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Air Force Health Study

An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides

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This report presents the results of the health assessment of the 1,016 Ranch Hands and the 1,293 Comparisons who participated in the 1985 followup examination of the Air Force Health Study. The purpose of the study is to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides. The result showed a subtle but consistent narrowing of medical differences between the two groups since the Baseline study in 1982; however, the Ranch Hands continue to manifest slightly more minor adverse health conditions then the Comparisons. Continued surveillance of these two groups is indicated. The report concludes that there is not sufficient evidence to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

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EXECUTIVE SUMMARY

FIRST FOLLOWUP MORBIDITY STUDY

The Air Force Health Study is an epidemiological study conducted to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study consists of mortality and morbidity components, based on a matched cohort design in a nonconcurrent prospective setting with followup studies. The Baseline study was conducted in 1982, and the first followup morbidity study was performed in 1985. The purpose of this report is to present the results of the first followup study.

In the Baseline morbidity study, each living Ranch Hand was matched to the first living and compliant member of a randomly selected Comparison mortality set based on age, race, and military occupation, producing an approximate 1:1 contrast. The Comparisons had served in numerous flying organizations that transported cargo to, from, and within Vietnam but were not involved in the aerial spray operations of Herbicide Orange. Recruitment for the first followup was in accordance with the Study Protocol: All previous participants and refusals, newly located study members, and replacements (matched to noncompliant Comparisons on self-perception of health) were invited. Of the living Baseline study participants, 99.2 percent were contacted to enroll in the followup on a strictly voluntary basis. Participation was very high, with 93 percent of both the Ranch Hands and the Comparisons fully compliant at Baseline also participating in the followup. Overall, the 2,309 followup participants (1,016 Ranch Hands and 1,293 Comparisons) represented a loss to the study of 159 individuals but a gain of 199 new participants since Baseline. Statistical analyses of selection and participation bias supported the use of the total Comparison group for the main analyses presented in this report.

The followup study was conducted under contract to the Air Force by Science Applications International Corporation, in conjunction with the Scripps Clinic and Research Foundation and the National Opinion Research Center. Most of the data were collected through face-to-face interviews and physical examinations conducted at the Scripps Clinic in La Jolla, California. Other data sources included medical and military records and the 1982 Baseline data base. As a contract requirement, all data collection personnel were blind to exposure status, and all phases of the study were monitored by stringent quality control. The statistical analyses were based on analysis of variance and covariance, chi-square tests, Fisher's exact tests, general linear models, Kolmogorov-Smirnov tests, logistic regression, proportional odds models, t-tests, and log-linear models.

The questionnaire and physical examination data were analyzed by major organ system. The primary focus was on the assessment of differences between the Ranch Hand and Comparison groups based on data from the first followup. Additionally, dose-response relationships within the Ranch Hand group were examined, and longitudinal assessments of differences in the changes of the two groups between the examinations were conducted for selected variables.

In terms of general health, Ranch Hand enlisted groundcrew rated their health as fair or poor more frequently than their enlisted Comparisons; differences were not observed for the enlisted flyers or the officers. Physician examiners detected no differences for appearance of illness or distress or for the appearance of relative age. The Ranch Hands had significantly lower percent body fat. They also had a higher proportion of sedimentation rate abnormalities than the Comparisons, but mean sedimentation rates were not statistically different between the two groups.

No significant differences between the Ranch Hand and Comparison groups were seen in the 1982-1985 interval for skin or systemic cancers. However, when overall lifetime basal cell carcinoma rates were adjusted for risk factors involved in the cause of such cancers (e.g., sun exposure, skin color, skin reaction to sun), Ranch Hands had a significantly higher proportion of basal cell carcinoma than Comparisons. No group differences were observed for systemic cancer, although two cases of possible dioxin-related cancer were noted in Ranch Hands, bringing the lifetime total to two of these cancers in each group. Overall, the cancer findings were not viewed as disturbing but as reason for continued medical surveillance.

The neurological assessment of cranial nerve function, peripheral nerve function, and central nervous system coordination did not reveal any consistently significant group differences, although abnormalities tended to aggregate in the Ranch Hands. The Babinski reflex (found adverse in the Ranch Hands at the 1982 Baseline examination) was equal in both groups at the 1985 followup. Age, alcohol, and diabetes showed classical effects with many neurological measures.

In the psychological evaluation based on the Minnesota Multiphasic Personality Inventory, the Comparisons had significantly more abnormalities for the denial and masculinity/femininity scales, whereas the Ranch Hands manifested marginally more abnormalities in the hysteria and social introversion scales. The Ranch Hands showed more abnormalities on the Cornell Medical Index scales than did the Comparisons, but no differences were detected between the two groups on the functionally oriented Halstead Reitan Battery. There were no group differences for current or past neuroses or psychoses. Age, educational level, and alcohol history showed strong and expected effects on the psychological measures.

Both the interval and the lifetime history of liver disease were equal in both groups, as was a lifetime history of peptic ulcer disease. Of nine liver function and two porphyrin laboratory tests, the Comparisons had significantly higher serum glutamic pyruvic transaminase and uroporphyrin means, whereas the Ranch Hands had a significantly higher mean alkaline phosphate level and a borderline elevated coproporphyrin value. There was no evidence to suggest an increased likelihood of porphyria cutanea tarda in the Ranch Hand group.

