

TABLE 6

**Overall Summary Results of Unadjusted and Adjusted  
Group Contrast Analyses of Neurological Variables**

<b>Variable</b>	<b>Unadjusted</b>	<b>Adjusted</b>	<b>Direction of Results</b>
<b><u>Questionnaire</u></b>			
Inflammatory Disease	NS	--	
Hereditary and Degenerative Disease	0.030	--	
Peripheral Disorders	NS	--	
Disorders of the Eye	NS	--	
Disorders of the Ear	NS	--	
Other Neurological Disorders	NS	--	
<b><u>Physical Examination: Cranial Nerve Function</u></b>			
Smell	NS	--	
Visual Fields	NS	--	
Light Reaction	NS	--	
Ocular Movement	NS	--	
Facial Sensation	NS	--	
Jaw Clench	NS	--	
Smile	NS	--	
Palpebral Fissure	NS	** (NS)	RH>C*
Balance	NS*	--	
Gag Reflex	NS	--	
Speech	NS	--	
Tongue Position Relative to Midline	NS	--	
Palate and Uvula Movement	NS	--	
Neck Range of Motion	NS	NS	
Cranial Nerve Index	NS	NS	
Cranial Nerve Index Without Range of Motion	NS	****	
<b><u>Physical Examination: Peripheral Nerve Status</u></b>			
Pin Prick	NS	NS	
Light Touch	NS	NS	
Muscle Status	NS	NS	
Vibration	NS	** (NS)	
Patellar Reflex	NS	NS	
Achilles Reflex	NS	NS	
Biceps Reflex	0.012	--	C>RH
Babinski Reflex	NS	--	

TABLE 6. (continued)

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

Variable	Unadjusted	Adjusted	Direction of Results
<b>Physical Examination: Central Nervous System Coordination Processes</b>			
Tremor	NS	NS	
Coordination	NS*	** (0.036)	RH>C
Romberg Sign	NS*	--	RH>C <sup>a</sup>
Gait	NS	NS	
CNS Index	NS	NS	

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

--Analysis not done.

\*\* (NS): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Table H-2 in the main report for a detailed description of this interaction.

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

RH>C: More abnormalities in Ranch Hands.

\*\*\*\*: Group-by-covariate interaction ( $p \leq 0.01$ ).

C>RH: More abnormalities in Comparisons.

\*\* (0.036): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); significant when interaction is deleted; refer to Table H-2 in the main report for a detailed description of this interaction.

<sup>a</sup>Balance (Romberg sign).

Seventeen variables were examined to assess group differences in cranial nerve function (smell, visual fields, light reaction, ocular movement, facial sensation, corneal reflex, jaw clench, smile, palpebral fissure, balance, gag reflex, speech, tongue position relative to midline, palate and uvula movement, neck range of motion, the cranial nerve index, and the index without neck range of motion). No group difference was statistically significant, although the prevalence of balance abnormalities based on four cases was marginally higher for the Ranch Hand group than for the Comparison group. The adjusted analyses revealed a significant group-by-lifetime alcohol history interaction for palpebral fissure and a significant group-by-insecticide

exposure interaction for the cranial nerve index without neck range of motion. Stratified results for the cranial nerve index without neck range of motion showed a relative risk significantly greater than 1 for participants who had never been exposed to insecticides and a relative risk marginally less than 1 for participants who had been exposed to insecticides. Stratified analyses for palpebral fissure failed to detect a significant group difference.

The variables analyzed to assess peripheral nerve status were pin prick, light touch, muscle status, vibration, patellar reflex, Achilles reflex, biceps reflex, and Babinski reflex. The prevalence of biceps reflex abnormalities was significantly less for Ranch Hands than for Comparisons. The unadjusted group contrasts for the other variables were not significant. Results of the adjusted analyses were also not significant, except for a group-by-diabetic class interaction that was found for vibration. Exploration of this interaction showed that the adjusted relative risk was marginally greater than 1 for participants categorized as having normal glucose metabolism.

Tremor, coordination, Romberg sign (balance), gait, and the CNS summary index were analyzed to assess the central nervous system coordination processes. Unadjusted group contrasts revealed that Ranch Hands had marginally significantly more abnormalities than Comparisons for the Romberg sign and for coordination. The adjusted analysis for coordination detected two significant group-by-covariate interactions (group-by-occupation and group-by-insecticide exposure). Stratified analyses showed a significant group difference for enlisted groundcrew who had never been exposed to insecticides. Further investigation found a significant group difference for enlisted groundcrew after excluding the group-by-insecticide exposure interaction, and a significant adjusted group difference overall after excluding both group-by-covariate interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis.

Results for the exposure index analyses were generally not significant for each occupational cohort. Isolated significant findings did not indicate an effect due to herbicide exposure.

In conclusion, the 1987 neurological assessment did not find the health of the Ranch Hand group to be substantially different from the Comparison group, but several differences were noted. Of the questionnaire variables, Ranch Hands had a higher incidence of hereditary and degenerative diseases than Comparisons. Unadjusted analyses for the physical examination variables showed that Ranch Hands had marginally more abnormalities than Comparisons for balance/Romberg sign and coordination, but significantly fewer biceps reflex abnormalities. No significant group differences were detected for the other 26 physical examination variables.

## PSYCHOLOGICAL ASSESSMENT

### INTRODUCTION

Emotional illnesses or psychological abnormalities are not generally recognized as primary clinical endpoints following exposure to chlorophenols, phenoxy herbicides, and dioxin. "Neurobehavioral effects" occasionally ascribed to such exposures have been, in fact, predominantly neurological symptoms for which causation is not disputed. Higher central nervous system (CNS) functioning, in terms of cognitive skills, personality, and reactivity, may be temporarily or permanently impaired depending on the exposure and the ability to measure accurately the psychological changes.

### DISCUSSION

Prior to the Air Force Health Study (AFHS) 1982 Baseline study, little scientifically validated information existed regarding the relationship between dioxin exposure and disturbances of cognition and emotions in man. The Baseline and 1985 followup studies attempted to explore these possible relationships using well-established questionnaires, personality inventories, and neuropsychological assessment techniques. These instruments included the Cornell Medical Index (CMI), the Minnesota Multiphasic Personality Inventory (MMPI), and the Halstead-Reitan Battery (HRB).

Analysis of extensive data generated by the CMI, MMPI, and HRB revealed few statistically significant differences between those Air Force veterans who sustained some level of exposure to dioxin (Ranch Hands) and their unexposed Comparison group. More specifically, the two groups did not differ significantly on several tests of cognitive (brain) function. The exposed (Ranch Hand) group reported a moderately greater number of diffuse medical (somatic) complaints on the CMI. They also registered moderately higher (but not statistically significant) scores on the MMPI scales that are influenced most heavily by physical complaints such as generalized feelings of lassitude and malaise, energy loss, mental and physical slowing, etc. The herbicide-exposed groundcrew group only demonstrated significantly higher scores on the MMPI depression scale.

Factors contributing to the modest differences between groups were not clearly indicated by estimated dioxin exposure data. It is possible that observed differences in psychological dependent variables might be related to some combination of negative expectations, anxiety, and amplified somatic sensitivity on the part of the exposed personnel. As the 1985 followup concluded, the possibility existed that subjectively experienced and reported symptoms were more accurate than available exposure data.

A limited number of previous dioxin exposure studies reported similar findings to those described above. Investigations of both military and civilian groups failed to reveal evidence for organic brain dysfunction. However, evidence of significantly elevated levels of tension/anxiety and anger/hostility were reported for at least one civilian group. Psychological tests employed by some of these previous studies were limited when viewed in relation to the range of psychological assessment included in the prior Air

Force studies. Nevertheless, the existence of independent corroborating data combined with previous AFHS findings indicated the importance of continuing some form of appropriate psychological assessment for the 1987 followup.

At the conclusion of the 1985 followup, a significant number of participants registered complaints regarding the lengthy and repetitious nature of the psychometric evaluation. Subsequent concern regarding potential loss of subjects for the 1987 followup led to specific changes in the psychometric component of the study. Previously unrevealing tests of cognition (HRB) were suspended, thereby reducing testing time by several hours. The issue of test-retest boredom was addressed by selecting two new psychometric instruments that would provide ongoing assessment of important psychological variables, while requiring one-half the administration time of the MMPI.

The SCL-90-R is a 90-item checklist of physical and mental symptoms that provides a reasonable measure of health-related concerns and associated anxiety, depression, and general emotional discomfort. The second test selected for the 1987 reevaluation was the MCMI. The MCMI provided backup measures of depression, anxiety, somatization, and hypochondriasis for the SCL-90-R, while also screening for personality disorders and major psychiatric syndromes including psychosis. Both the SCL-90-R and the MCMI have been extensively used in clinical and research settings requiring economical assessment of psychiatric disorder, physical disability status and response to specific therapies. Some methodological difficulties occurred when comparing data generated by these two tests to scores previously obtained using the MMPI. However, factor analysis and correlational studies indicated that specific scales and factors included in the new tests correlated reasonably well with comparable elements of the MMPI. Therefore, acceptable continuity of psychological dependent variables was assured.

