation. The results are presented in the summary Table 17-17.

These stratified group data showed a difference for nonblack enlisted groundcrew, but Comparisons had a lower adjusted mean urine specific gravity level than Ranch Hands (low specific gravity representing renal dysfunction).

Noteworthy is the contrast of results between this followup examination and the Baseline examination in 1982. The urine specific gravities of the followup examination appeared to be very substantially lower than those of the Baseline. A probable explanation was the difference in methods of assessing specific gravity. At the Baseline, the Ames' Clinilab automated procedure (falling drop) was used, as contrasted to the Ames' Multistick procedure at the followup. Both examinations used specimens obtained early on the second examination day, and did not use aliquots of 12- or 24-hour urine collections that were used for the porphyrin analyses. Although the

TABLE 17-17.

Adjusted Analysis of Urine Specific Gravity
by Race, Occupation, and Group

Race	Occupation	Group	Total	Adjusted Mean	p-Value
Nonblack	Officer	Ranch Hand	373	1.0153	0.734
		Comparison	474	1.0151	
	Enlisted Flyer	Ranch Hand	167	1.0158	0.631
		Comparison	193	1.0161	
	Enlisted Groundcrew	Ranch Hand	416	1.0174	<0.001
		Comparison	538	1.0157	
Black	Officer	Ranch Hand	7	1.0158	0.462
		Comparison	7	1.0186	
	Enlisted Flyer	Ranch Hand	10	1.0144	0.624
		Comparison	17	1.0158	
	Enlisted Groundcrew	Ranch Hand	43	1.0162	0.157
		Comparison	59	1.0183	

covariate effect of age upon specific gravity was not observed at the followup as it had been at the Baseline, both examinations demonstrated the marked effect of diabetes upon specific gravity, i.e., a higher specific gravity was detected in diabetics than in nondiabetics.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). The variables of kidney disease, urinary protein, urinary occult blood, and urinary white blood cell count were investigated (unadjusted for any covariates) using Pearson's chi-square test and Fisher's exact test. Adjusted analyses were performed by logistic regression for these variables, using age, race, diabetic class, and any significant pairwise interactions between the exposure index and these covariates. Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts of the proportion of abnormalities between medium and low exposure levels, and between the high and low exposure levels. Age was used as a continuous variable in the adjusted analyses, and dichotomized (born in or after 1942, born before 1942) when age was involved in an interaction with the exposure index.

Analyses of mean blood urea nitrogen and urine specific gravity (continuous variables) were performed, unadjusted for any covariates or interactions, using analysis of variance techniques and t-tests. Analysis of covariance models were used in adjusted analyses. Contrasts of medium versus low exposure and high versus low exposure were also studied. A square root transformation was applied to the blood urea nitrogen data.

Results of the adjusted analyses for these six variables are presented in Tables 17-18 and 17-19, and counterpart results for unadjusted analyses are presented in Table 0-1 of Appendix 0. Results from further investigation of exposure index-by-covariate interactions are given in Table 0-2 of Appendix 0.

Unadjusted analyses revealed no significant differences among exposure index levels for any occupation. Further investigation of these variables, for which the medium versus low and the high versus low contrasts were also examined, revealed only two variables having borderline significance: kidney disease in enlisted flyers, high versus low (Est. RR: 0.25, 95% C.I.: [0.05,1.26], p=0.091), and urinary occult blood in enlisted groundcrew, high versus low (Est. RR: 1.77, 95% C.I.: [1.00,3.13], p=0.061). The results for urinary occult blood in enlisted groundcrew supported an increase in the proportion of abnormalities from low to high exposure, whereas the kidney disease data showed the opposite effect.

The frequency of abnormalities (or mean levels closer to the abnormal range for continuous variables) for the different exposure index levels exhibited no graduated pattern across exposure levels. The number of combinations for which the medium exposure level had the smallest proportion of abnormalities (or more abnormal mean level) was greater than the other exposure levels.

Adjusted analyses revealed no significant differences among exposure index levels for any occupational stratum. Interactions were present for four of the six variables, however, and were observed in all occupations. A summary of these interactions is presented in Table 17-20.

No interaction patterns in either the covariates or occupations were observed. The only contrast observed approaching significance for an adverse effect at higher exposure levels was observed for urinary protein (officers in normal diabetic class, high versus low, p=0.097), but this contrast was highly affected by sparse cell sizes (see Table 0-2 of Appendix 0).

In summary, six renal variables showed no evidence of an increasing dose-response relationship at the followup examination. No patterns in the relationship of prevalence rates among the exposure index levels were seen within occupational strata. The exposure index level patterns observed at the Baseline examination for kidney disease in the enlisted flyer stratum were not seen at the first followup examination. Overall, both the Baseline and followup examinations showed very little evidence of a dose-response relationship.

TABLE 17-18.

Adjusted Categorical Exposure Index Analyses for Renal Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	127	130	123	Overall		0.314
					M vs. L	0.93 (0.37,2.34)	0.878
					H vs. L	1.67 (0.72,3.88)	0.236
Kidney Disease	Enlisted Flyer	55	65	57	Overall		0.124
					M vs. L	1.05 (0.34,3.22)	0.935
					H vs. L	0.26 (0.05,1.31)	0.102
	Enlisted Groundcrew	153	163	141	Overall		0.269
					M vs. L	0.57 (0.26,1.26)	0.163
					H vs. L	0.58 (0.25,1.31)	0.189
	Officer	127	130	123	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)
Urinary Protein	Enlisted Flyer	55	65	57	Overall		0.657
					M vs. L	0.34 (0.03,4.61)	0.420
					H vs. L	0.41 (0.03,4.99)	0.486
	Enlisted Groundcrew	154	163	142	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)

TABLE 17-18. (continued)

Adjusted Categorical Exposure Index Analyses for Renal Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	127	130	123	Overall		0.299
					M vs. L	0.80 (0.38,1.71)	0.566
					H vs. L	1.40 (0.70,2.80)	0.345
Urinary Occult Blood	Enlisted Flyer	55	65	57	Overall		0.187
					M vs. L	0.97 (0.39,2.43)	0.950
					H vs. L	0.43 (0.15,1.24)	0.118
	Enlisted Groundcrew	154	163	141	Overall		****(3)
					M vs. L	****(3)	****(3)
					H vs. L	****(3)	****(3)
	Officer	127	130	123	Overall		0.488
					M vs. L	0.55 (0.20,1.51)	0.247
					H vs. L	0.85 (0.34,2.10)	0.718
Urinary White Blood Cell	Enlisted Flyer	55	65	57	Overall		****(1,3)
					M vs. L	****(1,3)	****(1,3)
					H vs. L	****(1,3)	****(1,3)
	Enlisted Groundcrew	154	163	142	Overall		0.424
					M vs. L	0.68 (0.33,1.38)	0.284
					H vs. L	1.05 (0.53,2.08)	0.886

****(1): exposure index-by-diabetic class interaction -- relative risk, confidence interval, and p-value not presented.
****(2): exposure index-by-race interaction -- relative risk, confidence interval, and p-value not presented.
****(3): exposure index-by-age interaction -- relative risk, confidence interval, and p-value not presented.
****(1,3): exposure index-by-diabetic class and exposure index-by-age interaction -- relative risk, confidence interval, and p-value not presented.

TABLE 17-19.

Adjusted Continuous Exposure Index Analyses for Renal Variables

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
	Officer	n	127	130	123	Overall	****(2)
		Adj. Mean	****(2)	****(2)	****(2)	M vs. L	****(2)
		95% C.I.	****(2)	****(2)	****(2)	H vs. L	****(2)
Blood Urea Nitrogen	Enlisted Flyer	n	55	65	57	Overall	0.961
		Adj. Mean	13.59	13.76	13.77	M vs. L	0.808
		95% C.I.	(12.02, 15.26)	(12.32, 15.27)	(12.30, 15.32)	H vs. L	0.804
	Enlisted Groundcrew	n	154	163	142	Overall	0.829
		Adj. Mean	13.31	13.18	13.08	M vs. L	0.722
		95% C.I.	(12.50, 14.15)	(12.41, 13.98)	(12.30, 13.88)	H vs. L	0.544

TABLE 17-19. (continued)

Adjusted Continuous Exposure Index Analyses for Renal Variables

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
	Officer	n	127	130	123	Overall	0.755
		Adj. Mean	1.0161	1.0167	1.0165	M vs. L	0.457
		95% C.I.	(1.0131, 1.0191)	(1.0138, 1.0197)	(1.0136, 1.0194)	H vs. L	0.647
Urine Specific Gravity	Enlisted Flyer	n	55	65	57	Overall	0.378
		Adj. Mean	1.0159	1.0157	1.0142	M vs. L	0.861
		95% C.I.	(1.0128, 1.0191)	(1.0129, 1.0185)	(1.0113, 1.0171)	H vs. L	0.205
	Enlisted Groundcrew	n	154	163	142	Overall	0.974
		Adj. Mean	1.0166	1.0166	1.0164	M vs. L	0.976
		95% C.I.	(1.0148, 1.0184)	(1.0149, 1.0183)	(1.0147, 1.0182)	H vs. L	0.854

****(2): exposure index-by-race interaction -- adjusted mean, confidence interval, and p-value not presented.

TABLE 17-20.