In the dermatological assessment, not one case of chloracne was diagnosed on examination, nor was historical acne anatomically distributed in a pattern that suggested past chloracne in the Ranch Hand group. Exposure and longitudinal analyses were also essentially negative.

The cardiovascular evaluation showed no significant group differences for reported or verified hypertension, reported heart disease, or reported or

verified heart attacks. However, the frequency of verified heart disease was significantly greater in the Ranch Hands than the Comparisons. The assessment of the central cardiac function by systolic blood pressure and electrocardiogram did not reveal any meaningful group differences. Evaluation of peripheral pulses by the Doppler technique revealed group equivalence in marked contrast to the Baseline examination, which found significant pulse deficits in the Ranch Hands. This change was likely due to required tobacco abstinence before the pulse measurements. Overall, the groups were remarkably similar in cardiovascular health.

The assessment of eight hematological measures showed no significant group differences. In fact, the groups were more similar at the followup examination than at the Baseline examination. Age, race, and smoking were significant risk factors for most hematological measures.

The groups did not differ significantly in reported past kidney disease, although the Baseline questionnaire noted such in the Ranch Hands. Five laboratory measures of renal function were similar between groups in the unadjusted analyses. No pattern of results suggested a detriment to either group in the adjusted analyses.

For the endocrine function, TSH and testosterone means were significantly higher in the Ranch Hands, but these results were not supported by the categorical tests. The impaired category of the glucose tolerance test revealed an excess in the Comparison group. Examination results for past thyroid disease, thyroid and testicular abnormalities, and additional tests for cortisol level and T_3 % Uptake were similar in both groups. Age, race, occupation, percent body fat, and personality type were often significant adjusting variables. Overall, the endocrine health status was comparable in both groups.

Comprehensive immunological tests composed of six cell surface marker studies and three functional stimulation studies showed no significant group differences in the unadjusted analyses. Age, smoking, and alcohol usage were generally strong covariates. The assessment of delayed hypersensitivity by skin testing was declared invalid because of excessive reader variation and shifting diagnostic criteria.

The pulmonary assessment, consisting of past history, physical examination, and x-ray results did not indicate any consistently different disease patterns in the two groups. Age and lifetime smoking history were important risk factors for most pulmonary measures.

The exposure index analyses, which were stratified by occupation, revealed sporadic differences between exposure levels; however, there were no consistent dose-response relationships that supported an herbicide effect for any clinical area.

Longitudinal analyses were conducted for 19 variables, and 5 showed significant differences in the changes of the groups between the Baseline and followup examinations. Of these 5 variables, 1 (sedimentation rate) was believed to be related to a change in laboratory methods, and the other 4 (Babinski reflex, depression, platelet count, and manual all pulse index) were attributed to true changes over time for the groups. In comparing all results between the examinations as well as the formal longitudinal analyses,

a subtle, but consistent, decrease in group differences over the 3-year period has been observed.

The process of inferring causality is complex and must be based on careful consideration of many factors. Any interpretations of the data must consider the biological plausibility, clinical significance, specificity and consistency of the findings, and a host of statistical factors, such as strength of the association, lack of independence of the measurements, and multiple testing.

By direct and indirect evidence, it is concluded that this study is free of overt bias and that the measurement systems used to obtain the data were accurate and valid. By an overall pattern assessment, it is further concluded that the Ranch Hand and Comparison populations are similar.

Finally, this first followup examination report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has revealed a number of minor medical findings that require continued surveillance. In full context, the results of this study must be viewed as additional reassuring evidence that, at this time, the current state of health of the Ranch Hand participants is unrelated to herbicide exposure in Vietnam.

PREFACE

The release of this 1987 followup Morbidity Report marks more than 8-1/2 years of intensive Air Force research into the herbicide question. Since the commitment to Congress in October 1978 to conduct an epidemiologic investigation of Air Force personnel who aerially disseminated herbicides in the Vietnam War (code-named Operation Ranch Hand), the United States Air Force Surgeon General has issued the following publications: a Study Protocol, four annual mortality reports, the Baseline Morbidity Report, and this first followup morbidity report. Within the next 2 years, the second followup morbidity report, other annual mortality reports, and an expanded birth defects study are expected for publication. This level of commitment has used approximately $40 million of contract research funds, excluding significant Air Force in-house expenditures.

Nearly 100 Government, academic, and industry scientists have guided and contributed to the Air Force Health Study (AFHS) since its inception. The Air Force's current advisory committee, chaired by Dr. Robert W. Miller of the National Cancer Institute, is responsible for providing assistance on all scientific and medical matters pertaining to the AFHS. The distinguished panelists are listed in Appendix A.