Addition of data concerning sleep disorders, as well as the 29 scales and 3 indices comprising the SCL-90-R and the MCMI, produced a relatively substantial increase in the number of psychological dependent variables requiring analysis for the 1987 followup. Similarly, the number of dependent variable-covariate associations requiring examination increased, as did the probability of observing a proliferation of statistically significant interactions.

Examination of the psychological dependent variable-by-covariate associations reported to date indicates a host of statistically significant relationships. For example, previously well-known relationships between advancing age and disturbed sleep were noted, as was the well-known phenomenon of sleep disturbance following excessive consumption of alcohol. An additional predictable outcome involved a strong relationship between the presence of PTSD and a disturbance of virtually all sleep and psychological variables. Although the number of participants with PTSD was relatively small (approximately 1% of each group), the effects of this condition were quite striking and make this an important finding. A more definitive method for the diagnosis of PTSD is the structured psychiatric interview, a technique considered to be too logistically difficult in the context of this study. Therefore, the assessment of PTSD using a subscale of the MMPI was used. While the MMPI subscale may be less precise than the psychiatric interview, it was significantly associated with expected psychological endpoints in the covariate adjusted analyses, and it appears to be a useful technique in the assessment of PTSD in population-based studies.

On the other hand, some significant but puzzling and questionably valid or useful relationships were also demonstrated. For example, white subjects reported sleep disturbances more frequently than their Black counterparts. In addition, the study revealed a powerful relationship between education level and the number of sleep disorders registered. While 38.3 percent of high school-educated subjects reported sleep disturbances, only 30.4 percent of those with college-level education complained of disordered sleep. The 30.4 percent figure compares reasonably well with the 33.0 percent figure cited by sleep researchers as the number of adult Americans likely to report some sleep disturbances in any given year. The apparent fact that study subjects with 12 or fewer years of education experience more sleep disturbance might be caused by greater levels of dissatisfaction with employment, financial pressures, participation in higher rates of shift work, and less regular exercise.

Further inspection of the 1987 data revealed a general persistence of several psychological results that were described as noteworthy in the Baseline and 1985 followup studies. On the SCL-90-R, the Ranch Hand group demonstrated statistically greater levels of depression than Comparison group members. They also manifested more physical complaints (somatization) and health-related anxieties than their Comparison group counterparts. The Ranch Hands also recorded higher scores on those MCMI scales thought to reflect antisocial and passive-aggressive traits and psychotic delusional tendencies. These latter psychological variables might be described as "new" in that they were not reported in the earlier studies. However, the appearance of these maladaptive traits and symptoms probably represents the emergence of artifacts related more to differences in the psychometric properties of the tests used than in the appearance of some new symptom complex.

Continuing manifestations of depression, somatic complaints, and health-related anxiety by members of the Ranch Hand cohort are not surprising. A similar persistence of entrenched symptom complexes has been demonstrated by other populations who have received exposure to known or suspected toxins. Such individuals frequently demonstrate a pattern of self-perpetuating psychological and somatic symptoms that individual group members tend to experience in varying degrees. Air Force groundcrew members who report high levels of herbicide exposure may be particularly vulnerable to repeated suggestions that they have suffered negative psychological and physical consequences secondary to their exposure. Individuals with psychological makeups predisposing them to higher levels of anxiety, psychophysiological disturbances, and somatic concern tend to react rather dramatically to their situation. This type of response can operate to perpetuate a static and/or escalating number of physical and psychological symptoms.

Research has been conducted on the psycho-maintenance\* of chronic physical illness that clearly indicated that a significant percentage (5-10%) of any medical population possess a psychological makeup that predisposes them to the development of symptom-reactive anxiety and psychophysiological disturbances that tend to develop in an escalating manner. As a result, individuals of this type included in the current study may have obtained relatively high scores on those SCL-90-R and MCMI measures that are sensitive to the presence of anxiety, depression, and psychophysiological disturbances. Further,

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\*Psycho-maintenance refers to psychological and behavioral perpetuation and/or exacerbation of physical illness.

individuals who perceive themselves as injured may tend to harbor significant feelings of resentment and hostility that may contribute significantly to the previously noted high scores on antisocial, passive-aggressive, and psychotic delusion scales. In addition, a significantly higher level of alcohol consumption that may represent a form of self-medication may have also contributed to the significantly higher scale scores of the herbicide-exposed group members.

While factors other than dioxin exposure may have contributed to Ranch Hand test score abnormalities, previous studies in clinical medicine also suggest that caution may be appropriate. Studies have followed medical patients who were originally diagnosed as suffering from hysteria, hypochondriasis, or other psychiatric disorders. In some of these studies, more than 60 percent of the patients given psychiatric diagnoses eventually demonstrated neurological diseases, endocrine dysfunction, and other medical disorders. It is therefore important to monitor the health of the study participants over the ensuing years.

#### SUMMARY

The 1987 psychological assessment was based on verified psychological disorders; reported sleep disorders; and two psychological instruments, the SCL-90-R and the MCMI. The results of the psychological assessment are summarized in Table 7.

Five psychological disorders, which were self-reported and verified by medical record review, were analyzed in the psychological assessment: psychoses, alcohol dependence, drug dependence, anxiety, and other neuroses. No significant differences between the Ranch Hands and the Comparisons were detected based on the unadjusted analyses of psychoses, drug dependence, and anxiety. A marginally significant difference between the two groups was found for alcohol dependence and other neuroses ( $p=0.068$  and  $p=0.056$ , respectively), with a greater percentage of Ranch Hands than Comparisons having these conditions.

The sleep disorder segment of the psychological assessment consisted of self-reported responses on 12 individual sleep disorders, 2 composite sleep disorder variables (based on the individual sleep disorders), and average hours of sleep each night. The results of the analyses without adjustments for covariates indicated that significantly more Ranch Hands than Comparisons reported that they experience great or disabling fatigue during the day and that they talk in their sleep ( $p=0.026$  and  $p=0.041$ , respectively). The adjusted analysis of great or disabling fatigue during the day was marginally significant ( $p=0.065$ ). In the adjusted analysis of talking in sleep, there was a significant group-by-PTSD interaction. Further analysis identified that of the participants without PTSD, marginally more Ranch Hands than Comparisons reported that they talk in their sleep ( $p=0.089$ ).

The unadjusted analyses of the other 13 sleep disorder variables did not reveal any significant differences: trouble falling asleep, waking up during the night, waking up too early and can't go back to sleep, waking up unrefreshed, involuntarily falling asleep during the day, frightening dreams, sleepwalking, abnormal movement or activity during the night, sleep problems

TABLE 7.

**Overall Summary Results of Unadjusted and Adjusted  
Group Contrast Analyses of Psychology Variables**

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
<b><u>Psychological Disorders</u></b>				
Psychoses	D	NS	--	
Alcohol Dependence	D	NS*	---	RH>C
Drug Dependence	D	NS	---	
Anxiety	D	NS	---	
Other Neuroses	D	NS*	---	RH>C
<b><u>Sleep Disorders</u></b>				
Trouble Falling Asleep	D	NS	NS	
Waking up During the Night	D	NS	****	
Waking up Too Early and Can't Go Back to Sleep	D	NS	** (NS)	
Waking Up Unrefreshed	D	NS	NS	
Involuntarily Falling Asleep During the Day	D	NS	NS	
Great or Disabling Fatigue During the Day	D	0.026	NS*	RH>C
Frightening Dreams	D	NS	NS	
Talking in Sleep	D	0.041	****	RH>C
Sleepwalking	D	NS	NS	
Abnormal Movement/Activity During the Night	D	NS	** (NS)	
Sleep Problems Requiring Medication	D	NS	NS	
Snore Loudly in All Sleeping Positions	D	NS	NS	
Insomnia	D	NS	** (NS)	
Overall Sleep Disorder Index	D	NS	** (NS)	
Average Sleep Each Night	C	NS	NS	
<b><u>SCL-90-R</u></b>				
Anxiety	D	NS	NS	
Depression	D	NS*	NS	RH>C
Hostility	D	NS	****	
Interpersonal Sensitivity	D	NS	NS	
Obsessive-Compulsive Behavior	D	NS	NS	
Paranoid Ideation	D	NS	NS	
Phobic Anxiety	D	NS	NS	

TABLE 7. (continued)

