

significant unadjusted group difference. Examining the sun exposure-related malignant skin neoplasms by occupation produced a borderline significant group difference between the Ranch Hand and Comparison officers for verified malignancies of the ear, face, head, and neck.

The fixed size of the Ranch Hand cohort limits the ability of the study to detect group differences, particularly for the rare occurrences of soft tissue sarcoma and non-Hodgkin's lymphoma. The study has virtually no statistical power to detect low to moderate group differences for these malignancies. The study has good power to detect relative risks of 2.0 or more with respect to disease occurring at prevalences of at least 5 percent in the Comparison group, such as basal cell carcinoma.

### Neurological Assessment

The neurological health of the Ranch Hand group was not substantially different from the Comparison group. Of the six questionnaire variables relating to neurological disease, the only significant finding was that Ranch Hands had a higher incidence of hereditary and degenerative neurological disease, such as Parkinson's disease and benign essential tremor. The statistical results of the group contrasts for 30 physical examination variables relating to cranial nerve function, peripheral nerve status, and central nervous system coordination processes were generally not significant. Unadjusted analyses disclosed marginally more balance/Romberg sign and coordination abnormalities for Ranch Hands than for Comparisons. Conversely, Ranch Hands had significantly fewer biceps reflex abnormalities than Comparisons. The adjusted analyses revealed a significant group-by-insecticide exposure interaction for the cranial nerve index (excluding neck range of motion). Stratified results 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. The adjusted analysis for coordination detected differences in the relative risks with occupation and insecticide exposure. Stratified analyses found a significant group difference for enlisted groundcrew who had never been exposed to insecticides. There were no significant differences for the other strata. Further investigation found a significant group difference for enlisted groundcrew after excluding the insecticide interaction, and a significant adjusted group difference overall after excluding both interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis. The trend of increasing abnormality in the enlisted groundcrew for coordination will be more fully evaluated in the analyses of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels. The exposure index analyses for each occupational cohort did not reveal significant differences supportive of a herbicide effect. The longitudinal analyses for the cranial nerve index and the central nervous system index were not significant.

### Psychological Assessment

The psychological assessment was based on verified psychological disorders; reported sleep disorders; and two clinical psychological tests, the Symptom Check List-90-Revised (SCL-90-R) and the Millon Clinical Multiaxial

Inventory (MCMI). The verified data on lifetime psychological disorders showed no differences for psychoses, drug dependence, and anxiety. However, marginally more Ranch Hands than Comparisons had a verified history of alcohol dependence and other neuroses based on unadjusted analyses. The Ranch Hands reported experiencing great or disabling fatigue during the day and talking in their sleep more frequently than the Comparisons. No group differences were detected in the other 13 sleep disorder variables in the unadjusted analyses. Although no significant differences between the Ranch Hands and Comparisons were found in the unadjusted analyses of the 12 SCL-90-R variables, the Ranch Hands had marginally more abnormalities than the Comparisons for depression, somatization, and an index of the general severity of symptoms. The results of the unadjusted analyses of the MCMI scores revealed that the Ranch Hands had significantly higher mean antisocial and paranoid scores than the Comparisons. Marginally significant differences were identified on the narcissistic and psychotic delusion scores, where the mean score of the Ranch Hands exceeded that of the Comparisons. After adjustment for covariates, a significant difference remained on the narcissistic score. The Comparisons had a significantly higher mean dependent score than the Ranch Hands. Significant group-by-covariate interactions were frequently noted in the adjusted analyses, which made direct contrast of the two groups difficult. The exposure index analyses did not reveal evidence of consistent dose-response relationships.

#### Gastrointestinal Assessment

Overall, the gastrointestinal assessment did not find the health of the Ranch Hand group to be significantly different from the Comparison group. Group differences based on verified historical data from the questionnaire were not significant for eight categories of liver disease. No significant group difference was found for past or present occurrence of peptic ulcers. The prevalence of hepatomegaly diagnosed at the physical examination was also not significantly different between groups. The only significant finding from the laboratory examination variables was that the Ranch hands had a higher mean alkaline phosphatase than the Comparisons. This was also noted at the 1985 followup examination. Group differences for the other laboratory variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], total bilirubin, direct bilirubin, lactic dehydrogenase, cholesterol, high density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, creatine kinase, and fasting glucose) were not significant. Stratified analyses to explore group-by-covariate interactions did not disclose any consistent pattern of significant group differences within a subgroup. The exposure index data often exhibited positive dose-response relationships, but results of the statistical analyses were generally not significant. The longitudinal analyses of AST, ALT, and GGT showed that the group differences did not change significantly between the Baseline examination and the 1987 followup examination.

#### Dermatologic Evaluation

Except for more Ranch Hands reporting at least one occurrence of acne during their lifetime than Comparisons, no significant group differences were detected in the dermatologic evaluation. Subsequent analysis of the

occurrence of acne indicated that, for participants with no history of acne before the start of the first Southeast Asia (SEA) tour, a higher percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour. However, the anatomic distribution of these lesions did not suggest chloracne as a cause. No cases of chloracne were diagnosed in the physical examination. Analyses were conducted on historical occurrence and duration of acne, six dermatologic disorders, a composite variable of other disorders, and a dermatology index of four disorders. All of these analyses found no significant group differences. Exposure index analyses did not reveal consistent patterns that supported an increasing dose-response relationship. The longitudinal analysis, based on the dermatology index, showed no significant differences between groups over time.