There are numerous scientific strengths in the AFHS, beginning with the unequivocal exposure status of the Ranch Hand population, estimated to have been, on the average, 1,000 times that experienced by an unclothed man directly beneath a spraying aircraft. In the other direction, the Ranch Hand population was probably less exposed to dioxin than many studied industrial populations (based upon a lack of chloracne), and may not develop adverse health consequences because of a possible threshold mechanism. However, the participants of the AFHS have a more defined exposure than the ground troops and constitute a larger population under study than industrial cohorts.

The chief strength of the AFHS is its design. The interwoven study elements of multiple mortality assessments, a Baseline morbidity study, and five followup morbidity studies over 20 years provide a comprehensive approach to the detection of attributable adverse health effects. The weakest feature of the design is the mortality assessment which, in the absence of significant case clustering, cannot detect group differences for very rare conditions (e.g., soft tissue sarcoma) because of the inherent constraints of the limited size of the Ranch Hand population. To some extent, this problem may be offset for the more prevalent cancers by combining both living and fatal cancers for future analyses. The strength of the mortality studies should increase with the aging of the study population and the concomitant increase in death with the passage of time.

All four mortality assessments have shown that the Ranch Hand population is faring about the same as the Comparison group, with no unusual causes of death, increased frequency of death, or evidence suggesting death at younger ages. Because of the healthy veteran effect, both groups are surviving significantly longer than similarly aged civilians. The morbidity assessment, released in 1984, disclosed only minor differences between the Ranch

Hands and the Comparisons, and these differences were not traditional indicators of dioxin-related disease. Both the content and the progress of the AFHS has been presented on many occasions to Congress, to the media, and to scientific meetings around the world. On the whole, the AFHS has been very well received in these circles, giving additional strength and credence to this work.

This report of the first followup study is important as it marks the sustained commitment of Congress and the Air Force to pursue the Agent Orange question to its logical scientific conclusion. From the medical and scientific perspectives, this followup examination gives the first opportunity to confirm or refute some of the Baseline findings, and to explore subtle longitudinal changes while controlling for confounding factors. The fifth-year followup examination, which will have been initiated when this report is released, will be conducted at an average time of 20 years postexposure for the Ranch Hands, a critical period for the emergence of attributable cancer. Followup studies such as these provide the most powerful scientific means of detecting emerging herbicide effects.

This report differs slightly from the Baseline Morbidity Report in several ways. The populations under study have changed slightly (see Chapter 2), since some Ranch Hands and Comparisons have voluntarily dropped out of the study, and additional study participants have joined (via the Comparison replacement strategy, or the addition of formerly noncompliant participants). Further, a greater variety of statistical techniques are used to explore bias considerations, subgroup categorical differences (see Chapter 7), and "best" model fitting via the use of two- and three-way interactions. In addition, specific medical tests were included in this examination to clarify whether less specific Baseline findings were relevant (e.g., Doppler measurement of arterial pulses).

Early in both the examination and analysis phases of this followup examination, it became clear that a joint Air Force-contractor approach to the analysis of the data was required. The Air Force elected to perform much of the analytical work of this report (e.g., bias, compliance, longitudinal, and pulmonary analyses). Thus, this study has transitioned from "independent" contract work to a genuine team effort between the Science Applications International Corporation (SAIC) and the Air Force scientific staffs. In the spirit of this enriching teamwork, SAIC has listed the Air Force scientific staff co-equally on the cover page of this report. Because of the highly professional scientific interchanges on many challenging aspects of the analytical work, it is believed that this report represents a scientific product unattainable by either team independent of the other.

A brief explanation of this report to the reader is in order. This report is written primarily for clinical epidemiologists, clinicians, and biostatisticians so that they may fully evaluate the data and analytic techniques herein. There are segments of this report that will be difficult for even the most experienced of these specialists to understand. Complete familiarity with the Study Protocol and prior mortality and morbidity reports is essential in the full understanding of this report. Thus, this report is not intended for rapid distillation by the layman or by media representatives. It should be noted that the intent of the introductions of the clinical chapters is to provide only a broad overview of the literature with respect to dioxin endpoints. In addition, the statistical analyses in this report were generally prescribed by the Air Force (based primarily upon

analyses performed for the Baseline Morbidity Report) and are not ad hoc analyses. The report format has been established to be complete, rigorous, and straightforward on all issues so that maximum scientific credibility will be maintained. As with the Baseline Report, the contractor, with Air Force authority, or the Air Force itself, will respond to telephone or written inquiries about the content of this report.

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CHAPTER 1

BACKGROUND

This chapter briefly describes the background of the Air Force Health Study (AFHS) and provides an overview of the study design and purpose of this report. Portions of this chapter have been paraphrased from the Baseline Morbidity Report, 24 February 1984.

In January 1962, President John F. Kennedy approved a program of aerial herbicide dissemination, for the purpose of defoliation and crop destruction, in support of tactical military operations in the Republic of Vietnam (RVN). Under this program, code-named Operation Ranch Hand and in operation from 1962 to 1971, approximately 19 million gallons of herbicides were dispersed on an estimated 10 to 20 percent of South Vietnam.[1,2] Approximately 11 million gallons of Herbicide Orange, the primary defoliant of the six herbicides utilized in the program, were disseminated.