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

Variable	Type of Analysis	Unadjusted	Adjusted	Direction of Results
<b>SCL-90-R (continued)</b>				
Psychoticism	D	NS	NS	
Somatization	D	NS*	** (NS)	RH>C
GSI	D	NS*	NS	RH>C
PSDI	D	NS	** (NS)	
PST	D	NS	NS	
<b>MCHI</b>				
Schizoid Score	C	NS	NS	
Avoidant Score	C	NS	****	
Dependent Score	C	0.048	** (0.020)	C>RH
Histrionic Score	C	NS	** (NS)	
Narcissistic Score	C	NS*	0.015	RH>C
Antisocial Score	C	<0.001	0.001	RH>C
Compulsive Score	C	NS	** (NS)	
Passive-Aggressive Score	C	NS	** (NS)	
Schizotypal Score	C	NS	** (NS)	
Borderline Score	C	NS	** (0.050)	C>RH
Paranoid Score	C	0.011	0.014	RH>C
Anxiety Score	C	NS	****	
Somatoform Score	C	NS	NS	
Hypomania Score	C	NS	NS	
Dysthymia Score	C	NS	NS	
Alcohol Abuse Score	C	NS	** (NS)	
Drug Abuse Score	C	NS	NS	
Psychotic Thinking Score	C	NS	NS	
Psychotic Depression Score	C	NS	****	
Psychotic Delusion Score	C	NS*	NS*	RH>C

D: Discrete analysis performed.

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

--: Analysis not done.

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

RH>C: Higher prevalence rate or mean in Ranch Hands than in Comparisons.

\*\*\*\*: Group-by-covariate interaction ( $p \leq 0.01$ ); refer to Table I-2 in the main report for a detailed description of this interaction.

\*\* (NS): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Table I-2 in the main report for a detailed description of this interaction.

C: Continuous analysis performed.

\*\* (0.020) and \*\* (0.050): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); significant when interaction is deleted (p-value given).

C>RH: Higher mean in Comparisons than in Ranch Hands.

requiring medication, snoring loudly in all positions, insomnia, overall sleep disorder index, and average sleep each night. In general, this finding was supported by the results of the adjusted analyses, although significant group-by-covariate interactions were present in 5 of the 13 analyses. Further exploration of the interactions revealed no significant group differences in any stratum for three of the five variables. Of participants born in or before 1922, significantly more Comparisons than Ranch Hands were classified as having insomnia ( $p=0.012$ ). Marginally more Comparisons than Ranch Hands who were born in or before 1922 reported that they wake up during the night ( $p=0.078$ ).

The SCL-90-R, a multidimensional self-reported symptom inventory designed to measure symptomatic psychological distress, yields nine primary symptom dimensions and three global indices of distress. No differences between the two groups were found for 7 of the 12 SCL-90-R scores: anxiety, interpersonal sensitivity, obsessive-compulsive behavior, paranoid ideation, phobic anxiety, psychoticism, and positive symptom total. Marginally significant differences between the two groups were detected for depression ( $p=0.090$ ), somatization ( $p=0.073$ ), and GSI (an index of symptom severity) ( $p=0.081$ ), with a higher percentage of abnormalities in the Ranch Hands than in the Comparisons, based on the unadjusted analyses. For depression and the GSI, no differences were revealed after adjustment for covariates. In the adjusted analysis of somatization, there was a significant group-by-education interaction present in the model. Further investigation of the interaction showed that the high school-educated Ranch Hands had a significantly higher percentage of abnormalities on somatization than the Comparisons with a high school education ( $p=0.025$ ).

Although no difference between the two groups was revealed in the unadjusted analysis of the SCL-90-R PSDI (an index of symptom intensity), there was a significant group-by-race interaction in the adjusted analysis. Exploration of the interaction revealed that the Black Comparisons had a marginally higher percentage of abnormalities than the Black Ranch Hands on this index ( $p=0.079$ ). The unadjusted analysis of hostility from the SCL-90-R did not identify a significant difference between the two groups, and there was a significant group-by-PTSD interaction in the adjusted analysis. Stratifying by the presence or absence of PTSD did not reveal any significant differences between the Ranch Hands and the Comparisons in either stratum.

The MCMI, a self-administered test that measures eight basic personality patterns, three pathological personality disorders, and nine clinical symptom syndromes. The results of the unadjusted analyses of the MCMI scores showed no significant group differences for 15 of the 20 scores: schizoid, avoidant, histrionic, compulsive, passive-aggressive, schizotypal, borderline, anxiety, somatoform, hypomania, dysthymia, alcohol abuse, drug abuse, psychotic thinking, and psychotic depression. In the adjusted analyses of these variables, there were significant group-by-covariate interactions for 9 of the 15 analyses, which made the direct contrast of the two groups more difficult. Stratifying by the covariates in order to contrast the two groups within each stratum did not reveal a consistent pattern of significant detriment to either group. Significant differences were noted in 10 strata, and there were marginally significant differences detected in 6 strata. The mean score of the Ranch Hands exceeded that of the Comparisons for five of the significant strata and four of the marginally significant strata. However, many of these were strata where few participants were present (e.g., Blacks, participants with PTSD). Consequently, corresponding unadjusted results and models without

the significant group-by-covariate interaction are primarily nonsignificant. For all except one variable where the analysis was repeated without the group-by-covariate interaction(s), no significant differences were revealed. In the analysis of the borderline score without the significant interaction involving group, the results showed that the Comparisons had a significantly higher mean score than the Ranch Hands ( $p=0.050$ ).

The Ranch Hands were found to have significantly higher mean antisocial and paranoid scores than the Comparisons (antisocial:  $p<0.001$  for unadjusted and  $p=0.001$  for adjusted; paranoid:  $p=0.011$  for unadjusted and  $p=0.014$  for adjusted). On the psychotic delusion score, the mean score for the Ranch Hands was marginally higher than the Comparison mean score ( $p=0.061$  for unadjusted and  $p=0.062$  for adjusted). The results of the unadjusted analysis of the narcissistic score showed that the mean score for the Ranch Hands was marginally significantly higher than the mean score for the Comparisons ( $p=0.090$ ); after adjusting for covariates, a significant difference was detected ( $p=0.015$ ). Based on the unadjusted analysis, the Comparisons had a significantly higher mean dependent score than the Ranch Hands ( $p=0.048$ ). In the adjusted analysis, there was a significant group-by-race interaction. Stratifying by race revealed that the nonblack Comparisons had a significantly higher mean score than the nonblack Ranch Hands ( $p=0.005$ ) and the Black Ranch Hands had a marginally higher mean score than the Black Comparisons ( $p=0.086$ ). Without the group-by-race interaction in the model, the Comparisons had a significantly higher mean score than the Ranch Hands ( $p=0.020$ ).

The results of the exposure index analyses did not reveal a consistent pattern of an increasing dose-response relationship for any occupational cohort across the variables. The majority of the unadjusted analyses did not detect any significant differences among the exposure categories for the different occupational cohorts. Interactions involving the exposure index were frequently found in the adjusted analyses; however, exploration of the interactions did not identify a subgroup within the Ranch Hands that consistently demonstrated an increasing dose-response relationship. The occasional observation of significant and borderline findings in the officer cohort is difficult to interpret in view of the evolving understanding of the relatively low level of dioxin exposure experienced by officers.

Significant or marginally significant differences between the Ranch Hands and the Comparisons were found for some variables within each of the four psychological assessment instruments of verified psychological disorders, reported sleep disorders, and the self-administered SCL-90-R and MCMI psychological examinations. However, there was a lack of consistency across similar variables included on the SCL-90-R, MCMI, and reported information. For these differences the Ranch Hands generally manifested a higher percentage of abnormalities or a higher mean score than the Comparisons. However, this is not surprising in light of the fact that individuals who perceive themselves as having been harmed might be more likely to report the symptoms observed as significant in this analysis. Profound effects of PTSD were noted for most all psychological variables. These results should be reexamined carefully for positive correlations between the complaints and increased levels of dioxin exposure when data from the serum dioxin assay become available. Additionally, significant group-by-covariate interactions were observed frequently in the adjusted analysis, which often made direct contrast of the two groups with adjustment for significant covariates difficult.

## GASTROINTESTINAL ASSESSMENT

### INTRODUCTION

This system assessment centers on reported peptic ulcer and liver disease, and current hepatic function and porphyria as determined by comprehensive laboratory testing and the physical examination. The liver is a major target organ for single high-dose and continued low-dose exposure to chlorophenols and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Peptic and stomach ulcer disease and porphyria cutanea tarda (PCT) are suspected clinical endpoints following moderate- to high-level exposures.