Summary of Exposure Index-by-Covariate Interactions for Renal Variables

Variable	Occupation	Covariate	p-Value
Urinary Protein	Officer	Diabetic Class	0.004
Urinary Protein	Enlisted Groundcrew	Race	0.023
Urinary Occult Blood	Enlisted Groundcrew	Age	0.032
Urinary White Blood Cell Count	Enlisted Flyer	Age	0.015
Urinary White Blood Cell Count	Enlisted Flyer	Diabetic Class	0.029
Blood Urea Nitrogen	Officer	Race	0.009

LONGITUDINAL ANALYSES

One variable, the BUN level, was used to assess longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. This variable was selected from the five renal assays because it was judged that serial BUN levels would be more indicative of long-term renal health than the others; further, both examination measurements were made by the same high-precision automated analyzer, permitting a more valid comparison. Other commentary, contrasting general results of the other four renal variables to the Baseline, has been made for each variable above.

BUN was analyzed as a continuous variable by repeated measurements analysis of variance (see Chapter 7, Statistical Methods). A square root transformation was used. The data were not adjusted by covariates. The sample base for this analysis was the number of participants who attended both examinations; the results are given in Table 17-21.

These data indicated a slight and relatively symmetrical increase in the BUN level in both groups. Based upon longitudinal analyses of BUN, there was no evidence to assert a detriment in the renal health of the Ranch Hand group.

SUMMARY AND CONCLUSIONS

A summary of all renal variables, including unadjusted and adjusted analyses, is displayed in Table 17-22.

TABLE 17-21.

Longitudinal Analysis of BUN: A Contrast of Baseline and First Followup Examination Laboratory Means

Group	BUN Means		Total	p-Value (Equality of Difference)
	1982 Baseline	1985 Followup		
Ranch Hand	13.72	14.21	971	0.48
Comparison	13.93	14.30	1,139	

TABLE 17-22.

Overall Summary Results of Unadjusted and Adjusted Analyses for Renal Variables

Variable	Unadjusted	Adjusted
Reported Kidney Disease	NS	NS
Urinary Protein	NS	****
Urinary Occult Blood	NS	****
Urinary Leukocytosis	NS	****
BUN	NS	****
Urine Specific Gravity	NS*	****

NS: Not significant ($p>0.10$).

NS*: Borderline significant ($0.05<p\leq 0.10$).

****Group-by-covariate interaction.

A historical assessment of kidney disease/kidney stones by a review-of-systems questionnaire showed no significant differences between the Ranch Hand and Comparison groups. An adjusted analysis did not alter this conclusion as an adjusted relative risk of 0.95 (95% C.I.: [0.71,1.25], p=0.693) was demonstrated. These statistics appeared to be in marked contrast to the Baseline historical findings. Differences vis-a-vis the Baseline were most likely due to a difference in questionnaire techniques.

Current renal function was evaluated by five laboratory variables: urine protein, occult blood, urine, white blood cell counts (WBC's), blood urea nitrogen (BUN), and urine specific gravity. Invasive procedures were not used.

The unadjusted analysis of proteinuria showed no group differences (Est. RR: 1.18, 95% C.I.: [0.75,1.86], p=0.485), but the adjusted analysis showed an interaction of group and diabetic class; appropriate stratified analyses revealed that the prevalence of proteinuria was lower in the Ranch Hands than in the Comparisons in the diabetic and impaired strata, but higher in the normal strata for the Ranch Hands. These results were in contrast to the Baseline findings, which showed a marginally significant proteinuria in the Comparison group (p=0.055), and overall, lower prevalence rates of proteinuria.

The unadjusted prevalence rates for hematuria were similar for both groups (Est. RR: 1.14, 95% C.I.: [0.91,1.42], p=0.239). Three significant interactions involving group membership and covariates precluded a direct adjusted comparison of the estimated prevalence rates. Covariate analyses indicated increased hematuria in Blacks and among enlisted personnel. Ultimately via a series of stratified analyses, statistical equivalence was determined for the Black enlisted strata of both groups. Of particular note was the approximate tenfold increase in hematuria in both groups over that observed at Baseline, a finding most likely due to different laboratory techniques (reagent-strip testing versus microscopic observation).

Similar results were found for leukocyturia, i.e., a nonsignificant unadjusted analysis (Est. RR: 1.24, 95% C.I.: [0.93,1.64], p=0.145), and a significant three-way interaction (group, age, race) in the adjusted analysis. Significant covariate effects were noted for diabetic class and occupation for nonblack participants, whereas age was a significant adjusting variable for Blacks. A significant group difference was found only for the younger, nonblack Ranch Hands. The overall results were consistent with the Baseline findings.

BUN levels did not vary significantly by group (p=0.554, unadjusted). Adjusted analyses showed significant covariate effects for age and occupation and interactions for group and race and for race and diabetic class. An analysis stratified by race revealed no significant group differences for nonblacks, but a significantly higher adjusted mean BUN level in Black Comparisons than in Black Ranch Hands. Overall, the BUN results were similar to those observed at the Baseline examination.

Urine specific gravity levels manifested marginally significant group differences (p=0.082, unadjusted). The adjusted analysis disclosed significant covariate effects of diabetic class and the interactions of group and race and group and occupation. Analyses by race showed no strata with significantly lower mean levels for Ranch Hands. In contrast to the Baseline

values, the followup urine specific gravities were lower, a finding most likely attributable to differences in laboratory methodology (falling drop method versus multistick procedure).

Exposure index analyses showed very little evidence of a dose-response relationship at the followup examination. No patterns in the relationship of prevalence rates or mean levels among the exposure index levels were seen within occupational strata.

The longitudinal analysis was based solely upon a contrast of BUN levels between the two examinations. The unadjusted mean BUN value increased slightly from the Baseline to the followup examination, but the increases were symmetrical in the two groups and nonsignificant ($p=0.48$).

In conclusion, none of the six renal assessment variables showed a significant difference between the Ranch Hand and Comparison groups by unadjusted tests. However, in the adjusted analyses, all renal measurements except reported kidney disease revealed group-by-covariate interactions. These interactions were often complex, making it impossible to reach a firm conclusion as to the presence of an herbicide effect.

CHAPTER 17

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CHAPTER 18

ENDOCRINE ASSESSMENT

INTRODUCTION

The human endocrine system is generally not thought to be influenced by chlorophenol or TCDD exposure. This is not so in animals, however. A wide range of endocrine abnormalities in many animal species has been induced experimentally by TCDD, and includes hypoglycemia,[1] hypothyroxinemia,[1,2] reduced progesterone levels,[3] and increased testosterone levels, the latter presumably reflecting decreased liver catabolism due to parenchymal liver damage or an inhibition of the cytochrome P-450 system.[4] Further, thymic atrophy, one of the most sensitive indicators of TCDD toxicity, has been shown not to be mediated by the pituitary-adrenal axis.[5] Comparable animal data for the isolated effects of 2,4-D and 2,4,5-T have been noticeably meager.

Other animal studies have emphasized the endocrine system, and thyroid function in particular, as important in causing or ameliorating TCDD toxicity, and not simply as an endpoint response.[6,7] Mounting experimental evidence suggests that both natural and radiation-induced hypothyroidism protect against TCDD lethality and that this favorable process can be quickly reversed by treatments with T_4.[8,9]

If the protective reaction of hypothyroidism in animals can be extrapolated to humans, it suggests that cases of hypothyroidism or altered patterns of thyroid hormones may aggregate in groups of highly exposed workers (particularly in those with chloracne) and/or, alternatively, that severe sequelae of TCDD exposure may be associated with hyperthyroidism. In fact, such thyroid findings have not been commonly reported in dioxin morbidity studies. Occasional cases of hypothyroidism and thyromegaly have been linked to exposures to polybrominated biphenyls and hexachlorobenzene, but the data were too sparse and oblique to support a causal relationship for hypothyroidism and TCDD exposure.[10,11] An assessment of the Times Beach, Missouri, residents, whose community was contaminated with TCDD, did not reveal TSH or T_4 differences between the high- and low-risk groups.[12]

Temporary glycosuria and impaired glucose tolerance tests were noted in two studies of industrial workers exposed to TCDD.[13,14] However, neither abnormal glucose metabolism nor frank diabetes was specifically noted in other comparable studies.[15-18]

Overall, dioxin morbidity studies have not rigorously assessed the clinical or biochemical parameters of the endocrine system. A detailed description of endocrine function following TCDD exposure was the 1984 AFHS Baseline Morbidity Report, summarized below.

Baseline Summary Results

The 1982 Baseline examination did not explore historical endocrinological disorders by questionnaire sufficiently to merit analysis. Hence, a comprehensive biochemical assessment of the endocrine system was used for analysis.

Five measures of endocrine status were assessed, T_3 % Uptake, T_4, free thyroxine index (FTI), testosterone, and 2-hour postprandial glucose. Three hormones, follicle stimulating hormone, leutinizing hormone, and cortisol, and correlations of all hormones to various fertility measurements remain for future analysis.

Results showed significant group differences for T_3 % Uptake, predominantly in Ranch Hands 40 years old or less, and abnormally low T_3 % Uptake values, highest for those with high percent body fat. No group difference was noted for elevated 2-hour postprandial glucose values, and as classically expected, the prevalence of abnormal values was associated with older ages and higher percent body fat. Similarly, low testosterone levels were identical in both groups and were associated with increasing age and increasing percent body fat. Higher mean testosterone values (although still within "normal range") were significantly more prevalent in the Ranch Hand group. Significant mean shifts were not noted for the T_3 % Uptake, T_4, or FTI variable, although the T_3 % Uptake was associated with a group-by-age interaction.

The exposure index analyses were essentially negative for the T_3 % Uptake and T_4 variables. FTI, postprandial glucose, and testosterone analyses were marked by a series of covariate interactions in varying occupational categories. Of some note were the significant percent body fat-by-exposure interactions in two occupational strata in the glucose determination.