Operation Ranch Hand was the subject of intense scrutiny from the start due to the controversial nature of the program and political sensitivity to chemical warfare charges contained in enemy propaganda. The concerns, which were initially based on military, political, and ecological issues, shifted during 1977 to health issues. Numerous claims of exposure to herbicides, particularly Herbicide Orange and its dioxin contaminant, and subsequent adverse health effects among U.S. military service personnel have resulted in class action litigation and substantial controversy. Social concern for the Herbicide Orange issue continues to be manifest by continuing scientific research, media presentations, congressional hearings, and legal action.

The U.S. Air Force Medical Service's concern for the health of Air Force personnel exposed to herbicides was demonstrated in October 1978 when the Air Force Deputy Surgeon General made a commitment to Congress and to the White House to conduct a health study on the Ranch Hand population, the aviators who disseminated the majority of the defoliants in the RVN. The prevailing reasons for the study commitment included the availability of a definitive occupational exposure to herbicides, a sufficient sample size for survey and clinical research, the ability to ascertain the population at risk, and an opportunity for the Air Force Medical Corps to fulfill its adage "we care" to the Air Force community.

The Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas, was tasked by the Surgeon General to develop the Study Protocol. In 1982, after extensive peer review, the epidemiologic study began, and the Protocol was published.[3]

Since 1978, numerous animal and human studies of dioxin effects have been planned or initiated by governmental agencies, universities, and industrial firms. The key scientific issue in these studies was the extent of exposure, e.g., who was exposed and how much each individual was exposed. Unfortunately, population identification and exposure estimation, which are critical for a valid study of ground troops, have been scientifically elusive.

It is believed that of all the military personnel who served in the RVN, the Ranch Hand population was the most highly exposed to herbicides. Exposure estimates indicate that the average Ranch Hand received 1,000 times more exposure to Herbicide Orange and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) during his tour in the RVN than an average male would receive standing unclothed under a spraying aircraft in an open field. Based on the principle of dose-response, the Ranch Hands should manifest more and/or earlier evidence of adverse health. Thus, the results of the AFHS should serve as an indicator of herbicide effects in ground personnel.

STUDY DESIGN

The purpose of the study is to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study, consisting of mortality and morbidity components, is based on a matched cohort design in a nonconcurrent prospective setting with followup studies. Complete details on the design are provided in the Study Protocol.

The nonconcurrent aspect of the design results from the fact that the Ranch Hands were exposed over time between 1962 and 1971. This staggered exposure is accounted for in the design of the studies to address latency considerations.

For the Baseline study, the population ascertainment process identified 1,264 Ranch Hand personnel who served in the RVN between 1962 and 1971. By the time the first followup began in 1985, an additional 11 Ranch Hands had been identified, bringing the total Ranch Hand population to 1,275. A Comparison group was formed, consisting of individuals assigned to selected Air Force units with missions of flying cargo to, from, and within the RVN during the same period. Using a computerized nearest neighbor selection procedure, a maximum of 10 Comparisons was selected for each Ranch Hand, matching on age, race, and military occupation. After personnel record reviews, each Ranch Hand who was determined to be eligible and fully suitable for study had an average of 8.2 Comparison subjects.

The mortality component addresses mortality from the time of the RVN assignment. A Baseline mortality study was conducted in 1982, and the mortality followup consists of annual mortality updates for 20 years. For the Baseline study and the first four updates, five individuals were randomly selected from the matched Comparison set for a 1:5 design. Subsequent to 1986, the design will be expanded to include all of the individuals in the Comparison set.

The Baseline morbidity component, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical records. A cross-sectional element, designed to assess the participant's current state of mental and physical health, was based on comprehensive questionnaires and physical examinations given to the participants. For this component of the study, each living Ranch Hand and the first living member of his Comparison set were selected to participate in the examination. Sequential questionnaires, medical record reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002 comprise the morbidity study followup.

PURPOSE

The 1985 morbidity followup is the subject of this report. The objective of the morbidity followup is to continue the investigation of the possible long-term health effects following exposure to TCDD-containing herbicides. This report describes the procedures and results of the first morbidity followup of the AFHS. Analysis of reproductive and fertility data will be conducted by the U.S. Air Force and is not part of this report.

CHAPTER 1

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CHAPTER 2

POPULATION

This chapter provides a description of participant selection, the enrollment process, and the demographic characteristics of the population that participated in the clinical and questionnaire portions of the first followup morbidity study in 1985.

BASELINE CANDIDATE IDENTIFICATION

The study population for the first followup was defined by the Air Force investigators as part of the Baseline study design. Using detailed searches through Air Force and other Government record systems, a total of 1,264 personnel who had participated in Operation Ranch Hand was identified. Using the same historical data sources, a Comparison population of 24,971 individuals that had been assigned to a variety of military cargo missions in Southeast Asia during the same time period was identified.

The Ranch Hand and the Comparison populations were matched after all individuals who had been killed in the Vietnam conflict were removed. The matching process was conducted using a computer program employing iterative nearest-neighbor statistical techniques in order to associate each Ranch Hand with 10 Comparisons by race (Black/nonblack), closest date of birth, and occupational category during Vietnam service (officer-pilot, officer-navigator, officer-nonflying, enlisted flyer, and enlisted groundcrew). For each Ranch Hand, 1 of the 10 matched Comparisons was selected at random and designated the Original Comparison. The resulting exposed and multiple matched Comparison study design was used for the Baseline effort.