### DISCUSSION

Signs and symptoms referable to the gastrointestinal system are those most frequently encountered in ambulatory medicine. As screening tools in the outpatient investigation of digestive disorders, the historical, physical examination, and laboratory parameters included in the gastrointestinal assessment are well established in clinical practice. More definitive diagnostic studies, such as barium and endoscopic surveys of the bowel, were not included in the current study and, except in emergent circumstances, are rarely indicated in the initial evaluation of gastrointestinal disease.

In the diagnosis of digestive disorders it is important to recognize certain limitations in the extent to which data from the history and physical examination can be relied upon. Rather than pointing to a particular diagnosis, digestive symptoms are frequently nonspecific and intermittent. In this setting, even the best designed medical history questionnaire can be subject to error. "Ulcer" and "colitis" are diagnoses that are commonly reported but often not accurately established. In contrast, most cases of hepatitis are anicteric and escape detection. As a common target organ for situational stress, the bowel frequently gives rise to symptoms that can be severe but that are functional in nature and resolve in time. These caveats highlight the importance of the type of medical record verification conducted in the current study and, in the case of hepatitis, the need for serologic confirmation.

In contrast to some organ systems, the physical examination in gastrointestinal disease is often of limited value and can be misleading in the differential diagnosis. The ability of the examiner to detect hepatomegaly will be unreliable in the obese patient. In obstructive airway disease, with hyperinflation of the lungs and flattening of the diaphragms, the liver edge may descend abnormally below the right costal margin in the absence of hepatomegaly. In the best of circumstances, the span of the liver by palpation or percussion is often an unreliable index of liver size. Recognizing that in the most advanced stages of cirrhosis hepatomegaly is often not present, other stigmata of chronic liver disease were sought during the physical examination. Palmar erythema, ascites, telangiectasias, and gynecomastia were examined as part of this physical examination.

In contrast to the limitations of the history and physical examination outlined above, data collected in the laboratory can provide early insight into the presence of occult liver disease. The four hepatic enzymes analyzed

as dependent variables [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and lactic dehydrogenase (LDH)] are common to most chemistry panels ordered in the outpatient setting. Present in high intracellular concentration, these enzymes are released in virtually all toxic, inflammatory, and neoplastic diseases with hepatic involvement. As reliable laboratory markers of liver disease, the GGT is considered the most sensitive, while the LDH, with iso-enzymes derived from multiple organ systems, is the least specific.

As the hepatic enzymes are used in the detection and followup of parenchymal disease, so are the serum alkaline phosphatase and bilirubin reflective of hepatobiliary function in "cholestatic" or "obstructive" disease. Though present in virtually all organ systems, the serum alkaline phosphatase in the adult population under study is of dual origin and close to a 50-50 mixture of liver- and bone-derived fractions. An elevated alkaline phosphatase is by no means diagnostic of liver disease and can occur in a broad range of unrelated clinical conditions including drug-induced cholestasis, Paget's disease (3% of males over age 40), neoplasia with metastases to bone, and congestive heart failure.

Similarly, and pertinent to the current study, the bilirubin indices are subject to numerous hereditary and acquired disorders unrelated to intrinsic hepatic disease. The benign hyperbilirubinemia of Gilbert's syndrome will occur in 5 percent of the population under study. A long list of medications, including many over-the-counter preparations, have been implicated in the overproduction of bilirubin in the hemolytic reactions associated with glucose-6-phosphate dehydrogenase deficiency, which may occur in up to 15 percent of Black American males.

Most of the dependent variable-covariate associations analyzed in the present section are consistent with established clinical observations. Alcohol consumption was associated with hepatomegaly and elevated liver enzymes with the most sensitive GGT showing the greatest deviation from the normal. The difficulty in estimating alcohol consumption by history may account for the unexpectedly higher percentage of two enzyme abnormalities (ALT and GGT) in non- versus moderate alcohol consumption. Alcohol use per se should not affect consumption were not significant.

Documented in the adjusted analyses were a number of covariate associations that would be expected with age including gradual elevations in serum cholesterol, triglycerides, and fasting blood sugar. The decrease in ALT over time is not readily explained and probably not significant as an isolated finding. The decline in serum creatine kinase would be consistent with decreasing muscle mass over time.

Significant ( $p < 0.001$ ) race-related differences in two serum enzymes (GGT and creatine kinase) were documented and, in the case of the creatine kinase, the mean for Blacks was almost twice that for nonblacks. These data are consistent with observations confirmed in a small number of studies over the past decade. The elevation, not yet explained, appears to be race- and gender-specific and is limited to Black males.

With reference to prior herbicide exposure, most group differences were not statistically significant, though, as in the 1985 followup examination, Ranch Hands had a significantly higher mean alkaline phosphatase (93.7 U/L) than did the Comparisons (90.3 U/L). As an index subject to multiple organ variables, however, this difference should not be considered clinically significant. Longitudinal analysis of three enzyme variables confirmed no significant group differences over time. The decline in serum AST in both groups cannot be explained on the basis of any difference in methodology as the laboratory assay techniques in the 1985 and 1987 examination cycles were identical.

The gastrointestinal assessment data confirmed observations that are well established in clinical practice and reflect no apparent increase in organ-specific mortality or morbidity in the Ranch Hand group versus the Comparison group over time.

#### SUMMARY

Table 8 summarizes the statistical results of the Ranch Hand and Comparison group contrasts that were analyzed for the 1987 gastrointestinal assessment.

Information collected at the health interview was verified and grouped into eight categories of liver disorders. There were no significant group differences for any of these conditions. Self-reported data on history of ulcers and on occurrences of skin patches, bruises, and sensitivity also did not differ significantly between groups. In contrast, Ranch Hands reported significantly more skin patches, bruises, and sensitivity than Comparisons at both the Baseline and 1985 followup examinations.

Hepatomegaly was diagnosed at the physical exam. No significant group difference was found for the unadjusted analysis. The adjusted analysis detected a significant group-by-degreasing chemical exposure interaction; the group relative risk for participants never exposed to degreasing chemicals was marginally significant and less than 1. After excluding the interaction, the adjusted group difference was not significant.

Ranch Hand and Comparison group contrasts were assessed for 13 laboratory variables. Each variable was examined in both continuous and discrete forms. Statistical analysis of these variables revealed only one significant group difference. The Ranch Hand alkaline phosphatase mean was significantly higher than the Comparison mean, a finding also noted at the 1985 followup study. In contrast, the percentage of abnormal alkaline phosphatase values was very similar between groups. Aside from significant group-by-covariate interactions, results of the adjusted analyses always supported the unadjusted analyses results. Results based on stratified analyses to explore group-by-covariate interactions were generally not significant. The following stratum specific significant results were noted: for participants with more than 40 drink-years, the Ranch Hand ALT mean was marginally higher than the Comparison mean; the direct bilirubin mean for Black Ranch Hands was significantly higher than the mean for Black Comparisons; and Ranch Hands exposed to degreasing chemicals had significantly fewer direct bilirubin abnormal levels than Comparisons who had been exposed to degreasing chemicals.

TABLE 8.

**Overall Summary Results of Unadjusted and Adjusted  
Group Contrast Analyses of Gastrointestinal Variables**

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
<u>Questionnaire</u>					
Viral Hepatitis Acute and Subacute Necrosis of the Liver	NS	--	--	--	
Chronic Liver Disease and Cirrhosis (Alcohol Related)	NS	--	--	--	
Chronic Liver Disease and Cirrhosis (Nonalcohol Related)	NS	--	--	--	
Liver Abscess and Sequelae of Chronic Liver Disease	NS	--	--	--	
Other Disorders of the Liver	NS	--	--	--	
Jaundice (Unspecified)	NS	--	--	--	
Hepatomegaly	NS	--	--	--	
Reported Ulcer	NS	--	NS	--	
Skin Patches, Bruises, or Sensitivity	NS	--	--	--	
Verified Ulcer	NS	--	NS	--	
<u>Physical Examination</u>					
Diagnosed Hepatomegaly	NS	--	** (NS)	--	
<u>Laboratory</u>					
AST	NS	NS	NS	NS	
ALT	NS	NS	NS	** (NS)	
GGT	NS	NS	NS	NS	
Alkaline Phosphatase	NS	<0.001	NS	<0.001	RH>C
Total Bilirubin	NS	NS	** (NS)	NS	
Direct Bilirubin	NS	NS	****	** (NS)	
LDH	NS	NS	NS	NS	
Cholesterol	NS	NS	NS	NS	
HDL	NS	NS	NS	** (NS)	
Cholesterol-HDL Ratio	NS	NS	NS	NS	

TABLE 8. (continued)

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

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
Triglycerides	NS	NS	NS	NS	
Creatine Kinase	NS	NS	NS	NS	
Fasting Glucose	NS	NS	NS	NS	

--: Analysis not done.

