Chapter XVI-5

# RENAL DISEASE AND FUNCTION

## 1. Introduction

Overt kidney disease is not an acknowledged clinical end point following chronic exposure to low doses of Herbicide Orange or dioxin. However, since both 2,4-D and 2,4,5-T are excreted by the kidney as unmetabolized compounds, it is understandable that acute renal dysfunction, as measured by a variety of laboratory tests, has been reported following acute, high dose exposure to phenoxy herbicides and dioxin. Consequently, in this study, renal function and disease were determined by general laboratory testing and history obtained by a review-of-systems questionnaire administered at the examination site. The laboratory tests emphasized measures of glomerular function rather than those of tubular function. Age of the subject ($\leq$40, >40 years) and 2-hour postprandial glucose levels (<120, $\geq$120 mg/dl) were used as dichotomous covariates in all log-linear analyses, but were used as continuous variables in the analyses of covariance. Because of the small numbers of Black participants, the analyses are not race specific. The Ranch Hand denominator consists of all fully compliant individuals (1045) minus those few for whom covariate or dependent variable data were missing. The comparison group denominator is formed by the 773 original comparisons (i.e., shifted and replaced comparisons omitted) minus those few with missing data. Relative risks and confidence intervals are shown for all dependent variables in Appendix XVIII.

## 2. Laboratory Test Results

The presence of occult urinary blood and protein was measured by standard reagent strips for urinalysis. The results are shown in Table XVI-5-1. After these data were placed into normal-abnormal categories, log-linear models were fitted using the covariates of age and 2-hour postprandial glucose results. These covariates were not confounding or involved in higher order interactions. Therefore, unadjusted probability values from the likelihood-ratio chi-square test statistics are used.

Table XVI-5-1

URINARY OCCULT BLOOD AND PROTEIN RESULTS
BY GROUP MEMBERSHIP

| | Occult Blood | | Protein | |
|---|---|---|---|---|
| | 0 | >0 | 0 | >0 |
| Group | Number (%) | Number (%) | Number (%) | Number (%) |
| Comparison (N = 773) | 763 (98.7) | 10 (1.3) | 753 (97.4) | 20 (2.6) |
| Ranch Hand (N = 1045) | 1030 (98.7) | 14 (1.3) | 1030 (98.7) | 14 (1.4) |

Occult blood group contrast P = 0.94
Relative risk: 1.037, 95% Conf. Int. (.46, 1.18)

Protein group contrast P = 0.0545
Relative risk: .50, 95% Conf. Int. (.24, 1.07)

The data in Table XVI-5-1 show that there is no statistically significant difference in the prevalence of urinary occult blood between the Ranch Hand and comparison groups. However, the prevalence of proteinuria is borderline significant (P = 0.0545), comparisons greater than Ranch Handers.

For blood urea nitrogen (BUN), urine specific gravities, and the finding of white blood cells (WBC's) in the urine, abnormalities were too sparse for log-linear analysis. Distributional data of these 3 variables were tested by an analysis of covariance, again using age and 2-hour postprandial glucose levels as continuous covariates. These data analyses and the interaction of the covariates are displayed in Table XVI-5-2.

Table XVI-5-2

MEAN BUN, URINE SPECIFIC GRAVITY AND WHITE CELL RESULTS BY GROUP MEMBERSHIP: ANALYSIS BY COVARIANCE

| | (Adjusted Means) | | |
|---|---|---|---|
| Group | BUN (mg/dl) | Specific Gravity | WBC/HPF |
| Comparison | 14.65 | 1.02103 | 1.204 |
| Ranch Hand | 13.99 | 1.02099 | 1.192 |
| P Value | 0.18 | 0.91 | 0.83 |
| Dependent Variable Covariate Relationship P-Values | | | |
| Age: | < 0.001 | < 0.001 | 0.53 |
| Glucose: | 0.36 | < 0.001 | 0.59 |

The data in Table XVI-5-2 show that there are no statistically significant differences in the mean BUN, specific gravity, or urinary white cells between the Ranch Hand and comparison groups, although the directional difference in the mean BUN (P = 0.18), comparison greater than Ranch Hand, is of interest. As expected, the age covariate was significantly related to BUN and specific gravity, while the glucose covariate was associated only with the specific gravity. The pattern of such classical covariate effects lends credence to the lack of group differences for these 3 dependent variables.