During the questionnaire administration of the Baseline study, it was discovered that 18 percent of the Comparison population had been misselected with respect to their Southeast Asia military experience. After eliminating these ineligible Comparisons, the remaining Comparison set was collapsed to a 1:8 study design, which was used for all subsequent eligibility determinations.

During the course of the Baseline morbidity study, five new Ranch Hands were verified as eligible for the study and were added to the exposed group. In addition, two Ranch Hands who had been misclassified as Comparisons were identified during the questionnaire administration. These individuals were reclassified as exposed and new Comparisons were assigned appropriately. Following the completion of the Baseline morbidity study, 10 additional Operation Ranch Hand participants were located and added to the study population for the followup phases.

FOLLOWUP CANDIDATE IDENTIFICATION

One of the preliminary tasks associated with the followup study was to conduct a telephone survey of uncontacted replacement candidates. The purpose of the survey was to obtain new information on the candidate's general health, economic situation, and willingness to participate in the study.

The Air Force address file, assembled and maintained since 1981, provided the basis for the telephone survey contact list. A location algorithm described in Chapter 3 was developed in order to find those individuals no longer at the address and telephone number indicated in the Baseline file.

A total of 7,411 candidate replacements out of the candidate file of 7,963 was located, interviewed using computer-aided telephone interview (CATI) techniques, and confirmed as eligible candidate study participants. Of the 552 candidates who could not be interviewed, 26 were deceased, 335 refused, 190 were unlocatable, and 1 respondent had not served in Southeast Asia and was therefore ineligible for the study.

Table 2-1 provides the number of candidate participants by Baseline compliance category for the Ranch Hand and Comparison groups.

PARTICIPANT SELECTION

The participant selection protocol used for the followup was similar to that used at Baseline with one important exception. If the Original Comparison declined to participate, the next randomly ordered candidate for the corresponding Ranch Hand with the same self-perception of health was contacted and recruited for the study. This matching process was not feasible at Baseline because the addresses of the Comparison pool were not fully ascertained. Perception of health was subjectively determined by the candidate during the telephone interview. The rationale for matching replacement Comparisons on self-perceived health status was an attempt to minimize any bias that might result from differential compliance. All candidates who had been contacted and invited to participate during the Baseline, including those who were refusals and partial compliers, were contacted and invited to the followup along with newly verified or located Ranch Hands and their Comparisons.

ENROLLMENT

The enrollment of candidates was based on the Baseline lists and health status information from the telephone survey. Recruitment was conducted for questionnaire interviews and clinical examinations that began in May 1985 and ended in March 1986. Approximately 70 individuals were examined each week in two groups of 35. A total of 2,309 Ranch Hands and Comparisons participated in both the questionnaire and clinical examination portions of the AFHS followup. Since the followup questionnaire was administered at the physical examination site, there were no "partially compliant" participants at followup.

TABLE 2-1.

Candidate Followup Participants by Group and Baseline Compliance Status

Number	Category
	Candidate Ranch Hands (by Baseline Status)
1,045	Ranch Hands Who Completed Both Baseline Questionnaire and Physical Examination (Fully Compliant)
129	Ranch Hands Who Completed Only Baseline Questionnaire (Partially Compliant)
32	Ranch Hands Who Declined to Take Part in Baseline (Noncompliant)
10	Newly Verified or Located Ranch Hands
1,216	**Total**
	Candidate Comparisons (by Baseline Status)
936	Original Comparisons Who Completed Both Baseline Questionnaire and Physical Examination (Fully Compliant)
220	Original Comparisons Who Completed Only Baseline Questionnaire (Partially Compliant)
79	Original Comparisons Who Declined to Take Part in Baseline (Noncompliant)
288	Replacement Comparisons Who Completed Both Baseline Questionnaire and Physical Examination (Fully Compliant)
88	Replacement Comparisons Who Completed Only Baseline Questionnaire (Partially Compliant)
49	Replacement Comparisons Who Declined to Take Part in the Study (Noncompliant)
7,411	Replacement Comparisons Who Had Not Been Contacted Previously
9,071	**Total**

Enrollment was managed using an automated scheduling and tracking system to maintain and record all candidate recruitment contacts, actions, and status; clinical examination group scheduling; schedule modifications, cancellations, and completions; and a comprehensive set of logistic management reports. An effort was made to successfully recruit every individual eligible for the study. The number of participants who participated in the physical examination and questionnaire of the first followup is provided in Table 2-2.

Of the 1,016 Ranch Hands, all but 53 had matched Comparisons who also participated in the study. Due to the selection strategy used and the recruitment of previous noncompliants, several of the Ranch Hands had multiple Comparisons. The selection strategy resulted in 79 Ranch Hands having 2 Comparisons, 9 having 3 Comparisons, and 1 Ranch Hand having a total of 5 Comparisons completing the followup. In accordance with the Study Protocol, eligible Comparisons were enrolled without regard to the compliance status of the corresponding Ranch Hand. There were 229 Comparisons in the followup study whose matched Ranch Hand did not participate.