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

\*\*\*\*: Group-by-covariate interaction ( $p \leq 0.01$ ).

\*\* (NS): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted.

RH>C: Higher mean value Ranch Hands than in Comparisons.

The adjusted exposure index analyses detected one statistically significant result supportive of a herbicide effect (GGT discretized for the officer cohort), and one marginally significant result that suggested a herbicide effect (direct bilirubin treated as a continuous variable for the enlisted groundcrew cohort). Other significant or marginally significant results did not indicate an effect due to dioxin exposure. Although few exposure index results were statistically significant, trends in the data showed positive dose-response relationships for many variables, particularly for the officer and enlisted groundcrew cohorts.

Longitudinal analyses for AST, ALT, and GGT disclosed no statistically significant differences over time between groups.

In conclusion, results of the 1987 gastrointestinal assessment did not indicate an overall detriment to the health of the Ranch Hand group. The Ranch Hand alkaline phosphatase mean was significantly higher than the Comparison mean, but for all other variables, differences between groups were not statistically significant. In many instances, patterns in the data for the exposure index analyses supported a herbicide effect, but the results were generally not significant.

## DERMATOLOGIC EVALUATION

### INTRODUCTION

The skin is a major target organ following heavy exposure to chlorophenols and dioxin and, therefore, is a primary focus of the Air Force Health Study (AFHS) clinical examination.

### 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 of the main report. 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 9.

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 Southeast Asia (SEA) tour was present.

Table 9

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				
<u>Lifetime</u>	D	0.026	--	RH>C
<u>Relative to SEA Tour<sup>a</sup></u>				
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.

<sup>a</sup>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 ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Table K-2 in the main report for a detailed description of this interaction.

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.

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.

## CARDIOVASCULAR EVALUATION

### INTRODUCTION

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.

### DISCUSSION

Of the diseases encountered by the primary care physician, circulatory disorders are among the most common. The sources of the noninvasive data analyzed in the current chapter occupy a time-honored place in cardiovascular practice. Specifically, the history, physical examination, chest x ray, and resting electrocardiogram remain highly reliable indices that can alert the clinician to the presence of underlying cardiovascular disease and point to the need for additional, more specific, noninvasive, or invasive studies. Though arbitrary, dividing data collection into central and peripheral cardiovascular functions is convenient and forms a reasonable basis for comparison of the cohorts under study.

The limitations of the history in cardiovascular diagnosis deserve emphasis. In peripheral vascular disease, for example, signs and symptoms will vary depending on the degree of development of collateral circulatory channels. While hemodynamically significant arterial disease of lower extremities is almost always associated with claudication, severe carotid occlusive disease can be present in the absence of symptoms of transient cerebral ischemia. Further, conclusive evidence shows that advanced coronary artery disease can occur in the absence of angina and present as "silent" myocardial ischemia. Lastly, it is well recognized that the cardiovascular history, as related by patients, is often subject to error. The generic term "heart attack," for example, can be used to describe any type of cardiac event from an isolated episode of unstable angina or arrhythmia, to an actual myocardial infarction. These imperfections highlight the importance of the type of medical record verification conducted in the current study.

In the cardiovascular assessment, particularly, the physical examination can provide valuable clues to the presence of asymptomatic but significant underlying disease. Because the examinations were conducted by internists rather than cardiologists, steps were taken to simplify data collection and to reduce interobserver differences among the examining physicians. All blood pressure readings, for example, were taken by automated sphygmomanometric instruments. Auscultory endpoints--murmurs and bruits--were recorded as present or absent by anatomic location, thus eliminating speculation as to specific valvular or vessel origin and hemodynamic significance. As markers of occult arterial occlusive disease, vascular bruits are relatively easy to detect and were carefully sought.

Pertinent to the longitudinal design of the AFHS, several of the physical findings recorded must be viewed in the context of the aging population under

study. A gradual increase in systolic blood pressure will occur with advancing years. Related to the normal progression of arteriosclerosis and, more specifically, to arterial tortuosity, vascular bruits may occur in vessels free of occlusive disease, particularly in the carotid arteries. Again, all bruits were recorded by location without attempting to comment on the hemodynamic significance or specific vessel of origin (i.e., internal vs. external carotid). The occurrence of abnormal heart sounds, particularly S<sub>4</sub>, would also be expected to increase with age.

The data collected in the current chapter were limited to the resting 12-lead electrocardiogram and the standard two-view chest x ray. This x ray is used to detect the presence of cardiac enlargement or abnormalities in pulmonary vasculature, as reported in Chapter 20 of the main report, Pulmonary Disease. In current practice, these techniques are supplemented, but not replaced, by such noninvasive studies as the treadmill exercise test, nuclear isotope studies, and the echocardiogram. With few exceptions, these technically sophisticated and costly procedures do little more than confirm diagnoses that can be made based on data available in the current assessment. For example, when correlated with the history and physical examination, the chest x ray and electrocardiogram enable the clinician to draw highly accurate conclusions regarding the presence and hemodynamic significance of valvular heart disease of any etiology. As defined by the chest x ray, the pulmonary vascularity can provide reliable clues to the presence of global left ventricular dysfunction with pulmonary venous congestion and of pulmonary hypertension of any cause.

The dependent variable-covariate associations analyzed in the current chapter confirm findings that have been well documented in numerous long-term epidemiologic studies. The lack of clearly defined cardiovascular endpoints to dioxin exposure places a premium on the careful analysis of risk factors as potentially confounding variables. More than any other, the cardiovascular system is subject to the effects of lifestyle and heredity.

As a degenerative disease with multiple manifestations, arteriosclerosis develops in all organ systems over time. With few exceptions, an age-related increase in the incidence of abnormal physical findings was documented in both the Ranch Hand and Comparison groups. As expected, reported and verified heart disease and, particularly, previous myocardial infarction, were highly correlated with the classical risk factors of age, positive family history, and cigarette use. Although an apparent exception was the negative correlation between the systolic blood pressure and current cigarette use, this may reflect the contributions of former smokers, who have stopped smoking in response to a diagnosed disease. This is the group that had the highest percentage of abnormal systolic blood pressures (above 140 mm Hg). Lifetime cigarette use, on the other hand, was consistently positively associated with abnormalities in all variables analyzed.

The effects of current and lifetime alcohol consumption were less consistent. Clinically, it is clear that in cases of severe, chronic abuse, alcohol is directly cardiotoxic and can lead to an irreversible congestive cardiomyopathy. On the other hand, when consumed in moderation, alcohol may favorably influence the ratio of high density lipoprotein (HDL) to low density lipoprotein (LDL) cholesterol and may actually be protective with respect to the future development of cardiovascular disease.

Group comparisons generally revealed no significant differences between the Ranch Hand and Comparison cohorts. As in the Baseline examination (but not in the 1985 followup), Ranch Hands had a greater incidence of peripheral pulse abnormalities of the lower extremities than the Comparisons (15.3% vs. 12.2%). As noted above, the 1985 followup included Doppler ultrasound studies, which have proven to be more sensitive than traditional manual palpation. Further analysis of specific pulse sites suggests that the current group difference relates mainly to an increased incidence of femoral, rather than more peripheral, sites, a finding that should be relatively easy to confirm on subsequent examination cycles. Arterial occlusive disease is often unilateral rather than bilateral and can affect large vessels proximally or smaller vessels distally in segmental fashion. Distal circulation may be maintained by good collateral vessels even in the presence of proximal, partial pulse deficits. The Doppler should be more reliable than palpation in such cases, but neither method is perfect. This observed pulse difference does not appear to be related to exposure since abnormalities were not increased in the enlisted groundcrew, the group with the highest serum TCDD levels.

Recently, there has been renewed interest in the role of personality type as a risk factor for cardiovascular disease. In the current study, Type B personality was found to be associated with an increased incidence of elevated systolic blood pressure and with deficits in four of the five peripheral pulses assessed by palpation. Though at variance with classical teaching, these results are consistent with recent evidence that Type B personality may be at equal or greater risk than Type A for the development of coronary artery disease.

The historical, physical examination, and laboratory data provide a reasonable basis for comparison of the cohorts under study and indicate that neither the Ranch Hand nor the Comparison group is at significant health detriment relative to the other. The slightly greater incidence of heart disease documented in the Ranch Hand cohort in the 1985 followup examination was not evident after continuing review of medical records. The incidence is now similar in the two groups. Finally, as in the Baseline examination (but not in the 1985 followup), a slightly greater incidence of pulse deficits has been found in the Ranch Hand group and will bear continued surveillance in future examination cycles as more accurate methods to measure the body burden of dioxin become available.