Urine creatinine clearance levels were determined by the formula:

$$\frac{\text{Concentration of urine creatinine} \times \text{urine volume}}{\text{Concentration of plasma creatinine}}$$

Plasma creatinine was determined from blood samples obtained at the start of the 24-hour urine collection. Noncompliance to the full 24-hour urine collection was determined by direct questioning at the end of the sample collection and was noted to occur slightly more frequently in the comparison group (P = 0.18), and significantly more (P <0.001) in older members of both groups. Air Force monitors at the examination facility frequently noted that the study participants were not fully conscientious about collecting a complete specimen, thereby casting some doubt on the overall accuracy of the creatinine clearance data. The data were not adjusted for cases of mild congestive heart failure or for high dose aspirin usage because of the rarity of these conditions in a young ambulatory population. Notwithstanding, the creatinine clearance results were tested by a log-linear model with age and glucose levels as covariates, after removing the known noncompliants. The abnormality cutpoint of <110 ml/min was based upon data from the USAFSAM clinical data base, but this application produced unduly high abnormality proportions of 39.3% and 37.4% for the Ranch

Handers and comparisons, respectively (P = 0.52). Therefore, continuous creatinine clearance values were subjected to an analysis of variance. These data are presented in Table XVI-5-3.

Table XVI-5-3

MEAN VALUES OF CREATININE CLEARANCE BY GROUP, UNADJUSTED FOR COVARIATES

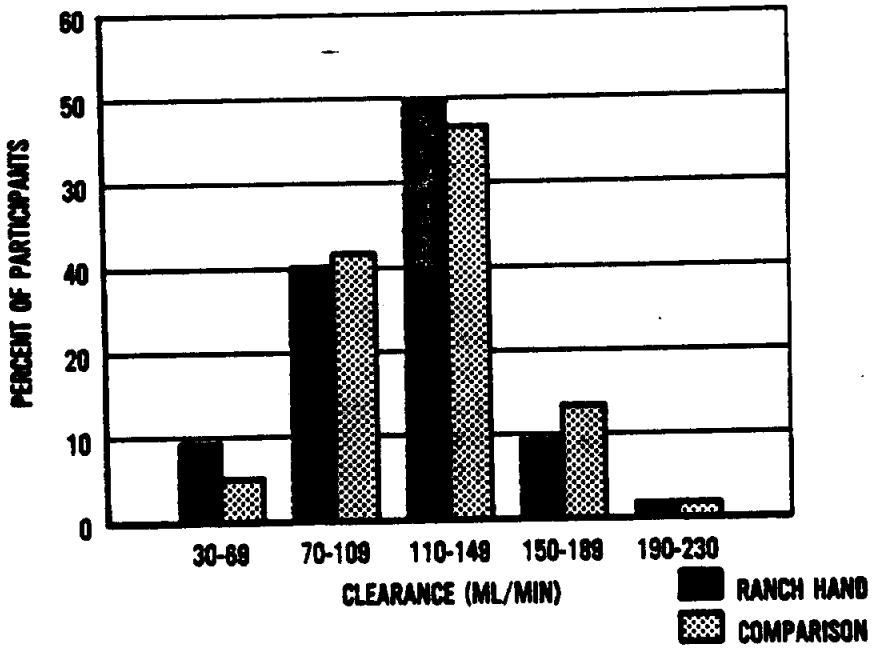
| Group | Number | Mean (ml/min) | Standard Deviation |
|---|---|---|---|
| Comparison | 439 | 119.43 | 30.70 |
| Ranch Hand | 628 | 116.60 | 31.26 |

P = 0.142

The concordance between group percents under 110 ml/min and the group means shown in Table XVI-5-3 is due to the left tail skew of the Ranch Hand creatinine clearance distribution as compared with that of the original comparisons. These are shown in Figure XVI-5-1.

Figure XVI-5-1

CREATININE CLEARANCE FREQUENCY DISTRIBUTION BY GROUP



An analysis of covariance using age and glucose values was also performed. The glucose slopes were nonhomogeneous (P = 0.075), indicating that the group creatinine clearance difference varies with the level of glucose.