PERSONAL CHARACTERISTICS AND HABITS OF FOLLOWUP POPULATION

The data on personal characteristics of the Ranch Hand and Comparison individuals were obtained from the followup questionnaire. The areas of tobacco, alcohol, and marijuana use; personal and family income; education; religious preference; active duty/retired/separated status; and risk-taking behavior received particular attention. These variables were examined to assess the similarity of the two groups in social and behavioral characteristics, which were not included in the statistical matching process.

The participants in the study were matched on age. The age characteristics of the study population are shown in Table 2-3. The mean and median ages of the Ranch Hand and Comparison groups were nearly identical.

The smoking and alcohol-use habits of the study subjects are displayed in Table 2-4. More participating Ranch Hands smoked cigarettes at the time of the followup physical examination than did the Comparisons (40.1% versus 35.0%). This difference in current smoking behavior was statistically significant ($p=0.01$). In the intervening years since the Baseline examination, 5.6 percent of the Ranch Hands and 4.6 percent of the Comparisons had stopped smoking. The proportions of participants who ever smoked cigarettes, pipes, or cigars were not significantly different in the two groups. Similarly, the number of participants who drank alcohol in the years since 1982 was not statistically different between groups.

Data concerning the use of marijuana were gathered by different methods in the two interviews. In the Baseline questionnaire in 1982, confidentiality of response was given to all participants, but answers were identifiable for each participant. At the 1985 followup, random response techniques[1] were used on the marijuana questions to overcome the problem of participants either refusing to respond or giving misleading replies to these highly sensitive and personal questions. With this technique, a coin was flipped by the respondent, who then answered either the marijuana question or a neutral unrelated question, which had an answer of known probability. The outcome of

TABLE 2-2.

Participants Enrolled in the Followup Study by Group and Baseline Compliance Status

Number	Category
	Enrolled Ranch Hands (by Baseline Status)
971	Ranch Hands Who Completed Both Baseline Questionnaire and Physical Examination (Fully Compliant)
39	Ranch Hands Who Completed Only Baseline Questionnaire (Partially Compliant)
0	Ranch Hands Who Declined to Take Part in Baseline (Noncompliant)
6	Newly Verified or Located Ranch Hands
1,016	**Total**
	Enrolled Comparisons (by Baseline Status)
872	Original Comparisons Who Completed Both Baseline Questionnaire and Physical Examination (Fully Compliant)
61	Original Comparisons Who Completed Only Baseline Questionnaire (Partially Compliant)
10	Original Comparisons Who Declined to Take Part in Baseline (Noncompliant)
12	New Original Comparisons
267	Replacement Comparisons Who Completed Both Baseline Questionnaire and Physical Examination (Fully Compliant)
32	Replacement Comparisons Who Completed Only Baseline Questionnaire (Partially Compliant)
11	Replacement Comparisons Who Declined to Take Part in Baseline (Noncompliant)
28	New Replacement Comparisons
1,293	**Total**

TABLE 2-3.

Age (in 1985) of
Participants of the Followup Examination by Group

	Group			
	Ranch Hand		Comparison	
Age Category	Number	Percent	Number	Percent
43 or Less	412	40.6	549	42.5
44 to 62	568	55.9	693	53.6
63 or More	36	3.5	51	3.9
Total	1,016	100.0	1,293	100.0

	Group	
	Ranch Hand	Comparison
Range	35-72 Years	35-77 Years
Mean	46.9 Years	46.8 Years
Median	47 Years	46 Years

the coin flip was unknown to the interviewer. Thus, no given reply could be traced, although the proportion of the population that had the sensitive characteristic (marijuana use) could be estimated.

There were no statistically significant differences between the Ranch Hand and Comparison groups in the reported use of marijuana in the 30 days preceding the examination (7.8% and 9.2%, respectively). A much higher percentage, 26.3 percent of the Ranch Hands and 31.0 percent of the Comparisons, reported smoking marijuana at some time in the past. At Baseline, only 5.1 percent of each group reported ever using marijuana. These differences over time were most likely due to a greater sense of confidentiality generated by the random response techniques used in the 1985 questionnaire.

The mean usage levels of tobacco and alcohol among those participants who did indulge in these habits are shown in Table 2-5 as pack-years, cigar-years, pipe-years, or drink-years. Mean alcohol use per day was 6.26 drinks per day for the Ranch Hands and 6.42 for the Comparisons. In most of the cumulative measurements, the median level of use was lower than the mean level, indicating that the heavy users of these substances skewed the distributions. Eighty-nine percent of both groups reported having consumed alcohol since the last physical examination. Differences in these calculated variables might have been due to either actual changes in behavior or to differences in the questionnaires used to collect the basic data.

TABLE 2-4.