In summary, the endocrine system, as measured by five biochemical assays, did not reveal clinically apparent abnormalities that could be attributed to Herbicide Orange exposure. However, significant mean shifts in several values (although still in normal range) presented trends that were both consistent and conflicting vis-a-vis an herbicide etiology.

These data, coupled with the emerging animal literature on the profound influence of the endocrine system on lethality and body fat metabolism following TCDD exposure, clearly underscore the importance of evaluating the endocrine system more comprehensively, as was done in the third-year followup study in 1985.

Parameters of the 1985 Endocrine Assessment

The 1985 AFHS endocrine test battery was slightly altered from Baseline and included T_3 % Uptake, TSH, testosterone, 2-hour postprandial glucose, and timed paired cortisols. The 100 gram glucose load was standardized by a Glucola® challenge (as contrasted to an estimated 100 gram carbohydrate breakfast at Baseline) in preparation for a more definitive assessment of diabetes. Specific questionnaire data on past diabetes and thyroid disease were collected for assessment.

Thus, the analyses of endocrine function were comparable to those conducted on Baseline data. Additional refinements included adding diabetes (past and current) as a dependent variable, and the covariates race and personality type, when appropriate. Continuous dependent variables were dichotomized into normal/abnormal categories when necessary using the SCRF values of normal range. Numerous exclusion criteria, e.g., thyroidectomy, orchiectomy, supplemental steroid medication, and diabetes, were used for specific dependent variables. Variations in the numbers of observations in the tables, therefore, reflect these exclusions in addition to rare missing data from the dependent or adjusting variables. Comparable analyses using the Original Comparisons are found in Tables P-4 to P-6 of Appendix P. Log-linear models (BMDP®-4F), general linear models (SAS®-GLM), and logistic regression models (BMDP®-LR) formed the core of the statistical approach.

RESULTS AND DISCUSSION

Questionnaire Data

General screening questions on thyroid function and disease were posed to each participant. Two instruments were used: a self-administered review-of-systems form containing five questions (e.g., goiter or thyroid trouble, use of thyroid medication?) and the interval health questionnaire with the single question, "thyroid problems?" administered by a trained interviewer. These data are summarized in Table 18-1.

Table 18-1 shows that past and current thyroid problems vary according to the interview technique; the group difference in the self-administered questionnaire response was not significant, but the group difference in the interviewer-obtained response was borderline significant. The higher proportion of thyroid disease with the review-of-systems questionnaire was most likely due to the broader range of prompting questions or interpretation of the questions by the study participant.

Since the interviewer-administered questionnaire contained medical provider information for each positive response, verification by medical record review was possible. These data are summarized in Table 18-2 and demonstrated equivalent verification findings in the Ranch Hand and Comparison groups. Thus, the relative absence of reported thyroid disease in the Ranch Hand group appears valid.

Physical Examination Data

Physical examination of the endocrine system was necessarily limited to manual palpation of the thyroid gland and the testes. Thyroid abnormalities consisted of an enlarged gland with or without nodules or tenderness, while abnormal testes were noted for atrophied glands. The overall palpation results are summarized in Table 18-3.

The physical examination data for thyroid abnormalities were clearly supportive of the findings of the questionnaire/review of systems analysis. The proportion of testicular abnormalities (only atrophy represented in the above analysis) was essentially equivalent in both groups.

TABLE 18-1.

Unadjusted Analysis for Reporting of Thyroid Symptoms/Disease by Questionnaire Method by Group

Questionnaire Method	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value*
Self-Administered	n	1,016		1,293			
	Diseased[a]	48	4.7	57	4.4	1.08 (0.73,1.59)	0.763
	Not Diseased	968	95.3	1,236	95.6		
Interviewer Administered	n	1,016		1,293			
	Diseased[b]	7	0.7	21	1.6	0.42 (0.18,0.99)	0.054
	Not Diseased	1,009	99.3	1,272	98.4		

*Fisher's exact test.

[a]Participants answered positively to having thyroid or goiter trouble, high thyroid level, low thyroid level, lump in throat, or taking thyroid medication.

[b]Participants answered positively to having thyroid problems since last interviewed.

TABLE 18-2.

Medical Record Verification Results of Reported Thyroid Disease by Group

Verification Status	Group	
	Ranch Hand	Comparison
Number with Reported Thyroid Conditions	7	21
Medical Records Reviewed	7	21
Medical Records Pending	0	0
Percent Thyroid Conditions Verified	100	100

TABLE 18-3.

Unadjusted Analysis for Thyroid and Testicular Conditions by Group

Variable	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
		Number	Percent	Number	Percent		
Thyroid[a]	n	1,015		1,293			
	Abnormal	342	33.7	431	33.3	1.02 (0.85,1.21)	0.860
	Normal	673	66.3	862	66.7		
Testicular[b]	n	1,002		1,289			
	Abnormal	26	2.6	41	3.2	0.81 (0.49,1.34)	0.454
	Normal	976	97.4	1,248	96.8		

[a]Thyroidectomies omitted; thyroid abnormal if palpably tender or enlarged, or if nodules present.

[b]Orchiectomies omitted; testes abnormal if atrophied (compared to normal).

Laboratory Test Data

General

The collection of relatively scant endocrinological data by questionnaire and physical examination techniques was due to competing priorities of the examination and to the primary reliance upon laboratory testing as established by the 1982 Baseline examination. With research-grade laboratory quality control and reasonably large sample sizes, it was judged that even small mean shifts could be discerned in the test variables. In the presence of corroborating data, these shifts may be ascribed to an herbicide effect if, in fact, one exists.

The endocrinological assessment centered upon analysis of laboratory data for T_3 % Uptake, TSH, testosterone, timed paired cortisol specimens (the latter three assays conducted by radioimmunoassay [RIA]), 2-hour postprandial glucose, and a composite indicator of past and current diabetes. Normal values of these measurements, as determined by the SCRF Laboratory, are categorized in Table 18-4.

It is noted that some of these variables have associated "cutpoints" that differ considerably from those used by the 1982 examining laboratory. Based upon the SCRF laboratory norms, the endocrinological variables distributed into normal and abnormal proportions as displayed in Table 18-5. Unadjusted Ranch Hand and Comparison group means are also provided for quick contrast.

TABLE 18-4.

Laboratory Endocrinological Variables: SCRF Normal and Abnormal Ranges

Variable	Abnormally Low	Normal	Abnormally High
T_3 % Uptake	<24%	24-32%	>32%
TSH	-	≤7.5 µU/ml	>7.5 µU/ml
Testosterone	<270 mg/dl	270-1,100 mg/dl	>1,100 mg/dl
2-Hour Postprandial Glucose	-	<140 mg/dl	≥140-<200 mg/dl (impaired) ≥200 mg/dl (diabetic)
Cortisol	<7 µg/dl	7-25 µg/dl	>25 µg/dl

TABLE 18-5.

Unadjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Est. Relative Risk (95% C.I.)	p-Value
T_3 % Uptake	n	1,003	1,270			
	Mean	27.79	27.73			
	95% C.I.	(27.67,27.91)	(27.62,27.84)		--	0.457[a]
	Number/%					
	Low	7 0.7%	18 1.4%			
	Normal	969 96.6%	1,221 96.1%	Overall		0.248[b]
	High	27 2.7%	31 2.4%	Low vs. Normal	0.49 (0.20,1.18)	0.110[c]
				High vs. Normal	1.10 (0.65,1.85)	0.789[c]
TSH	n	1,003	1,270			
	Mean	1.158	1.107			
	95% C.I.	(1.13,1.19)	(1.08,1.13)		--	0.019[a]
	Number/%					
	Normal	996 99.3%	1,264 99.5%			
	High	7 0.7%	6 0.5%		1.48 (0.50,4.42)	0.579[c]
Testosterone	n	1,000	1,288			
	Mean	597.3	578.3			
	95% C.I.	(584.0,610.8)	(566.9,589.9)		--	0.035[a]
	Number/%					
	Low	38 3.8%	49 3.8%			
	Normal	949 94.9%	1,225 95.1%	Overall		0.896[b]
	High	13 1.3%	14 1.1%	Low vs. Normal	1.00 (0.65,1.54)	0.999[c]
				High vs. Normal	1.20 (0.56,2.56)	0.698[c]

TABLE 18-5. (continued)

Unadjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Initial Cortisol	n	1,009	1,284			
	Mean	11.62	11.68		--	0.668[a]
	95% C.I.	(11.39,11.85)	(11.48,11.89)			
	Number/%					
	Low	52 5.2%	64 5.0%	Overall		0.708[b]
	Normal	950 94.2%	1,207 94.0%	Low vs. Normal	1.03 (0.71,1.50)	0.924[c]
	High	7 0.7%	13 1.0%	High vs. Normal	0.68 (0.27,1.72)	0.501[c]
2-Hour Cortisol	n	1,009	1,284			
	Mean	9.30	9.27		--	0.793[a]
	95% C.I.	(9.10,9.51)	(9.10,9.44)			
	Number/%					
	Low	0 0.0%	0 0.0%			
	Normal	1,005 99.6%	1,281 99.8%			
	High	4 0.4%	3 0.2%		1.70 (0.38,7.61)	0.706[c]
Differential Cortisol	n	1,009	1,284			
	Mean	2.30	2.46		--	0.349[a]
	95% C.I.	(2.05,2.55)	(2.24,2.69)			

TABLE 18-5. (continued)

Unadjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Est. Relative Risk (95% C.I.)	p-Value
2-Hour Post-prandial Glucose	n	976	1,235			
	Mean	107.9	109.0		--	0.435[a]
	95% C.I.	(105.9,110.0)	(107.3,110.7)			
	Number/%					
	Normal	836 85.7%	1,026 83.1%	Overall		0.038[b]
	Impaired	106 10.9%	176 14.3%	Impaired vs. Normal	0.74 (0.57,0.96)	0.024[c]
	Diabetic	34 3.5%	33 2.7%	Diabetic vs. Normal	1.26 (0.78,2.06)	0.382[c]
Diabetes (Composite Indicator)	n	1,016	1,293			
	Number/%					
	Yes	74 7.3%	87 6.7%		1.09 (0.79,1.50)	0.622[c]
	No	942 92.7%	1,206 93.3%			

--Relative risk not given for continuous analyses of variables.