#### SUMMARY

The cardiovascular evaluation of the Ranch Hand and Comparison groups was based upon reported and verified heart disease events (essential hypertension, cardiac disease, and myocardial infarction); assessment of central cardiac function [systolic blood pressure, heart sounds, and electrocardiograph (ECG) findings]; and assessment of peripheral vascular function (diastolic blood pressure, funduscopic abnormalities, carotid bruits, and peripheral pulse abnormalities). Table 10 presents a summary of all of the unadjusted and adjusted group comparisons for these variables.

TABLE 10.

**Overall Summary Results of Unadjusted and Adjusted Group  
Contrast Analyses of Cardiovascular Variables**

Variable	Unadjusted	Adjusted	Direction of Results
<b><u>Questionnaire Variables</u></b>			
Reported/Verified Essential Hypertension*	NS	NS	
Reported Heart Disease (Excluding Hypertension)	NS	NS	
Verified Heart Disease (Excluding Hypertension)	NS	NS	
Reported/Verified Myocardial Infarction*	NS	** (NS)	
<b><u>Central Cardiac Function</u></b>			
Systolic Blood Pressure (continuous)	NS	NS	
Systolic Blood Pressure (discrete)	NS	** (NS)	
Heart Sounds	NS	NS	
ECG-Overall	NS	NS	
RBBB	NS	NS	
LBBB	NS	--	
Nonspecific T-Waves	NS	****	
Bradycardia	0.049	NS*	C>RH
Tachycardia	NS	--	
Arrhythmia	NS	NS*	RH>C
ECG-Other Diagnoses	NS	NS	

TABLE 10. (continued)

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

Variable	Unadjusted	Adjusted	Direction of Results
<b>Peripheral Vascular Function</b>			
Diastolic Blood Pressure (continuous)	NS*	** (NS*)	RH>C
Diastolic Blood Pressure (discrete)	NS	** (NS)	
Funduscopy Examination	NS	--	
Carotid Bruits	NS*	--	RH>C
Radial Pulses	NS*	--	C>RH
Femoral Pulses	0.016	0.018	RH>C
Popliteal Pulses	NS	NS	
Dorsalis Pedis Pulses	NS*	NS*	RH>C
Posterior Tibial Pulses	NS	****	
Leg Pulses	0.049	NS*	RH>C
Peripheral Pulses	NS*	NS	RH>C
All Pulses	NS*	NS	RH>C

\*All conditions reported were verified; therefore, reported and verified analyses are the same.

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

\*\* (NS): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Table L-2 in the main report for a detailed description of this interaction.

--Adjusted analyses not performed (sparse data).

\*\*\*\*: Group-by-covariate interaction ( $p \leq 0.01$ ); refer to Table L-2 in the main report for a detailed description of this interaction.

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

C>RH: Higher mean in Comparisons than in Ranch Hands.

RH>C: Higher prevalence rate or mean in Ranch Hands than in Comparisons.

\*\* (NS\*): Group-by-covariate interaction ( $0.01 < p \leq 0.05$ ); borderline significant when interaction is deleted; refer to Table L-2 in the main report for a detailed description of this interaction.

In the evaluation of heart disease from questionnaire data, there were no statistically significant differences, unadjusted or adjusted, in the frequency of reported/verified essential hypertension, reported heart disease, or verified heart disease. For reported/verified myocardial infarction, there was no statistically significant difference between the two groups in the unadjusted analysis, but in the adjusted analyses, there was a statistically significant group-by-family history of heart disease interaction ( $p=0.042$ ). The relative risk was less than 1 in those with no family history of heart disease and greater than 1 in those with a family history of heart disease; neither within-stratum estimate of risk was statistically significant. An adjusted model fit after deletion of the interaction term was not statistically significant.

For the parameters of central cardiac function there were no statistically significant differences, unadjusted or adjusted, in the mean systolic blood pressure, nor in the percentage of individuals with abnormal heart sounds, overall ECG abnormalities, right bundle branch block (RBBB), left bundle branch block (LBBB), tachycardia, or other ECG diagnoses. In the discrete analysis of systolic blood pressure, there was no significant difference between the Ranch Hands and Comparisons in the unadjusted analysis, but a significant group-by-cholesterol-HDL ratio interaction was detected in the adjusted analysis ( $p=0.020$ ). The adjusted relative risk was less than 1 in those with cholesterol-HDL ratios less than or equal to 4.2 and less than 1 in those with ratios between 4.2 and 5.5, but greater than 1 in those with cholesterol-HDL ratios greater than 5.5. However, none of these within-stratum relative risks was statistically significant, nor was the group comparison after deletion of the interaction term from the model. For nonspecific T-waves, the unadjusted difference was not statistically significant. However, there was a highly significant ( $p=0.004$ ) group-by-lifetime cigarette smoking history interaction in the adjusted analysis. The relative risk was less than 1 in nonsmokers and moderate lifetime smokers and greater than 1 in heavy smokers. None of these within-stratum risks reached statistical significance. Significantly fewer Ranch Hands than Comparisons had bradycardia (Est. RR: 0.67, 95% C.I.: [0.44,1.00],  $p=0.049$ ). The adjusted relative risk for bradycardia was borderline significant (Adj. RR: 0.69, 95% C.I.: [0.46,1.04],  $p=0.068$ ). For arrhythmia there was no significant difference in the unadjusted analysis, but there was a borderline significant difference in the adjusted analysis (Adj. RR: 1.56, 95% C.I.: [0.98,2.49],  $p=0.062$ ).

In the analysis of peripheral vascular function, no unadjusted or adjusted statistically significant differences were detected in funduscopic abnormalities or in popliteal pulses. The mean diastolic blood pressure was borderline significantly different in the two groups (unadjusted  $p=0.099$ ); in the adjusted analysis, a significant group-by-age interaction was detected ( $p=0.028$ ). In individuals born in or after 1942, the Ranch Hand adjusted mean was significantly greater than the Comparison adjusted mean (74.91 vs. 73.56 mm Hg,  $p=0.026$ ). In those born between 1923 and 1941 and in those born in or before 1922, the adjusted group means were not significantly different. (The difference in the overall adjusted group means was borderline significant [ $p=0.100$ ] after deleting the interaction term from the model.) The percent with abnormal diastolic blood pressure was not significantly different in the two groups in the unadjusted analysis, but in the adjusted discrete analysis there was a significant group-by-family history of heart disease before age 50 interaction ( $p=0.043$ ). The relative risk was greater than 1 in those with a family

history before age 50 and nearly equal to 1 in those without such a history. The former was of borderline significance ( $p=0.057$ ) but was based on small numbers (5 of 26 Ranch Hands, 1 of 30 Comparisons). After deletion of the interaction term from the model, the adjusted relative risk was not statistically significant.

There was a borderline significant difference in the percentage of individuals with carotid bruits (Est. RR: 2.97, 95% C.I.: [0.91,9.67],  $p=0.058$ ). For radial pulse abnormalities, there was also a borderline significant difference; in this case, the estimated relative risk was less than 1 (Est. RR: 0.29, 95% C.I.: [0.06,1.34],  $p=0.076$ ). Adjusted analyses could not be performed because these abnormalities were so rare.

Both the unadjusted and the adjusted analyses of femoral pulses revealed a significantly greater percentage with abnormalities in the Ranch Hand group than in the Comparison group ( $p=0.016$ , unadjusted and  $p=0.018$ , adjusted). The estimated relative risk was 2.52 (95% C.I.: [1.16,5.44]) and the adjusted relative risk was 2.52 (95% C.I.: [1.15,5.56]). Both unadjusted and adjusted differences in dorsalis pedis pulses were borderline significant, with a higher percent abnormal in the Ranch Hands than in the Comparisons (Est. RR: 1.30, 95% C.I.: [0.98,1.72],  $p=0.071$  and Adj. RR: 1.29, 95% C.I.: [0.97,1.72],  $p=0.078$ ). In the case of posterior tibial pulses, there was no significant difference in the unadjusted analyses, but a highly significant group-by-differential cortisol interaction emerged in the adjusted analysis ( $p=0.004$ ). There was little group difference in those with differential cortisol response less than or equal to 0.6, but the risk was significantly greater than 1 in those with differential cortisol levels between 0.6 and 4.0 (Adj. RR: 3.04, 95% C.I.: [1.06,8.68],  $p=0.030$ ). The relative risk was less than 1 and not statistically significant in those with differential cortisol response greater than 4.0. In the variable combining all leg pulses, the Ranch Hands exhibited significantly more abnormalities than the Comparisons (Est. RR: 1.30, 95% C.I.: [1.00,1.67],  $p=0.049$ ). The adjusted relative risk for leg pulses was of borderline significance ( $p=0.079$ ). For peripheral pulses, the estimated relative risk was borderline significant (Est. RR: 1.26, 95% C.I.: [0.97,1.62],  $p=0.082$ ). This was also the case for all pulses (Est. RR: 1.26, 95% C.I.: [0.97,1.62],  $p=0.081$ ).