History of Tobacco and Alcohol Use
of Participants of the Followup Examination by Group

Habit	Group								
	Ranch Hand				Comparison				
	Yes	Percent	No	Percent	Yes	Percent	No	Percent	p-Value
Current Use of Cigarettes	407	40.1	609	59.9	453	35.0	840	65.0	0.01
Past History of Cigarettes	752	74.0	264	26.0	944	73.0	349	27.0	0.58
Past History of Cigar Use	249	24.5	767	75.5	345	26.7	948	73.3	0.24
Past History of Pipe Use	265	26.1	751	73.9	340	26.3	953	73.7	0.92
Past History of Marijuana Use*		26.3		73.7		31.0		69.0	0.15
Marijuana Use* within Past 30 Days		7.8		92.2		9.2		90.8	0.52
Use of Alcohol since Last Interview	901	88.7	115	11.3	1,147	88.7	146	11.3	0.98

*Estimates based on random response technique.

TABLE 2-5.

Average Use of Tobacco Products and Alcohol for Those Reporting Use of These Substances: Participants of the Followup Examination by Group

Substance	Group			
	Ranch Hand		Comparison	
	Mean	Median	Mean	Median
Cigarettes per Day (Current Use)	26.54	25.00	25.77	25.00
Cigarettes, Pack-Years (Cumulative)	17.69	13.00	17.61	13.00
Cigar-Years (Cumulative)	11.25	1.30	10.96	1.00
Pipe-Years (Cumulative)	20.03	6.10	16.90	4.00
Alcohol Drinks per Day (Current Use)	6.26	6.00	6.42	5.00
Drink-Years (Since Last Interview)	1.81	0.80	1.89	0.74
Drink-Years (Cumulative)	26.59	12.80	25.04	13.00

Educational background and religious preference for the two groups are presented in Tables 2-6 and 2-7. The current military status of each individual was classified as active duty, retired, separated, reserve duty, or deceased. There were no significant differences between the two groups. These data are presented in Table 2-8 and showed equivalence of the two groups in these social variables.

Data on income were collected in a categorical form, and the median income levels of the Ranch Hand and Comparison groups were comparable. The median personal income in both groups was in the $25,000 to $30,000 range, and the median total family income ranged from $40,000 to $45,000 in each group.

Risk-taking behavior patterns of the study population were assessed by a series of questions that emphasized participation in potentially dangerous recreational activities. These data are summarized in Table 2-9. In motor-vehicle racing (automobiles, boats, and motorcycles) and scuba diving, there were group differences of borderline significance ($p=0.07$ and $p=0.09$, respectively). Slightly more Comparisons were scuba divers (12.4% versus 10.1%), and more Ranch Hands raced motor vehicles (12.9% versus 10.4%). There was a significant difference in scuba diving at Baseline ($p=0.04$), when more Comparisons were scuba divers (12.7% versus 9.9%).

TABLE 2-6.

Educational Background of Participants of the Followup Examination by Group

	Group			
	Ranch Hand		Comparison	
Educational Level	Number	Percent	Number	Percent
High School/GED	522	51.4	655	50.7
Associate Degree	84	8.3	114	8.8
BA/BS Degree	194	19.1	271	21.0
Graduate Degree	203	20.0	239	18.5
Unknown	13	1.3	14	1.1
		p=0.64		

TABLE 2-7.

Religious Preference of Participants of the Followup Examination by Group

	Group			
	Ranch Hand		Comparison	
Religious Preference	Number	Percent	Number	Percent
Protestant	671	66.0	856	66.2
Catholic	215	21.2	281	21.7
Jewish	9	0.9	15	1.2
Other	37	3.6	54	4.2
None	84	8.3	87	6.7
		p=0.60		

TABLE 2-8.

Military Status of Participants of the Followup Examination by Group

Military Status	Group			
	Ranch Hand		Comparison	
	Number	Percent	Number	Percent
Active Duty	89	8.8	118	9.1
Retired	553	54.4	683	52.8
Separated	313	30.8	420	32.5
Reserve Forces	55	5.4	65	5.0
Deceased[a]	6	0.6	7	0.5
		p=0.90		

[a]Died after the followup examination.

These data reflected the overall equivalence of the two groups in social and behavioral characteristics. The differences observed when these data were contrasted to similar data at Baseline might have reflected differences in data collection methods or slight changes in the cohorts rather than changes in behavior among group members.

LONGITUDINAL LOSSES AND GAINS

A total of 2,269 Ranch Hands and Comparisons was fully compliant with the Baseline study. The study population of 2,309 for the followup included a loss of 159 participants and the addition of 199 individuals.

Loss to the followup occurred either because the participant was deceased, refused to participate, or was unlocatable. The loss to followup was 7 percent in both the Ranch Hand and Comparison groups. Of the 69 Comparisons lost to the followup study due to refusal or inability to locate, 17 were replaced. For the remaining 52, no replacement who satisfied the health status matching criterion and was willing to participate was identified from the candidate replacements. The categories of these individuals are provided in Table 2-10. A total of 199 new participants were recruited into the study based on the selection methodology used. Information on the new participants is provided in Table 2-10.

TABLE 2-9.