[a] t-test.

[b] Chi-square test.

[c] Fisher's exact test.

The following representative statistical power statements (for power 0.8, 2-sided $\alpha = 0.05$) may be applied to parameters of several variables listed in Table 18-5. The sample sizes were sufficient to detect a 1.9-fold increase in the frequency of percent abnormal high values for T_3 % Uptake and a 2.5-fold increase in percent abnormal high values for testosterone, relative to that observed in the Comparison group. In addition, the sample sizes were sufficient to detect a 2.7 percent mean shift in TSH and a 1.5 percent mean shift in the first cortisol specimen, over those means observed in the Comparison group.

Table 18-5 shows remarkably comparable unadjusted group means and distributional parameters for Ranch Hands and Comparisons in T_3 % Uptake, initial cortisol, and 2-hour cortisol. For TSH, testosterone, and 2-hour postprandial glucose, however, there was disparity between the statistical results of the means test and the distributional chi-square test, suggesting that significant differences may exist between the Ranch Hand and Comparison groups.

Since all endocrinological variables were known to depend upon classical covariates such as age and race, each variable was reanalyzed by general linear models (using transformations when necessary), logistic regression analyses, or log-linear models adjusted for these covariates. The results of these adjusted analyses are presented in a series of functional endocrine groups below. Table 18-6 presents complete details on the adjusted analyses for all the endocrinological variables.

Thyroid Function: T_3 % Uptake and Thyroid Stimulating Hormone (TSH)

Assessment of both thyroid assays excluded all participants on thyroid medication (as determined by both the self-administered questionnaire and the structured NORC questionnaire) as well as participants with partial or total thyroidectomies. Thus, 13 Ranch Hands and 20 Comparisons were omitted from the following analyses.

T_3 % Uptake

The T_3 % Uptake categorical data, as summarized in Table 18-5, were reanalyzed controlling for the covariate effects of occupation, race, age, and personality type. Group data were pooled to reveal the marginal effects of the four covariates. These data are summarized in Table 18-7.

The analysis of these data showed a significant effect of occupation ($p=0.024$) on the percentage of participants with abnormal T_3 % Uptake results. Specifically, this was mostly attributable to a relatively high percentage of officers with high T_3 % Uptake levels (31 observed versus 21.5 expected, see Table 18-7) and a low percentage of enlisted flyers with high T_3 % Uptake results (5 observed versus 9.8 expected).

Table 18-7 also shows a marginal effect of personality type on T_3 % Uptake results (however, this effect was significant [$p=0.035$] when analysis was restricted to Ranch Hands and Original Comparisons). Most of the personality-type effect was due to larger numbers than expected of Type A

TABLE 18-6.

Adjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
T_3 % Uptake	n	1,003	1,270	Overall		0.250	
				Low vs. Normal	0.50 (0.21,1.19)	0.117	OOC (p=0.025)
				High vs. Normal	1.10 (0.50,2.44)	0.809	
TSH	n	998	1,267				
	Adj. Mean	1.158	1.109		—	0.025	AGE*PERSTYPE(p=0.037)
	95% C.I.	(1.13,1.19)	(1.08,1.14)				
	n	1,003	1,270	High vs. Normal	1.48 (0.50,4.42)	0.579	
Testosterone	n	1,000	1,287				
	Adj. Mean	****	****		—	****	GRP*BFAT (p=0.024)
	95% C.I.	****	****				AGE*BFAT (p=0.024)
							RACE (p=0.004)
				Overall		0.949	AGE (p<0.001)
				Low vs. Normal	1.00 (0.64,1.55)	0.986	%BFAT (p<0.001)
				High vs. Normal	1.13 (0.48,2.64)	0.774	
Initial Cortisol	n	1,004	1,280				AGE (p<0.001)
	Adj. Mean	11.42	11.49		—	0.659	%BFAT (p<0.001)
	95% C.I.	(10.59,12.31)	(10.66,12.38)				PERSTYPE (p=0.002)
							RACE*OCC (p=0.009)

TABLE 18-6. (continued)

Adjusted Continuous and Categorical Analyses for
Laboratory Endocrinological Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Differential	n	1,004	1,280				GRP*AGE*RACE Cortisol (p=0.032)
	Adj. Mean	****	****		—	****	PERSTYPE (p=0.005)
	95% C.I.	****	****				%BFAT (p<0.001)
2-Hour Post-prandial Glucose	n	976	1,234				%BFAT (p<0.001)
	Adj. Mean	114.4	115.3		—	0.487	OCC (p<0.001)
	95% C.I.	(107.3,122.0)	(108.2,123.0)				AGE*RACE (p=0.002)
				Overall		0.034	AGE (p<0.001)
				Impaired vs. Normal	0.73 (0.56,0.96)	0.022	RACE (p=<0.016)
				Diabetic vs. Normal	1.26 (0.72,2.22)	0.421	%BFAT (p<0.001)
Diabetes (Composite Indicator)	n	1,016	1,292				%BFAT (p<0.001)
				Diseased vs. Normal	1.12 (0.80,1.56)	0.500	AGE*RACE (p=0.005)

*Abbreviations:
GRP: Group
OCC: Occupation
PERSTYPE: Personality type (A or B)
%BFAT: Percent body fat

—No relative risk or confidence interval given for continuous analyses.

****Group-by-covariate interaction—Adjusted mean/relative risk, confidence interval, and p-value are not presented.

TABLE 18-7.

Association Between T_3 % Uptake and
Age, Race, Occupation, and Personality Type
in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal		p-Value
			Low	High	
Age	Born ≥1942	953	1.05	2.52	0.977
	Born <1942	1,320	1.14	2.58	
Race	Black	143	1.40	1.40	0.628
	Nonblack	2,130	1.08	2.63	
Occupation	Officer	842	0.59	3.68	
	Enlisted Flyer	383	1.04	1.31	0.024
	Enlisted Groundcrew	1,048	1.53	2.10	
Personality Type	A Direction	997	1.60	2.91	0.071
	B Direction	1,268	0.71	2.21	

participants with lower T_3 % Uptake levels. The covariates age and race were not correlated with T_3 % Uptake abnormalities. Log-linear models were then used to assess possible group differences in T_3 % Uptake abnormalities, adjusting for occupation (OCC), race, age, and personality type (PERSTYPE). The covariates age, race, and personality type did not contribute significantly to the fit of the adjusted model and were deleted to yield the simplest model, which included occupation. This analysis was summarized in terms of adjusted relative risks and is displayed in Table 18-8.

There were no significant differences in percent abnormalities of T_3 % Uptake between the Ranch Hand and the Comparison groups. Occupation demonstrated a significant effect (p=0.025). Personality type, although marginally significant (p=0.068), did not affect the assessment of group differences.

Thyroid Stimulating Hormone (TSH)

TSH laboratory values were analyzed in both discrete and continuous forms. As noted in Table 18-5, an unadjusted t-test of group means showed a statistically significant elevation of TSH in the Ranch Hand group, whereas the categorical analysis did not reveal a statistically significant group difference in the percentage of abnormalities. Exclusion categories and the number of participants were identical to the T_3 % Uptake analyses.

TABLE 18-8.

Adjusted Categorical Analysis for T_3 % Uptake

Analysis Contrast	Adjusted Relative Risk	95% C.I.	p-Value	Covariate Remarks
Overall[a]			0.250	Occupation(p=0.025)
Abnormally Low vs. Normal	0.50	(0.21,1.19)	0.117	
Abnormally High vs. Normal	1.10	(0.50,2.44)	0.809	

[a]Chi-square test (2 d.f.) for group difference.

Unadjusted covariate analyses of discrete TSH data from the combined Ranch Hand and Comparison groups showed a borderline significant difference (p=0.071) among occupational groups, with a higher proportion of enlisted flyers with abnormally high TSH levels than observed in the officer or enlisted groundcrew population. The covariates age (born in or after 1942, born before 1942), race, and personality type were nonsignificant.

A stepwise logistic regression analysis was performed. The final model was identical to the unadjusted analysis as none of the covariates were significantly associated with TSH. The adjusted percent TSH abnormalities by group were expressed as relative risks. For completeness this summary analysis is shown again in Table 18-9.

TSH was subsequently analyzed as a continuous variable. The unadjusted group contrast (determined by a t-test following transformation of TSH values to an inverse square root scale) showed a statistically significant (p=0.019) increase in the mean TSH of the Ranch Hand group, as depicted in Table 18-5. After suitable model fitting, group mean data were adjusted for age (continuous), personality type, and an age-by-personality type interaction. Adjusted results are shown in Table 18-10.

As shown, the Ranch Hand TSH mean was significantly elevated over the Comparison group mean after covariate adjustment. However, the group mean values were well below the observed cutoff value of 7.5 μU/ml.

The herbicide literature suggests a possibility of primary or secondary hypothyroidism as an endpoint following TCDD exposure. Hypothyroidism, as manifest by the test parameters in this study, should produce a tendency toward depressed T_3 % Uptake levels and increased levels of TSH.[19] In the Ranch Hand group, the T_3 % Uptake did not indicate hypothyroidism, whereas the TSH mean value showed an increase consistent with hypothyroidism. Questionnaire, physical examination, and laboratory data on thyroid function

TABLE 18-9.