There was agreement between the physical examination findings and the past medical history, with a number of positive and statistically significant associations detected between various physical parameters and the heart disease history.

Exposure index analyses conducted within the Ranch Hand group did not detect any significant effects in any of the three occupational cohorts for reported/verified essential hypertension, reported/verified myocardial infarction, heart sounds, overall ECG findings, RBBB, LBBB, tachycardia, fundoscopic examination findings, and carotid bruits, nor in any of the pulse variables or pulse aggregates. For reported and verified heart disease, there were no significant differences in the enlisted flyers or enlisted groundcrew. In the officers, the group with the lowest current serum TCDD levels, the adjusted medium versus low exposure level contrast was significantly less than 1 ( $p=0.019$ ), and the high versus low contrast was also less than 1 and of borderline significance ( $p=0.082$ ).

No significant differences were detected in the analysis of systolic blood pressure in the officers and enlisted groundcrew, but in the enlisted flyers there was a significant difference in the means that was consistent with a dose-response relationship ( $p=0.037$ )--mean values were 124.14, 128.79, and 133.55 in the low, medium, and high exposure level categories, respectively. After covariate adjustment, however, the differences were no longer statistically significant ( $p=0.181$ ). There were no statistically significant differences in nonspecific T-wave findings in the officers or enlisted groundcrew. Although not entirely consistent with a dose-response relationship, there was a borderline significant difference in the enlisted flyers ( $p=0.075$ , unadjusted and  $p=0.091$ , adjusted).

No statistically significant exposure level effects were detected in the unadjusted analyses of bradycardia, nor in the adjusted analyses within the enlisted flyers or enlisted groundcrew. In the officers, however, a significant exposure index-by-cholesterol-HDL ratio interaction was detected ( $p=0.045$ ). Upon stratification, there were fewer abnormalities in the medium and high exposure level categories than in the low exposure level category for those with cholesterol-HDL ratios less than or equal to 4.2 and for those with levels between 4.2 and 5.5, but slightly more abnormalities in the medium and high exposure level categories as compared to the low category for those with ratios greater than 5.5. These were all based upon small numbers.

For arrhythmia, there were no significant differences in the officers or enlisted groundcrew, but in the enlisted flyers, there were six abnormalities in the high exposure level category as compared to none in the low category and none in the medium category ( $p=0.025$  for the high vs. low contrast). Adjusted analyses could not be performed due to the small numbers. For other ECG diagnoses, no significant differences were found except for a significant exposure index-by-age interaction in the officer cohort ( $p=0.018$ ). The differences within each of the age strata were not consistent with a dose-response relationship, however. Finally, there were no significant exposure level effects on diastolic blood pressure in the enlisted flyers. In the officers, there was a significantly greater percentage of abnormalities in the higher exposure level category as compared to the low exposure level category ( $p=0.039$ ), but there was no excess risk in the medium exposure level group. Also, in the enlisted groundcrew there was a significant exposure index-by-personality type interaction ( $p=0.012$ ), but the within-stratum differences were not consistent with a dose-response relationship.

Longitudinal analysis of the overall ECG findings did not detect any significant differences between the Ranch Hand and Comparison groups in the change in the overall ECG status from Baseline to the 1987 followup examination. Mortality-morbidity analyses did not indicate excess cardiovascular risk in the Ranch Hands.

In summary, the cardiovascular evaluation showed that the health of the Ranch Hand and Comparison groups was similar for reported and verified heart disease and central cardiac function. For peripheral vascular function, the Ranch Hands had a marginally higher percentage of individuals with carotid bruits. There were also significant, or marginally significant, differences (more abnormalities in the Ranch Hands than in the Comparisons) in femoral

pulses, dorsalis pedis pulses, and in the three pulse aggregates (leg, peripheral, and all pulses), as determined by manual palpation. These findings emphasize the importance of including further evaluations of peripheral pulses in subsequent examinations in this study.

## HEMATOLOGIC EVALUATION

### INTRODUCTION

Animal experiments have confirmed both direct and indirect hematopoietic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin). Although direct impairment of the hematopoietic system may result from exposure to chlorophenols or dioxin, marked abnormalities in many of the circulating hematologic elements may also be due to the severe toxicity observed in other organs or organ systems.

### DISCUSSION

The complete blood count is the most frequently ordered laboratory test in ambulatory medicine. As indices of the three peripheral blood cell lines (erythrocytes, leukocytes, and platelets) the eight variables examined in the current section are heavily relied upon to indicate disease of the hematopoietic system and, perhaps more often, to alert the clinician to the presence of disease in other organ systems as well.

In contrast to most organ systems, in which disease is usually apparent based on the history and physical examination, particular emphasis is placed on the laboratory in the detection of hematologic disorders. As quantitative indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) can provide helpful insight into the morphologic classification of anemias.

The total white cell count (WBC) is subject to variation in a broad range of disease states. Though lacking specificity, leukocytosis or leukopenia can serve as a sensitive clue to the presence of a host of infectious, inflammatory, and neoplastic disorders, and point to the need for further investigation.

As essential elements to normal coagulation, the platelets have a short half-life and are most subject to decreased survival in the presence of a wide range of diseases and numerous prescription and over-the-counter medications. The wide range of normal (130,000-400,000/cubic mm) is such that subtle changes in platelet survival could occur and not be identified as abnormal. Conversely, small differences in the total platelet count do not have a clinically significant effect on clotting mechanisms. Seven participants were found to have platelet counts greater than 500,000/cubic mm, with the highest count of 595,000/cubic mm. Detailed chart review failed to reveal any common diagnosis in this subgroup, and the similar distribution (four Ranch Hands, three Comparisons) weighs against the presence of a herbicide effect.

Analysis of the covariate-dependent variable data confirmed several expected clinical associations. In cigarette smokers, cellular hypoxia related to carboxyhemoglobin formation and systemic arterial desaturation in obstructive airway disease combine to raise the hemoglobin and hematocrit in comparison to nonsmokers. Less understood but recognized clinically is an elevation in the total white cell count, a finding that may relate to the increased incidence of chronic bronchitis in a nicotine dependent population.

While finding anemia should be considered abnormal at any age and should prompt appropriate medical evaluation, it is common to find a gradual decline in selected red cell (RBC) indices with aging, an observation confirmed in the current study. Older participants were found to have statistically significant reductions in total red cell count and hemoglobin, associations that may reflect the increased incidence of chronic disease of multiple etiologies with advancing age. Several mechanisms have been suggested for the "anemia of chronic disorders," including a decreased red cell life span, diminished erythropoietin production, and impaired gastrointestinal absorption of iron.

The race-related associations can be explained on the basis of established clinical observations. In relation to nonblacks, Black participants had statistically significant reductions (or a higher percentage of individuals with abnormally low levels) in all red cell indices and in the total white cell count. In other studies, the mean hemoglobin level of Blacks averages 0.5 to 1.0 g/dl below that of nonblacks, a finding that may relate to the increased incidence of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and of hemoglobin variants (S and C) associated with heterozygous sickling disorders.

Blacks were found to have a greater incidence of abnormally low white cell counts than nonblacks (19% versus 6%). While the degree of leukopenia was slight and not likely of clinical significance, the cause of this finding is uncertain.

Of the eight laboratory variables examined, only two significant group differences were found. The Ranch Hands had a slightly higher (geometric) mean WBC count than the Comparisons. This small difference was not significant after covariate adjustment. Consistent with the Baseline and 1985 followup examinations, the Ranch Hands had a higher mean platelet count than the Comparisons and, in the present study, the difference has become statistically significant. The percentage of individuals with abnormally high platelet count values was also significantly greater in the Ranch Hands than in the Comparisons. Examination of the data from the three cycles shows that there has been a gradual reduction in platelet counts in both groups (although greater in the Ranch Hands) over time, suggesting an effect of age common to all participants. As a nonspecific reaction, the platelet count can be elevated in any occult disease process; this may be related to the slightly elevated erythrocyte sedimentation rate found in the Ranch Hands and reported in the General Health chapter. There is a highly significant association between sedimentation rate and platelet count, with 8.9 percent of those with abnormally high sedimentation rates exhibiting abnormally high platelet counts, compared to only 1.8 percent in those with normal sedimentation rates ( $p < 0.001$ ); the correlation between the (log) sedimentation rate and platelet

count was also statistically significant ( $r=0.156$ ,  $p<0.001$ ). Whatever the cause, the difference in means of less than 10,000 per cubic mm is not clinically significant.

**SUMMARY**

The hematologic status of the Ranch Hand and Comparison groups was assessed by eight variables--RBC, WBC, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count. Table 11 presents a summary of all of the unadjusted and adjusted group comparisons for these variables.