### Cardiovascular Evaluation

The cardiovascular evaluation was based on reported and verified heart disease (essential hypertension, overall heart disease, and myocardial infarction) and measurement of central cardiac function and peripheral vascular function. Based on reported and verified hypertension and heart disease, the health of the two groups was similar. For reported/verified myocardial infarction, there was a statistically significant difference in the relative risk with family history of heart disease. 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, although neither of these within-stratum relative risks was statistically significant. The assessment of the central cardiac function also found the groups to be similar, although significantly fewer Ranch Hands than Comparisons had bradycardia and more had arrhythmias (borderline significant). There were differences in the relative risk with levels of covariates for systolic blood pressure and nonspecific T-waves, but none of the relative risks was statistically significant in any particular stratum of individuals. For the peripheral vascular function, significant or borderline differences were detected for five of the eight measurements. The Ranch Hands had a higher or marginally higher mean or percent abnormal for diastolic blood pressure (continuous), carotid bruits, femoral pulses, and dorsalis pedis pulses than did the Comparisons. (No difference between the two groups was detected in the discrete analysis of diastolic blood pressure.) The percentage of radial pulse abnormalities was marginally higher in the Comparisons than in the Ranch Hands. On the three pulse indices (leg, peripheral, and all pulses), the Ranch Hands had marginally or significantly higher percentages of abnormalities than the Comparisons. 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. The peripheral pulses were measured by manual palpation in the 1987 followup and at Baseline, when differences were also detected. In the 1985 followup, pulses were assessed manually and by the Doppler technique, and the two groups were found to be similar. The exposure index analyses did not reveal consistent patterns suggestive of a dose-response relationship, except possibly for the presence of arrhythmias in the enlisted flyer cohort, where there were six abnormalities in the high exposure-level category, compared to none in the medium and low exposure-level categories. Longitudinal analysis of electrocardiograph findings and combined mortality-morbidity analyses did not indicate excess cardiovascular risk in the Ranch Hands.

## Hematologic Evaluation

The hematologic status of the Ranch Hand and Comparison groups was assessed by the examination of eight variables: red blood cell count (RBC), white blood cell count (WBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count. There were no statistically significant differences between the two groups for RBC, hemoglobin, hematocrit, MCV, MCH, and MCHC, in analyses either unadjusted or adjusted for the covariates of age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history. For WBC, the mean level was significantly greater in the Ranch Hands than in the Comparisons, but the magnitude of the difference was small. The difference was not statistically significant after adjustment for covariates, nor were significant differences detected in the percentage of individuals with abnormal values. Mean platelet counts were also significantly greater in the Ranch Hands than in the Comparisons, as was the percentage of individuals with abnormally high values. While these differences remained significant after adjustment for covariates, no platelet count was elevated into a pathologic range. Exposure index analyses detected significant exposure level effects in the discrete analysis of hematocrit in the officer cohort, in the continuous analysis of MCV in the enlisted groundcrew, in the continuous analysis of MCHC in the enlisted flyers, and in the discrete analysis of platelet count in the enlisted flyers. Several exposure index-by-covariate interactions were also significant. Only the hematocrit and MCV findings were consistent with a dose-response relationship, however. Longitudinal analyses detected a significantly greater decrease in the mean platelet count from Baseline to the 1987 followup examination in the Ranch Hands than in the Comparisons, despite the higher overall mean count. The clinical importance of these observations is unclear.

## Renal Assessment

Without adjustments for covariates, none of the variables of reported history of kidney disease/stones, urinary protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, and urine specific gravity showed a significant difference between the two groups. In general, these findings were supported by the adjusted analyses. Examination of the group-by-covariate interactions did not yield a consistent pattern to suggest renal detriment to either group. Lack of a group difference in the reported history of kidney disease/stones (consistent with the 1985 followup results) was in contrast with the Baseline findings, where Ranch Hands reported significantly more disease. A nonsignificant difference in the percentage of participants with urinary protein was also inconsistent with the Baseline examination, when the Comparisons had a marginally significant higher prevalence rate. Like the 1982 and 1985 studies, the exposure index analyses showed very little evidence of a dose-response relationship. In the longitudinal analysis of blood urea nitrogen, no difference in the change over time was detected.