Adjusted Categorical Analysis for TSH

Adjusted Relative Risk	95% C.I.	p-Value
1.48	(0.50,4.42)	0.579

TABLE 18-10.

Adjusted Continuous Analysis for TSH by Group

Group	Total*	Adjusted Mean	95% C.I.	p-Value	Covariate Remarks
Ranch Hand	998	1.158	(1.13,1.19)	0.025	Age-by-Personality Type (p=0.037)
Comparison	1,267	1.109	(1.08,1.14)		

*Eight participants excluded because of missing data on personality type; 35 participants excluded because of thyroid medication.

and disease led to the conclusion that there were no essential differences indicating thyroid disease between the Ranch Hand and the Comparison groups.

Testosterone

Serum testosterone levels were measured by RIA on all participants. Normal range values from the SCRF Laboratory were used to categorize all data into abnormally low, normal, abnormally high determinations (see Table 18-4). All analyses omitted participants with unilateral or bilateral orchiectomies, and those participants on supplemental testosterone medication.

The unadjusted categorical analysis (see Table 18-5) showed no significant differences ($p=0.896$) in the proportions of abnormalities between the Ranch Hand group and the total Comparison group.

The groups were combined and the relationships between categorized testosterone levels and the covariates occupation, race, age, percent body fat (%BFAT), and personality type were examined. Significant statistical differences were noted for occupation ($p=0.012$), increasing age ($p<0.001$), and increasing percent body fat ($p<0.001$). No effect was found due to race or personality type.

An adjusted analysis was done to determine the simplest model using the significant covariates, and relative risks were calculated. This analysis is depicted in Table 18-11. These results showed that neither percent low testosterone abnormalities nor percent high testosterone abnormalities were excessive in the Ranch Hand group, as the confidence interval of the adjusted relative risks included the value 1.00.

TABLE 18-11.

Adjusted Categorical Analysis for Testosterone

Analysis Contrast	Adjusted Relative Risk	95% C.I.	p-Value	Covariate Remarks
Overall[a]			0.949	
Abnormally Low vs. Normal	1.00	(0.64,1.55)	0.986	Age($p<0.001$) Percent Body Fat ($p<0.001$)
Abnormally High vs. Normal	1.13	(0.48,2.64)	0.774	

[a]Chi-square test (2 d.f.) for group difference.

In contrast to the negative categorical analyses, the unadjusted test of testosterone means showed a significant elevation in the Ranch Hand group (see Table 18-5).

Using similar covariates as in the adjusted categorical analyses, the group means were contrasted by an analysis of covariance. A significant group-by-percent body fat interaction was found (p=0.024). This was due to Ranch Hands having a significantly lower mean than Comparisons (654.4 mg/dl versus 1042.8 mg/dl, p=0.012), for the less than 10 percent body fat category, but a significantly higher mean for the 10 to 25 percent body fat category (603.3 mg/dl versus 582.4 mg/dl), and a nonsignificantly higher mean for the greater than 25 percent body fat category (463.0 mg/dl versus 456.7 mg/dl). However, the number of participants in the less than 10 percent body fat category was very small: six Ranch Hands and four Comparisons, and without these, the overall Ranch Hand mean testosterone level was higher than that for Comparisons. An age-by-percent body fat interaction (p=0.024) and race (p=0.004) were significant covariates. The group interaction is summarized in Table P-1 of Appendix P.

The adjusted analysis showed a significantly elevated mean testosterone level in the Ranch Hand group for the 10 to 25 percent body fat category, which comprised 80 percent of the Ranch Hand and 79 percent of the Comparison participants, whereas the categorical analyses did not reveal any group differences. These findings might be viewed as supportive of an herbicide effect.

Cortisol: Initial, 2-Hour, and Differential

Cortisol measurements were obtained in the AFHS for two reasons: as a general indicator of the integrity of the endocrine system (and specifically as a functional measure of the pituitary-adrenal circuit), and as an important secondary risk factor in coronary artery disease (CAD).[20,21]

As cholesterol is a metabolic precursor to cortisol, there has been longstanding scientific interest on cause-and-effect relationships between these substances. Clearly, steroid and ACTH treatments have been implicated in induced hypercholesterolemia and possibly resulting CAD.[22-24] Cholesterol elevations have been consistently noted following exposure to TCDD (see Chapter 15) and, therefore, are of prime interest in this study. Consequently, exploration of the cholesterol-TCDD or cholesterol-CAD relationship must also account for cortisol differences, if any.

Timed serum specimens were obtained from all participants at a 2-hour interval early on the second day of the examination. The difference between the timed paired specimens was termed the "differential cortisol." The value of the first specimen was generally higher than the value of the second specimen (due to liver catabolism). The mean values of the two cortisol determinations (initial and 2-hour) for the Ranch Hand and the Comparison groups (as reflected in Table 18-5) did not differ by unadjusted t-tests (p=0.668, p=0.793, respectively). Further, the unadjusted categorical analyses for both specimens based on the normal values of the SCRF Laboratory also did not demonstrate significant group differences (p=0.708, p=0.706, respectively).

By an analysis of covariance, using the covariates age, occupation, race, percent body fat, and personality type, the mean value of the initial cortisol specimen was adjusted and contrasted by group. These results are given in Table 18-12, and as indicated, there was no statistically significant group difference.

Tests of association between the differential cortisol and the covariates (Table 18-13) disclosed significant effects by percent body fat and personality type ($p=0.002$, $p=0.006$, respectively). Age was only slightly suggestive of an effect.

An adjusted analysis was performed using the above covariates. A group-by-age-by-race interaction was found ($p=0.032$). Personality type ($p=0.005$) and percent body fat ($p<0.001$) were significant covariates. The interaction found a significantly lower mean differential cortisol level for Black Ranch Hands ($p=0.003$) born in or after 1942 (unadjusted mean 0.17 µg/dl, adjusted mean -0.46 µg/dl) versus corresponding Comparisons (unadjusted mean 2.78 µg/dl, adjusted mean 2.33 µg/dl); no significant differences were found for older Blacks or nonblacks. The interaction is summarized in Table P-1 of Appendix P.

The analyses discussed above showed that the Ranch Hand and Comparison groups did not differ with regard to both paired cortisol specimens, and the differential cortisol of those specimens for all nonblacks and Blacks born before 1942. For Blacks born in or after 1942 (32 Ranch Hands, 47 Comparisons) the mean differential cortisol level was lower for Ranch Hands than Comparisons.

The mean cortisol levels for each personality type and percent body fat category were plotted over time. Figure 18-1 shows the rate of decrease in cortisol for Type A and Type B personalities, adjusted for percent body fat and age. Similarly, Figure 18-2 shows the rate of decrease in cortisol in three categories of percent body fat, adjusted by personality type and age.

The effect of personality type and percent body fat upon the levels of cortisol and the rate of change of cortisol over the 2-hour period are noteworthy. Age was also a significant covariate. Type A personalities began with slightly lower cortisol levels but had a lower rate of decrease of cortisol over the next 2 hours as contrasted to Type B personalities. This analysis demonstrated the ability of the Jenkins Activity Scale to differentiate personality type in this cohort, as measured by differential cortisol levels. The strong effect of percent body fat upon cortisol was not expected.

Glucose Metabolism: 2-Hour Postprandial Glucose and Composite Diabetes Indicator

The 1985 examination at SCRF presented two major changes in the assessment of glucose metabolism as contrasted to the 1982 Baseline examination: (1) the accepted laboratory criteria by which to diagnose diabetes shifted from the standard of 120 mg/dl or more at 2 hours to a designation of "impaired" glucose tolerance (at least 140 but less than 200 mg/dl) and "diabetic" glucose tolerance (at least 200 mg/dl),[25] and (2) participants were given a standardized 100 gram Glucola® challenge rather than an estimated 100 gram carbohydrate breakfast. Further, most known diabetics were encouraged not to take the Glucola® challenge.

TABLE 18-12.

Adjusted Continuous Analysis for Initial Cortisol by Group

Group	Total*	Adjusted Mean	p-Value	Covariate Remarks
Ranch Hand	1,004	11.42	0.659	Age (p<0.001) Personality Type (p=0.002) Percent Body Fat (p<0.001) Occupation-by-Race (p=0.009)
Comparison	1,280	11.49		

* Nine participants omitted due to missing data on personality type and body fat.

TABLE 18-13.

Association Between Differential Cortisol and Age, Race, Occupation, Percent Body Fat, and Personality Score in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Mean Differential Cortisol Level	p-Value
Age	Born ≥ 1942	955	2.24	0.122[a]
	Born < 1942	1,338	2.51	
Race	Black	143	2.16	0.575[a]
	Nonblack	2,150	2.41	
Occupation	Officer	852	2.55	
	Enlisted Flyer	385	2.48	0.203[b]
	Enlisted Groundcrew	1,056	2.23	
Percent Body Fat	<10%	10	1.80	
	10-25%	1,846	2.54	0.002[b]
	>25%	436	1.79	
Personality Type	A Direction	1,002	2.12	0.006[a]
	B Direction	1,283	2.60	

[a]By t-test.

[b]By analysis of variance.