**TABLE 11.**

**Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Hematologic Variables**

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
RBC	NS	NS	NS	NS	
WBC	NS	0.038	NS	NS	RH>C
Hemoglobin	NS	NS	NS	NS	
Hematocrit	NS	NS	NS	NS	
MCV	NS	NS	NS	NS	
MCH	NS	NS	NS	NS	
MCHC	NS	NS	--	NS	
Platelet Count	0.035	0.017	0.035	0.018	RH>C, RH <sup>H</sup> >C <sup>H</sup>

--Analysis not performed (no abnormalities present).

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

RH>C: Ranch Hand mean greater than Comparison mean.

RH<sup>H</sup>>C<sup>H</sup>: Ranch Hand percent abnormally high greater than Comparison percent abnormally high ( $p=0.027$ ).

There were no unadjusted or adjusted statistically significant differences between groups for RBC. For WBC, there was a statistically significant difference between groups in the mean unadjusted (log) levels (geometric means in the Ranch Hand and Comparison groups were 6.875 and 6.703 thousand per cubic mm, respectively). The adjusted mean counts were not significantly different.

No statistically significant differences were detected in either the unadjusted or adjusted analyses of hemoglobin, hematocrit, MCV, MCH, and MCHC. For platelet count, the mean level was significantly greater in the Ranch Hands than in the Comparisons (265.47 vs. 259.62 thousand per cubic mm;  $p=0.017$ ), and the percent of participants with elevated abnormally high values was also greater in the Ranch Hands than in the Comparisons (2.9% vs. 1.6%, Est. RR: 1.92, 95% C.I.: [1.08, 3.41],  $p=0.027$  [overall  $p$ -value = 0.035]). These differences remained statistically significant after adjustment for covariates ( $p=0.018$  and  $p=0.035$  for the continuous and overall discrete analyses, respectively). The elevation of platelets is not what one would expect based on the results of animal studies.

Exposure index analyses in the Ranch Hand group did not detect any significant dose-response relationships or interactions in any of the occupational cohorts (officers, enlisted flyers, enlisted groundcrew) for WBC or MCH. There was a statistically significant ( $p=0.029$ ) exposure index-by-age interaction in the continuous analysis of RBC in the enlisted flyers. There were highly significant exposure index-by-age interactions in the continuous analysis of hemoglobin and hematocrit in the enlisted flyers ( $p=0.003$  and  $p=0.002$ , respectively), as well as significant exposure index-by-lifetime cigarette smoking history interactions for these variables in the enlisted groundcrew ( $p=0.012$  and  $p=0.010$ , respectively). Within each of the stratum, however, these results did not suggest a dose-response relationship. In the case of hematocrit, there was also a significant ( $p=0.025$ ) exposure level effect in the unadjusted discrete analysis for the officers, with five individuals having abnormally low values in the high exposure index group, compared to one and none in the low and medium exposure level categories, respectively. This effect was of borderline significance after adjustment for covariates ( $p=0.086$ ). For MCV, in the enlisted groundcrew, there was a significant difference in the mean values for the three exposure level categories, both unadjusted ( $p=0.015$ ) and adjusted ( $p=0.028$ ). These were consistent with a dose-response relationship. A significant difference in the adjusted means for MCHC emerged in the enlisted flyers ( $p=0.049$ ). A significant difference was also detected for platelet count in the discrete analysis of the enlisted flyers ( $p=0.046$ ). Continuous adjusted analyses of platelet count in the enlisted flyers detected a highly significant exposure index-by-race interaction ( $p=0.008$ ) and a significant exposure index-by-current cigarette smoking interaction ( $p=0.014$ ). The MCHC and platelet count findings did not generally support dose-response relationships.

Longitudinal analyses found no significant difference between the Ranch Hand and Comparison groups in the change in MCV and MCH from Baseline to the 1987 followup examination. However, the mean change in platelet count (a decrease) was significantly greater ( $p=0.015$ ) in the Ranch Hand group than in the Comparison group.

In summary, there is little consistent evidence in this study to implicate an adverse effect of herbicide exposure on hematologic status. The Ranch Hands exhibited a slight, but statistically significant, increase in platelets, but data from animal studies suggest that TCDD exposure should cause a lowering of the platelet count, rather than an elevation.

## RENAL ASSESSMENT

### INTRODUCTION

Renal dysfunction and overt renal disease are not generally considered to be important clinical sequelae of exposure to phenoxy acids, chlorophenols, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However, renal failure due to acute intoxication from another phenoxy herbicide (MCPP) has been shown in two human cases, along with other severe toxic symptoms.

### DISCUSSION

In clinical practice, the presence of renal or urinary tract disease can be determined with confidence based on the medical history, physical examination, and the five laboratory indices included in the present study.

Though subject to some day-to-day variation related to diet and state of hydration, the blood urea nitrogen is considered a reliable index of glomerular filtration, while the integrity and concentrating ability of the renal tubular system are reflected in the urinary specific gravity. In documenting the presence of red or white blood cells in significant numbers, the examination of the urinary sediment can provide valuable clues to the presence of a broad range of infectious, inflammatory, and neoplastic conditions intrinsic to the upper and lower urinary tracts.

The frequent finding in ambulatory medicine of isolated abnormalities in the routine urinalysis of healthy individuals who in fact have no disease of the genitourinary system is pertinent to interpretation of the renal assessment data. With normal fluid balance, the healthy kidneys can excrete up to 100-150 mg of total protein in 24 hours. The qualitative dipstick test used in the current study is sensitive to protein concentrations as low as 10-15 mg per deciliter and, particularly in specimens collected after overnight fasting, will often give a trace to 1+ positive reaction in the absence of parenchymal renal disease. Similarly, on microscopic examination of the urinary sediment, it is not uncommon to intermittently find a few red or white blood cells in the absence of definable neoplastic or inflammatory cause, trauma, or kidney stones. When documented as an isolated finding in the absence of symptoms or other signs, such intermittent microcyturia can usually be considered benign.

With reference to the current study, no significant group differences in the renal indices were found between the Ranch Hands and Comparisons in the unadjusted analyses. In the dependent variable-covariate analysis, several associations were defined that are consistent with established clinical observations.

In the adjusted analyses, significant covariate associations with age were documented. The twofold increased historical incidence of genitourinary disease would be expected with aging in this all male population with the development of benign prostatic hypertrophy and bladder outlet obstruction.

In association with benign nephrosclerosis of the normally aging kidney, there is a gradual reduction in renal mass (from an average of 260 grams in the young adult to 190 grams in the eighth decade) and a 50 percent reduction in renal plasma flow (from 600 cc/min to 300 cc/min). An age-related increase in blood urea nitrogen and proteinuria would be expected findings and were documented in the current study.

Several of the race-dependent variable associations can be explained on the basis of established clinical correlations. The increased incidence of hypertension with hypertensive nephropathy in Blacks is well recognized and might account for the increased incidence of proteinuria, hematuria, and elevated blood urea nitrogen in this population. Though the numbers are small, microinfarction of the renal medulla in sickle cell trait (8-10% incidence in Blacks) might have been a minor contributing factor in the incidence of hematuria. The cause of the twofold increased incidence of leukocyturia in Blacks is uncertain and the very slight difference in mean specific gravity (1.0209 vs. 1.0198) is not clinically significant.

In the diabetic class, the increased incidence of hypertensive and arteriosclerotic vascular disease and of urinary tract infections related to glycosuria provide reasonable explanation for the significant covariate association of proteinuria, leukocyturia, and elevated blood urea nitrogen in this population.

The renal assessment data revealed abnormalities in five laboratory indices at a prevalence that is common in ambulatory practice. There were no significant overall differences between the Ranch Hand and Comparison cohorts. Most of the covariate associations can be explained on the basis of established clinical correlations. Finally, when documented as isolated findings, the benign nature of these abnormalities should be emphasized.

#### SUMMARY

The 1987 renal assessment was based on six variables. The results of the Ranch Hand and Comparison contrasts are summarized in Table 12.

The historical assessment of kidney disease/stones based on self-reported data showed no significant differences between the Ranch Hand and Comparison groups. These results are consistent with the results of the 1985 followup but appear to be in marked contrast to the Baseline findings. The Comparison cohort is different between the Baseline report and the 1987 followup study (Original Comparisons vs. all Comparisons), and the definition of kidney disease has been expanded from the Baseline study to include kidney stones. However, when the analysis of the 1987 followup data was restricted to the Original Comparisons and kidney stones were not included in the definition of kidney disease, the prevalence rate of kidney disease was comparable between the two examinations, but the difference between groups was still nonsignificant ( $p=0.952$ ).