3. Questionnaire Versus Laboratory Results

Log-linear models were fitted to data obtained at the time of physical examination from the question, "Have you ever had kidney disease?" with age and the 2-hour postprandial glucose level as covariates. This analysis is presented in Table XVI-5-4. These data show that the Ranch Hand group reported significantly more past kidney disease than the comparison group. Age and glucose values were not statistically significant as adjusting variables.

Table XVI-5-4

HISTORY OF KIDNEY DISEASE BY GROUP

| Group | History of Kidney Disease | | Total |
|---|---|---|---|
| | No (%) | Yes (%) | |
| Comparison | 745 (96.5) | 27 (3.5) | 772 |
| Ranch Hand | 985 (94.4) | 58 (5.6) | 1043 |

Report disease group contrast: P = 0.039 (unadjusted)
Relative risk: 1.6, 95% Conf. Int. (1.00, 2.59)

Although analyses of 6 clinical variables had been negative with respect to group membership, it was theoretically possible that cumulative numbers of abnormalities might corroborate the historical findings. To test this notion, abnormalities were scored for 5 of the variables which exceeded normal range, i.e., BUN >26 mg/dl, creatinine clearance <110 ml/min, presence of occult blood, urine WBC ≥5/HPF, and the presence of urine protein. These data were analyzed by a log-linear model, using age and glucose values as covariates. The results are presented in Table XVI-5-5.

Table XVI-5-5

ABNORMALITIES FROM FIVE RENAL FUNCTION TESTS
BY HISTORY OF KIDNEY DISEASE AND GROUP MEMBERSHIP

| Group | Abnormalities | No History (%) | History (%) | Total |
|---|---|---|---|---|
| Comparison | 0 | 406 (96.4) | 15 (3.6) | 421 |
| | ≥ 1 | 339 (96.6) | 12 (3.4) | 351 |
| Ranch Hand | 0 | 524 (94.4) | 31 (5.6) | 555 |
| | ≥ 1 | 462 (94.5) | 27 (5.5) | 489 |

P = 0.94 (History by abnormality interaction)

These data show that the reporting of kidney disease is associated only with group membership and not with abnormal findings on the physical examination.

4. Herbicide Exposure Analyses

Each Ranch Hand member was placed into an occupational stratum of flying officer, flying enlisted, or ground enlisted, which was further categorized into low, medium, or high exposure to herbicide (see Chapter VIII). Nonflying officers were assigned to the "low" exposure category of the flying officer group because of their nonherbicide administrative duties. Log-linear models were constructed for the variable of history of kidney disease, creatinine clearance, occult blood, and urinary protein; analyses of covariance were performed on the variables of BUN and urinary WBC's. Both tests used covariate adjustments based on age and 2-hour postprandial glucose results. Of the 18 exposure analyses, only 1 was borderline significant; these data are presented in Table XVI-5-6.

Table XVI-5-6

HISTORY OF KIDNEY DISEASE IN RANCH HAND FLYING ENLISTED PERSONNEL
BY EXPOSURE CATEGORY

| Ranch Hand Occupational Category | Exposure | History of Kidney Disease No (%) | Yes (%) | Total |
|---|---|---|---|---|
| Flying Enlisted | Low | 58 (98.3) | 1 (1.7) | 59 |
| | Med | 52 (88.1) | 7 (11.9) | 59 |
| | High | 64 (97.0) | 2 (3.0) | 66 |

P = 0.0504

While these exposure data are borderline significant, the association is nonlinear from low to high and is based upon very low numbers of positive histories.

## 5. Summary

Six clinical measures of renal function and data from a review-of-systems questionnaire were tested for group membership differences by log-linear models or analysis of covariance with age and 2-hour postprandial glucose results as covariates when appropriate. A two-fold increase in proteinuria ($P = 0.0545$) was found in the comparison group. Ranch Hand versus comparison group creatinine clearance differences were difficult to assess due to manifest compliance problems to the 24-hour urine collection process. While the Ranch Handers reported a significantly higher history ($P = 0.0389$) of past kidney disease, these historical differences were not correlated to cumulative abnormalities of 5 clinical variables. Herbicide exposure analyses in the Ranch Hand group were essentially negative.