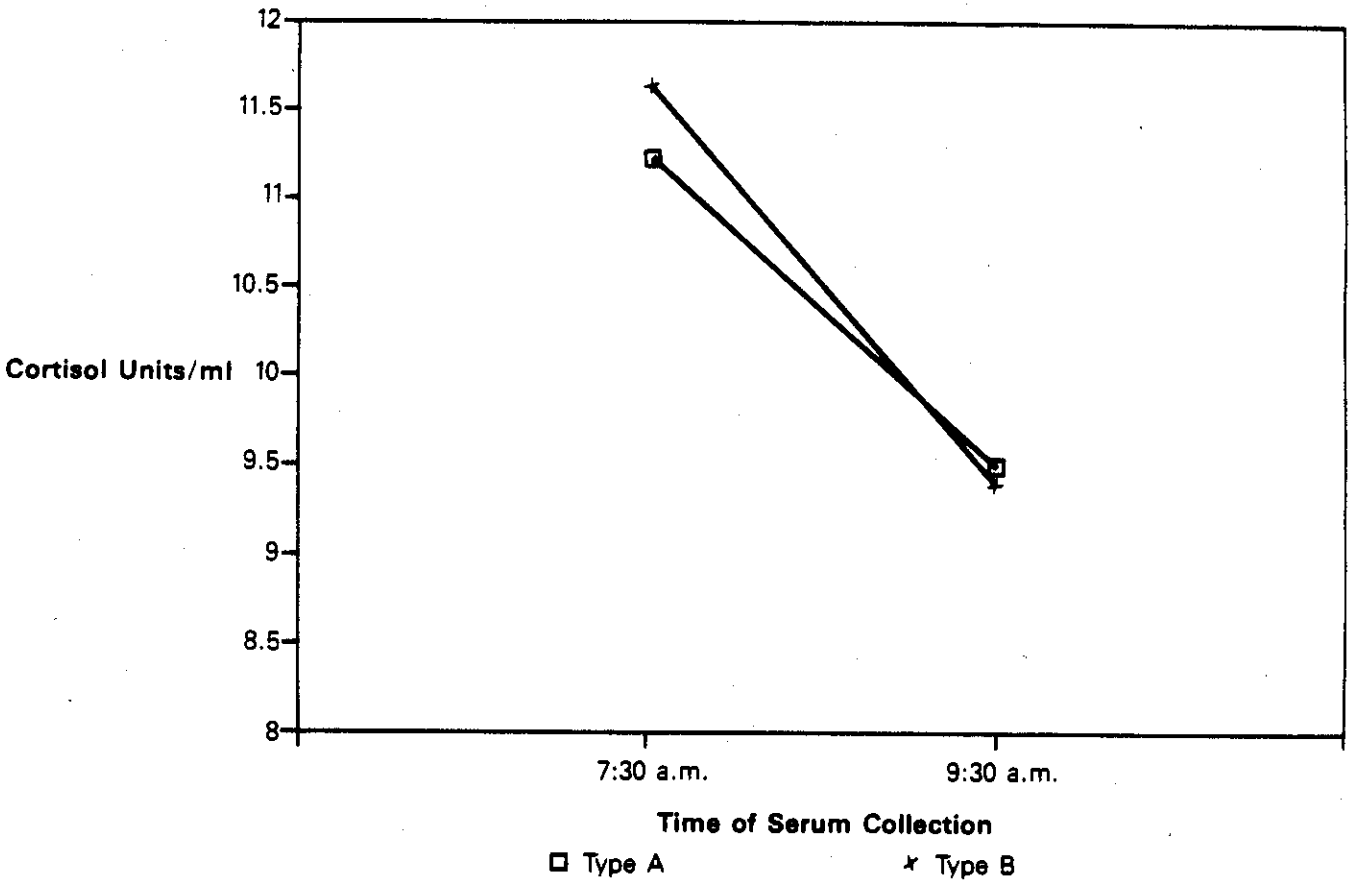

Figure 18-1.
Mean Cortisol Levels by Personality Type, Adjusted for Age and Percent Body Fat, by Time of Specimen Collection

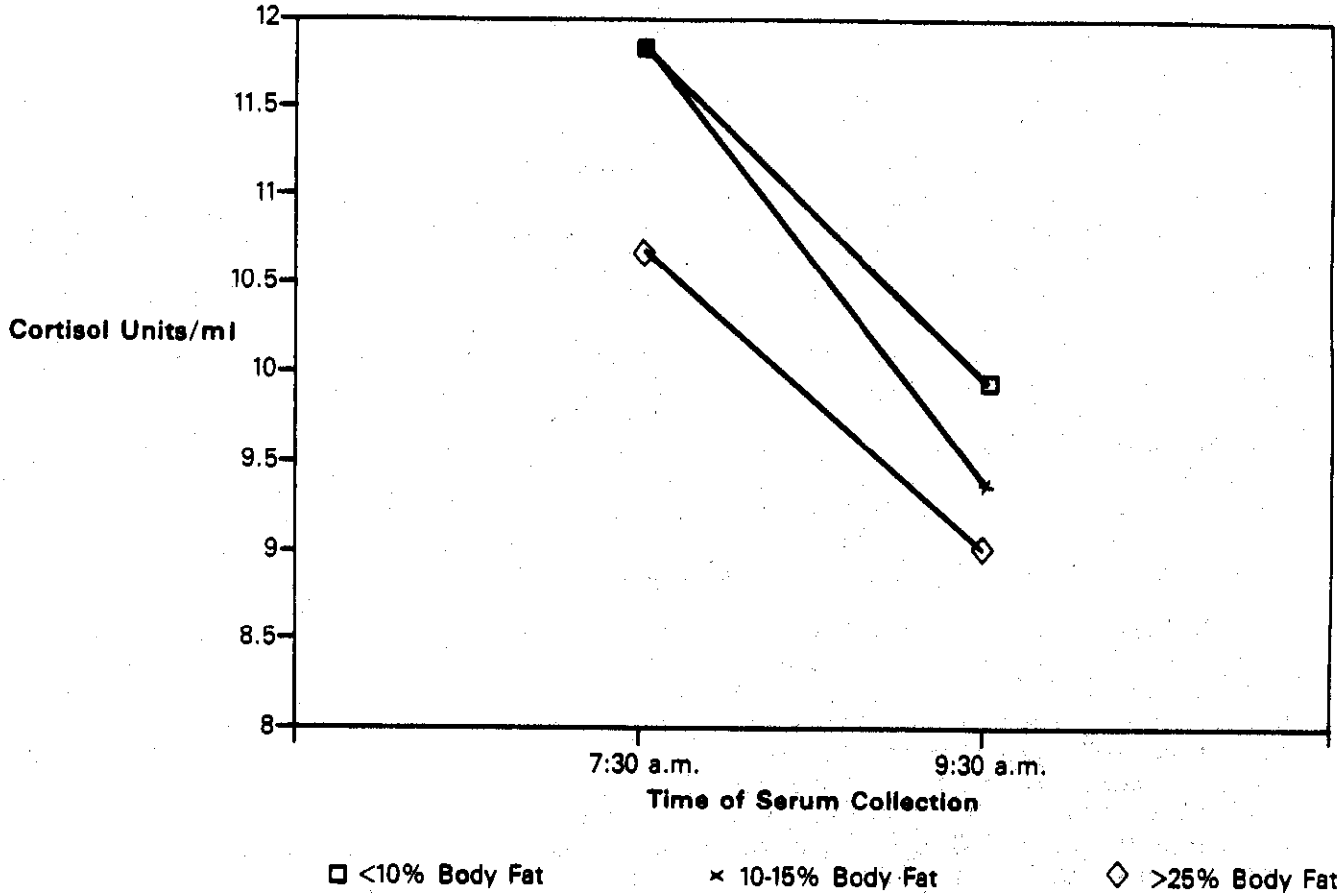

Figure 18-2.
Mean Cortisol Levels by Percent Body Fat, Adjusted for Age and Personality Type, by Time of Specimen Collection

All participants were provided high carbohydrate menus preceding the examination, and were encouraged to consume high calorie meals for 3 days immediately before their examination to improve the diagnostic efficiency of the glucose tolerance test. At the examination site, compliance or noncompliance to the carbohydrate diet was recorded but reported compliance was not analyzed. These data, however, were not used to exclude participants from the analyses, as the 1984 Baseline Report showed that compliance to the diet was inconsequential to the analyses.

All known diabetics, as determined by the Baseline history and the 1982-1985 interval questionnaire, were excluded from the glucose tolerance analyses. However, the 43 Ranch Hands and the 59 Comparisons comprising the exclusion group were included in the composite diabetes analysis.

2-Hour Postprandial Glucose

As noted in Table 18-5, a trichotomized contrast of the 2-hour postprandial glucose showed a statistically significant difference ($p=0.038$) between the Ranch Hand and the Comparison groups. This was due to a slightly higher percentage of Ranch Hands in the diabetic category, and a lower percentage of them in the impaired category relative to the Comparison group.

Both study groups were pooled to assess the covariate main effects of age, race, occupation, and personality type. The results showed a significant effect for occupation ($p=0.030$), largely due to a higher proportion of enlisted flyers having impaired glucose levels. Race, age, and percent body fat were significant covariates ($p=0.037$, $p<0.001$, $p<0.001$, respectively), with Blacks, older ages, and high body fat categories having many more observed abnormalities than nonblack, younger age, and normal body fat categories. Personality type showed no effect ($p=0.562$).

Using the three covariates age, race, and percent body fat, the percent impaired and percent high glucose categories were adjusted and relative risks were calculated. These data are summarized in Table 18-14 and revealed that significantly fewer Ranch Hands had impaired glucose levels (at least 140 but less than 200 mg/dl) than did Comparison members, as demonstrated by the fact that the relative risk was bracketed by a confidence interval with upper limit less than 1.00. Conversely, more Ranch Hands had diabetic levels of glucose (at least 200 mg/dl) on the 2-hour postprandial test than did the Comparisons, but this excess was not statistically significant.