## Endocrine Assessment

Findings from the endocrinologic assessment did not disclose any statistically significant differences between the Ranch Hand and Comparison

groups. The percentage of participants who indicated problems with current thyroid disease was similar between groups, as were the percentages of thyroid and testicular abnormalities determined by palpation at the physical examination. Of the six laboratory examination variables that were examined (triiodothyronine percent [T, %] uptake, thyroid stimulating hormone [TSH], follicle stimulating hormone, testosterone, 2-hour postprandial glucose, and a composite diabetes indicator), the Ranch Hand TSH mean was marginally significantly higher than the Comparison TSH mean, a finding that was statistically significant at the 1985 followup examination. Ranch Hand and Comparison mean levels for the other laboratory variables, including testosterone, were similar. For all laboratory variables, the percentage of Ranch Hands with abnormal values was higher than the percentage of Comparisons with abnormal values, but none of these differences was statistically significant. Exposure index results generally did not support the presence of a herbicide effect. The enlisted groundcrew and officer cohorts exhibited increasing dose-response patterns for diabetes, but the associations were not significant. Conversely, the overall result for diabetes was significant for enlisted flyers, but was due to the presence of relatively more diabetics in the medium exposure category than in either the low or high categories. The longitudinal analyses for the T, % uptake, TSH, and testosterone did not show significant differences between groups in the changes over time.

### Immunologic Evaluation

For the immunologic assessment of the 1987 followup examination, composite skin reaction test results were analyzed from the physical examination data, and various laboratory examination measurements from cell surface marker studies, three groups of functional stimulation tests, and quantitative immunoglobulins were also analyzed. Ranch Hands had a higher frequency of individuals with possibly abnormal reactions on skin testing than the Comparisons. The analysis of the composite skin test results, adjusting for covariate information, contained a significant group-by-lifetime cigarette smoking history interaction. Followup analyses showed that, among those individuals with the heaviest smoking histories, Black Ranch Hands had a higher frequency of possibly abnormal readings when contrasted with Comparisons. Within the other strata, there were no significant differences. The unadjusted analyses of the laboratory examination data indicated no significant group difference between Ranch Hands and Comparisons. For the adjusted analyses of the natural killer assay measurements with and without Interleukin 2, significant interactions between group and race were present. Exploration of these interactions revealed that the Black Ranch Hands had higher adjusted means than the Black Comparisons for the natural killer assay measures. The clinical significance of these findings is not apparent and does not point to any known clinical endpoints. In general, the immunologic assessment revealed no medically important differences between the Ranch Hands and Comparisons.

### Pulmonary Disease

The pulmonary assessment was based on five self-reported respiratory illnesses, seven clinical observations, and eight laboratory measurements. No evidence of a herbicide effect was detected in the assessment of the reported respiratory illnesses. The health of the two groups was reasonably comparable

based on the clinical and laboratory variables, although the Ranch Hands had a significantly higher percentage of thorax and lung abnormalities on examination than the Comparisons, based on the unadjusted analysis, and a marginally higher percentage after adjustment for covariates. No significant group differences were detected in the adjusted analyses without significant interactions involving group. Exploration of the group-by-covariate interactions did not reveal a consistent pattern indicating a herbicide effect. The adverse effects of smoking on pulmonary status were evident in all analyses.

## CONCLUSIONS

In the 1987 followup, relatively few differences in health status were found between the Ranch Hands and Comparisons. No cases of chloracne or porphyria cutanea tarda, the most commonly accepted effects of dioxin exposure, were detected in this study. There was a single case of soft tissue sarcoma in each group and one case of non-Hodgkin's lymphoma in a Ranch Hand. The results do not indicate that the health of the Ranch Hands is related to herbicide exposure in Vietnam. Although few differences were noted, reanalysis of the data using the dioxin body burden levels and continued medical surveillance are warranted.

In summary, there is not sufficient scientific evidence at this time to support a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

## CHAPTER 23

### FUTURE DIRECTIONS

The scope and complexity of the Air Force Health Study (AFHS) has required gradual refinement and correction to meet the challenges of changing technology and scientific direction, and to ensure continued participation of all participants.

The selection of procedures to be included in each of the followup physical examinations has been driven by the findings and experiences of the earlier phases of the study. Similarly, changes for the 1992 followup examination will be based on the findings covered in this report. As noted in Chapter 8, the opportunity to measure dioxin accurately in the blood of study participants will significantly enhance the ability to identify relationships between dioxin and medical findings. It is anticipated that additional serum studies to further explore and characterize dioxin half-life will be performed as part of the 1992 examination.

Additional modifications to the examination format being considered for 1992 include enhanced assessments of psychological and neurological status. The evaluation of immune function will continue to be emphasized in the next examination and the current set of skin test reagents will be used; however, modifications may be made in the dosages of the antigens to reflect World Health Organization recommendations. Modifications to the battery of cell surface marker and functional studies may be made to reflect state-of-the-art laboratory practice. Similarly, advances in laboratory technology, such as the use of fluorometric enzyme assays for thyroid function, will be incorporated as well.

Statistical methodology in the longitudinal analyses will be modified so that data from all four physical examinations can be included in these important analyses. In addition, it is anticipated that a more complete characterization of sun exposure will be available through the use of data that describe the average hours of daily sunshine at each geographic location.

The next 12 to 16 months will see several significant milestones in the AFHS: (1) completion of the reanalysis of verified birth defect and reproductive outcome data; (2) reanalysis of the 1987 examination data in conjunction with the serum dioxin results; and (3) a mortality analysis of deaths through December 1989. These reports should provide information that will be useful in the resolution of the scientific and political questions surrounding the military use of Agent Orange in Vietnam.