The 2-hour postprandial glucose level was also analyzed as a continuous variable. Group data were transformed to a logarithmic scale and were adjusted by a general linear model using the covariates age, race, occupation, and percent body fat. This analysis is reflected in Table 18-15.

These results showed no group difference for the 2-hour postprandial glucose variable. Significant covariate effects are noted for percent body fat ($p<0.001$), occupation ($p<0.001$), and the age-by-race interaction ($p=0.002$).

TABLE 18-14.

Adjusted Categorical Analysis for 2-Hour Postprandial Glucose

Analysis Contrast	Adjusted Relative Risk	95% C.I.	p-Value	Covariate Remarks
Overall[a]			0.034	
Impaired vs. Normal	0.73	(0.56,0.96)	0.022	Age (p<0.001) Race (p=0.016) Percent Body Fat (p<0.001)
Diabetic vs. % Normal	1.26	(0.72,2.22)	0.421	

[a]Chi-square test (2 d.f.) for group difference.

TABLE 18-15.

Adjusted Continuous Analysis for 2-Hour Postprandial Glucose by Group

Group	Total	Adjusted Mean	95% C.I.	p-Value	Covariate Remarks
Ranch Hand	976	114.4	(107.3,122.0)	0.487	Age-by-Race(p=0.002) Occupation(p<0.001) Percent Body Fat(p<0.001)
Comparison	1,234	115.3	(108.2,123.0)		

Composite Diabetes Indicator

This variable was constructed by selecting participants with a known history of diabetes via the Baseline or interval (1982-1985) questionnaire, and adding them to the group whose 2-hour postprandial glucose level was at least 200 mg/dl at the 1985 examination. Thus, this pool represents all "true diabetics," past and present. These data were contrasted to the "nondiabetics," recognizing the mild degree of misclassification introduced by considering glucose-impaired individuals as normal. The unadjusted frequencies (Table 18-5) were 7.3 percent diabetics in the Ranch Hand group and 6.7 percent diabetics in the Comparison group (p=0.622).

A series of analyses were conducted to determine the best adjusting model for these data, using stepdown procedures from a model containing all main effects and two- or three-way interactions. The final adjustment used the significant covariates of percent body fat and an age-by-race interaction to adjust the proportions of diabetes in each group. These results, formulated as a relative risk, are presented in Table 18-16. The adjusted results indicated no significant difference in the frequency of past and current diabetes in the Ranch Hand and Comparison groups.

The analyses above provide a firm platform to conclude that both study groups were essentially equal with respect to glucose metabolism, and past and current diabetes. Although the herbicide literature suggests a possible endpoint of diabetes, this followup study provides no support for that notion. The slight discrepancies between the categorical tests of glucose abnormalities and the assessment of mean values are probably explained on distributional grounds.

EXPOSURE INDEX ANALYSES

Within each occupational category, exposure index analyses were carried out to assess possible dose-response relationships (see details in Chapter 8). The variables T_3 % Uptake, TSH, testosterone, initial and 2-hour cortisol, differential cortisol, and 2-hour postprandial glucose were analyzed as continuous variables by t-tests and analysis of variance (unadjusted by any of the covariates). Adjusted analyses were performed using general linear models; adjusting covariates were age, race, occupation, and as appropriate, percent body fat and personality type. Group-by-covariate interactions were explored for each analysis, and tests were made of differences in means among the three exposure levels as well as contrasts of means between the medium and low exposure levels, and between the high and low exposure levels. The dependent variables were transformed prior to analysis as described earlier in this chapter.

TABLE 18-16.

Adjusted Analysis for Diabetes (Composite Indicator)

Adjusted Relative Risk	95% C.I.	p-Value	Covariate Remarks
1.12	(0.80,1.56)	0.500	Age-by-Race(p=0.005) Percent Body Fat (p<0.001)

Results of the adjusted analyses are presented in Table 18-17 and parallel results for unadjusted analyses are given in Table P-2 of Appendix P. Results of investigation of any exposure index by covariate interactions are given in Table P-3 of Appendix P.

Unadjusted analyses showed significant differences either among exposure levels or in the high versus low or medium versus low exposure level contrasts for testosterone for officers, and initial cortisol, differential cortisol, and 2-hour postprandial glucose for enlisted flyers. For officers, a significantly lower mean testosterone level was seen for the medium exposure level as contrasted to the low exposure level (547.4 mg/dl versus 599.4 mg/dl, p=0.041). Enlisted flyers had significantly lower mean initial cortisol in the medium as contrasted with low exposure level (11.08 µg/dl versus 11.97 µg/dl, p=0.001); participants in the high exposure level also had a much lower mean, 11.13 µg/dl, as contrasted with the low exposure level but the difference was not significant. Enlisted flyers had a significant difference in differential cortisol among exposure index levels (p=0.003). The mean differential cortisol levels were 3.43 µg/dl, 1.20 µg/dl, 2.30 µg/dl for the low, medium, and high exposure levels, respectively; the medium versus low contrast was very significant (p<0.001), and the high versus low contrast was marginally significant (p=0.092). Mean 2-hour postprandial glucose for enlisted flyers in the medium exposure category was much higher than in the low category: 118.0 mg/dl versus 100.9 mg/dl (p=0.015). However, the mean glucose level for the high exposure category was not as high as that for the medium level, 110.9 mg/dl. The difference among all the exposure levels was close to significance (p=0.051).

Adjusted analyses (Table 18-17) showed patterns very similar to unadjusted analyses. A summary of exposure index by covariate interactions found are listed in Table 18-18. The adjusted mean TSH level for enlisted flyers was significantly higher in the high exposure level as contrasted with the low exposure level (p=0.045); moreover, there was a steady trend upwards with low, medium, and high exposure levels. Enlisted flyers in the medium exposure level had a higher adjusted mean 2-hour cortisol level than the low exposure level (p=0.034), but no trend was apparent. There was a significant difference in differential cortisol among the exposure levels of enlisted flyers (p=0.008) and the medium exposure level had a much lower adjusted mean than the low exposure level (p=0.002). No clear trend with increasing exposure was apparent. Further, enlisted flyers in the medium exposure level had a higher mean postprandial glucose than the lower level (p=0.012), and the overall test for differences among the three levels was significant (p=0.042).

In summary, the emergent pattern was that the enlisted flyers in the medium exposure level were significantly different from those in the low exposure level for 2-hour cortisol, differential cortisol, 2-hour postprandial glucose and marginally significantly different (p=0.098) for testosterone. However, the corresponding high versus low contrasts were not statistically significant.

LONGITUDINAL ANALYSES

Three endocrine variables were chosen for longitudinal analysis: testosterone, T_3 % Uptake, and TSH. Only participants attending both examinations were eligible. The three variables were measured by relatively comparable laboratory techniques at the Kelsey-Seybold Laboratory in 1982 and

TABLE 18-17.

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
T_3 % Uptake	Officer	n	126	124	120	Overall	0.180
		Adj. mean	28.17	28.58	28.15	M vs. L	0.120
		95% C.I.	(27.36,29.01)	(27.78,29.41)	(27.35,28.98)	H vs. L	0.928
	Enlisted Flyer	n	55	65	55	Overall	0.388
		Adj. mean	27.45	27.62	27.95	M vs. L	0.639
		95% C.I.	(26.69,28.24)	(26.90,28.36)	(27.24,28.68)	H vs. L	0.178
	Enlisted Groundcrew	n	153	160	140	Overall	0.853
		Adj. mean	28.00	27.96	27.87	M vs. L	0.857
		95% C.I.	(27.60,28.41)	(27.56,27.96)	(27.45,28.30)	H vs. L	0.579
TSH	Officer	n	126	124	120	Overall	0.262
		Adj. mean	1.263	1.212	1.343	M vs. L	0.513
		95% C.I.	(1.045,1.555)	(1.011,1.479)	(1.107, 1.664)	H vs. L	0.332
	Enlisted Flyer	n	55	65	55	Overall	0.120
		Adj. mean	0.899	1.005	1.058	M vs. L	0.155
		95% C.I.	(0.768,1.067)	(0.860,1.191)	(0.904,1.254)	H vs. L	0.045
	Enlisted Groundcrew	n	153	160	140	Overall	0.807
		Adj. mean	1.135	1.151	1.174	M vs. L	0.775
		95% C.I.	(1.041,1.243)	(1.054,1.263)	(1.070,1.294)	H vs. L	0.513

TABLE 18-17. (continued)

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
Testosterone	Officer	n	125	128	116	Overall	0.560
		Adj. mean	482.6	461.0	464.5	M vs. L	0.312
		95% C.I.	(414.7,555.5)	(395.8,531.2)	(397.9,536.2)	H vs. L	0.405
	Enlisted Flyer	n	55	63	57	Overall	0.251
		Adj. mean	507.7	571.3	536.1	M vs. L	0.098
		95% C.I.	(427.6,594.7)	(492.7,655.7)	(462.6,614.9)	H vs. L	0.454
	Enlisted Groundcrew	n	153	161	137	Overall	****[a]
		Adj. mean	****	****	****	M vs. L	****
		95% C.I.	****	****	****	H vs. L	****
Initial Cortisol	Officer	n	124	130	119	Overall	
		Adj. mean	****	****	****	M vs. L	****[a]
		95% C.I.	****	****	****	H vs. L	****
	Enlisted Flyer	n	55	65	57	Overall	0.533
		Adj. mean	11.69	11.11	11.08	M vs. L	0.335
		95% C.I.	(10.38,13.17)	(9.96,12.39)	(9.97,12.32)	H vs. L	0.320
	Enlisted Groundcrew	n	154	160	140	Overall	0.948
		Adj. mean	11.11	10.98	11.01	M vs. L	0.757
		95% C.I.	(9.96,12.40)	(9.87,12.23)	(9.88,12.27)	H vs. L	0.809

TABLE 18-17. (continued)

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Contrast	p-Value
2-Hour Cortisol	Officer	n	124	130	119	Overall	
		Adj. mean	****	****	****	M vs. L	****[a]
		95% C.I.	****	****	****	H vs. L	****[a]
	Enlisted Flyer	n	55	65	57	Overall	0.102
		Adj. mean	8.10	9.35	8.87	M vs. L	0.034
		95% C.I.	(6.96,9.43)	(8.13,10.74)	(7.75,10.16)	H vs. L	0.179
	Enlisted Groundcrew	n	154	160	140	Overall	****[b]
		Adj. mean	****	****	****	M vs. L	****
		95% C.I.	****	****	****	H vs. L	****
Differential Cortisol	Officer	n	124	130	119	Overall	0.663
		Adj. mean	2.52	2.11	2.45	M vs. L	0.398
		95% C.I.	(0.93,4.12)	(0.55,3.68)	(0.86,4.04)	H vs. L	0.876
	Enlisted Flyer	n	55	65	57	Overall	0.008
		Adj. mean	3.55	1.42	2.46	M vs. L	0.002
		95% C.I.	(2.02,5.08)	(0.02,2.82)	(1.10,3.82)	H vs. L	0.113
	Enlisted Groundcrew	n	154	160	140	Overall	****[c]
		Adj. mean	****	****	****	M vs. L	****
		95% C.I.	****	****	****	H vs. L	****

TABLE 18-17. (continued)

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Medium	High	Contrast	p-Value
2-Hour Post-prandial Glucose	Officer	n	121	124	111	Overall	0.411
		Adj. mean	111.1	106.8	108.1	M vs. L	0.191
		95% C.I.	(100.8,122.4)	(97.1,117.5)	(98.1,119.3)	H vs. L	0.383
	Enlisted Flyer	n	54	62	56	Overall	0.042
		Adj. mean	113.7	134.4	121.9	M vs. L	0.012
		95% C.I.	(97.9,132.0)	(117.2,154.2)	(106.5,139.6)	H vs. L	0.286
	Enlisted Groundcrew	n	150	155	138	Overall	0.706
		Adj. mean	107.1	110.4	109.2	M vs. L	0.413
		95% C.I.	(96.2,119.3)	(99.2,122.7)	(98.2,121.6)	H vs. L	0.597

****Group-by-covariate interaction--adjusted mean, confidence interval, and p-value not given.

[a]Exposure index-by-percent body fat interaction.

[b]Exposure index-by-race interaction.

[c]Exposure index-by-race and exposure index-by-personality type interactions.

TABLE 18-18.

Summary of Exposure Index-by-Covariate Interactions Encountered in Analyses of Endocrinological Variables

Variable	Occupation	Covariate	p-Value
Testosterone	Enlisted Groundcrew	Percent Body Fat	0.001
Initial Cortisol	Officer	Percent Body Fat	0.037
2-Hour Cortisol	Officer	Percent Body Fat	0.011
2-Hour Cortisol	Enlisted Groundcrew	Race	0.006
Differential Cortisol	Enlisted Groundcrew	Race	0.007
		Personality Type	0.021

at the SCRF Laboratory in 1985. As described in Chapter 7, "Statistical Methods," each variable was analyzed continuously by a repeated measurements analysis of variance. Testosterone data were subjected to a square root transformation, and TSH values received a logarithmic transformation. Results of the analysis are shown in Table 18-19.

As shown in Table 18-19, all three variables declined from their Baseline values, but the reductions over time were relatively proportional for each group by variable. It is concluded that significant differences between groups did not exist for the change in levels between the Baseline examination and the first followup examination. The symmetrical changes in the testosterone and T_3 % Uptake variables are speculatively attributed to a 3-year aging effect, but the change in TSH values is suggestive of a change in laboratory methods. There is no suggestion of an adverse rate change in either the Ranch Hand or Comparison group.

SUMMARY AND CONCLUSIONS

The physical examination and laboratory testing results of all endocrinological variables are summarized in Table 18-20.

Questionnaire and review-of-systems data for past thyroid disease were essentially equivalent in both the Ranch Hand and Comparison groups. These historical data were confirmed by medical record reviews. Physical examination findings were necessarily limited to data from palpation of thyroid glands and testicles; the unadjusted results showed no significant group differences.

TABLE 18-19.

Longitudinal Analysis for Testosterone, T_3 % Uptake, and TSH: A Contrast of Baseline and First Followup Examination Test Means

Variable	Group	Means			p-Value (Equality of Difference)
		Total	1982 Baseline	1985 Followup	
Testosterone	Ranch Hand	971	585.16	570.73	
	Comparison	1,139	581.77	552.25	0.20
T_3 % Uptake	Ranch Hand	971	30.30	27.83	
	Comparison	1,139	30.29	27.81	0.93
TSH	Ranch Hand	971	1.744	1.094	
	Comparison	1,139	1.721	1.081	0.83

Evaluation of the endocrine system was conducted primarily by laboratory testing of hormone levels. The thyroid test battery consisted of T_3 % Uptake and TSH assays. The T_3 % Uptake data showed no group differences for either mean values or frequency of abnormally low or high values. Occupation was a significant covariate. TSH results revealed a significantly higher mean level in the Ranch Hand group, but this difference was not found by categorical testing of proportions of abnormally high TSH results.

Mean levels of testosterone were significantly elevated among Ranch Hands as contrasted with Comparisons in the 10 to 25 percent body fat category, but this was not reflected by the categorical tests. For the few participants with less than 10 percent body fat (six Ranch Hands, four Comparisons), mean testosterone levels were lower for Ranch Hands than for Comparisons. Age, occupation, and percent body fat were significant adjusting variables.

Two timed cortisol specimens showed no significant group differences in mean values and percent abnormalities. The difference between the timed cortisol results, termed the differential cortisol, showed no significant group differences for nonblacks or Blacks born before 1942, but Black Ranch Hands born in or after 1942 had a lower mean differential cortisol level than Comparisons. Age, percent body fat, and personality type were significant covariates in these analyses.

Group means of 2-hour postprandial glucose levels were not statistically different, but categorical testing revealed that there was a significantly higher frequency of glucose-impaired (at least 140 but less than 200 mg/dl) Comparisons than Ranch Hands. A constructed variable comprised of known diabetics and individuals classified as diabetic by the glucose tolerance test, showed no difference between the Ranch Hand and Comparison groups. As expected, past and current diabetes were highly influenced by the covariates age, race, and percent body fat.

TABLE 18-20.

Overall Summary Results of
Unadjusted and Adjusted Continuous
and Categorical Analyses of Endocrinological Variables

Test	Unadjusted		Adjusted	
	Mean	Categorical	Mean	Categorical
Questionnaire and Physical Examination				
Past Thyroid Disease (Self-Administered)	--[a]	NS	--[a]	--[b]
Past Thyroid Disease (Interviewer Administered)	--[a]	NS*	--[a]	--[b]
Thyroid Abnormalities	--[a]	NS	--[a]	--[b]
Testicular Abnormalities	--[a]	NS	--[a]	--[b]
Laboratory Testing				
T_3 % Uptake	NS	Overall: NS Low vs. Normal: NS High vs. Normal: NS	--[b]	Overall: NS Low vs. Normal: NS High vs. Normal: NS
TSH	0.019	NS	0.025	NS
Testosterone	0.035	Overall: NS Low vs. Normal: NS High vs. Normal: NS	****	Overall: NS Low vs. Normal: NS High vs. Normal: NS
Initial Cortisol	NS	Overall: NS Low vs. Normal: NS High vs. Normal: NS	NS	--[b]
2-Hour Cortisol	NS	NS	--[b]	--[b]
Differential Cortisol	NS	--[a]	****	--[a]
2-Hour Postprandial Glucose	NS	Overall: 0.038 Impaired vs. Normal: 0.024 Diabetic vs. Normal: NS	NS	Overall: 0.034 Impaired vs. Normal: 0.022 Diabetic vs. Normal: NS
Diabetes (Composite Indicator)	--[a]	NS	--[a]	NS

--[a] Analysis not feasible.
NS: Not significant ($p>0.10$).
--[b] Analysis not performed.
NS*: Borderline significant ($0.05<p\leq 0.10$).
****Group-by-covariate interaction.

Exposure index analyses did not reveal any pattern consistent with a dose-response relationship. Enlisted flyers in the medium exposure level were significantly different from those in the low exposure level for 2-hour cortisol, differential cortisol, and 2-hour postprandial glucose. However, the corresponding high versus low contrasts were not statistically significant.

Longitudinal analyses of T_3 % Uptake, TSH, and testosterone levels on all individuals attending both the Baseline and followup examinations revealed only symmetrical and nonsignificant changes in the Ranch Hand and Comparison groups in the interval between examinations.

In conclusion, both limited historical and physical examination data, seven endocrinological laboratory variables, and a composite indicator of diabetes did not demonstrate consistent patterns indicating an herbicide effect. However, there was a significant interaction between group and percent body fat for testosterone that could be interpreted as an herbicide effect. TSH and testosterone means tests were statistically significant, and in the expected direction of an herbicide effect, but these results were not confirmed by categorical testing. Also significant was the impaired category of the glucose tolerance test, which showed an excess in the Comparison group. The consistent demonstration of the classical effects of the covariates age, race, occupation, and percent body fat on appropriate endocrine variables provided support for these conclusions. Overall, the endocrine health status of both groups was reasonably comparable.

Chapter 18

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