Risk-Taking Behavior of Participants of the Followup Examination by Group

	Group								
	Ranch Hand				Comparison				
Activity	Yes	Percent	No	Percent	Yes	Percent	No	Percent	p-Value
Scuba Diving	103	10.1	913	89.9	160	12.4	1,133	87.6	0.09
Auto, Boat, or Motorcycle Racing	131	12.9	885	87.1	135	10.4	1,158	89.6	0.07
Acrobatic Flying	43	4.2	973	95.8	43	3.3	1,250	96.7	0.25
Sky Diving	22	2.2	994	97.8	32	2.5	1,261	97.5	0.62
Hang Gliding	11	1.1	1,005	98.9	14	1.1	1,279	98.9	1.00
Mountain Climbing	82	8.1	934	91.9	102	7.9	1,191	92.1	0.86
Surfboard Riding	81	8.0	935	92.0	91	7.0	1,202	93.0	0.40
Long-Distance Sailing	54	5.3	962	94.7	55	4.3	1,238	95.7	0.23
Fast Downhill Skiing*	170	16.7	846	83.3	184	14.2	1,108	85.8	0.10
				p=0.10					

*One Comparison was unwilling to respond.

TABLE 2-10.

Losses/Gains of Participants Between the Baseline and Followup Examinations

Losses

Number	Category
10	Ranch Hands Deceased
59	Ranch Hand Refusals
5	Ranch Hands Unlocatable
74	**Total Ranch Hands Lost**
16	Comparisons Deceased
55	Comparison Refusals
14	Comparisons Unlocatable
85	**Total Comparisons Lost**

Gains

Number	Category
39	Ranch Hands Partially Compliant at Baseline
6	Newly Verified or Located Ranch Hands
45	**Total Ranch Hands Added to Study**
61	Partially Compliant Original Comparisons at Baseline
32	Partially Compliant Replacement Comparisons at Baseline
11	Newly Selected Original Comparisons (For Newly Verified Ranch Hands)
16	Replacements for Compliant Comparisons Who Refused Followup
10	Noncompliant Original Comparisons Who Agreed to Attend Followup
11	Noncompliant Replacement Comparisons Who Agreed to Attend Followup
1	Original Comparison Not Locatable at Baseline but Found at Followup
3	Replacement Comparisons Not Locatable at Baseline but Found at Followup
9	Replacement Comparisons Not Contacted at Baseline
154	**Total Comparisons Added to Study**

SUMMARY

Participants were recruited for the first followup in accordance with the Study Protocol. All participants (Ranch Hands and Comparisons) who were contacted for enrollment at Baseline were recruited for this phase of the study. Newly verified and located Ranch Hands, since Baseline, and their respective Comparisons were invited to join the study. Due to refusals among the Comparisons, replacements from the previously uncontacted Comparisons were selected for enrollment. The replacements were matched to the refusing Comparisons on self-perception of health; health status data were obtained in the telephone survey.

Personal characteristics of the two groups were compared, based on data obtained from the followup questionnaire. Contrasts of age, educational background, religious preference, current military status, and income revealed no significant differences between the Ranch Hand and Comparison groups. Significantly more Ranch Hands smoked cigarettes at the time of the followup examination than did Comparisons, although there were no significant differences found for past history of cigarettes, cigars, or pipe use or for recent or past use of marijuana. A much higher percentage of both groups reported smoking marijuana at some time in the past at the followup than at Baseline. This difference was most likely due to a greater sense of confidentiality generated by the random response techniques used in 1985. The use of alcohol since the Baseline examination was not significantly different between the two groups. The difference in the risk-taking behavior patterns of the Ranch Hands and the Comparisons was marginally significant. Slightly more Ranch Hands than Comparisons raced motor vehicles, and more Comparisons were scuba divers.

The followup study population included the loss of 159 participants (74 Ranch Hands and 85 Comparisons) who were fully compliant at Baseline and the addition of 199 participants (45 Ranch Hands and 154 Comparisons). The 199 newly examined study subjects consisted of 132 participants (39 Ranch Hands, 61 Original Comparisons, and 32 replacement Comparisons) who were partially compliant at Baseline, 21 participants (10 Originals and 11 replacements) who refused at Baseline, and 46 participants (6 Ranch Hands, 12 Originals, and 28 replacements) who were new to the study.

Thus, the study population for the first followup of the AFHS consisted of 2,309 individuals: 1,016 who had been associated with Operation Ranch Hand and 1,293 Comparisons.

CHAPTER 2

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CHAPTER 3

QUESTIONNAIRE METHODOLOGY

This chapter discusses the development and the implementation of the questionnaires used in the study: the participant interval questionnaire, the spouse interval questionnaire, the Baseline participant and spouse questionnaires, and the telephone survey of previously uncontacted Comparisons.

The participant interval questionnaire was designed to capture the study participant's health history in the 3 years since his participation in the Baseline study. Data collection was comparable to the Baseline effort: The questionnaire was very similar, and it was administered using the same face-to-face methodology to virtually the same population. In the Baseline study, interviews were conducted in the participants' homes and the followup interview was conducted at the physical examination site. The revised methodology was more efficient and better subject to quality control.

The spouse interval questionnaire collected reproductive data similar to those collected at Baseline from spouses for the interval since Baseline. The spouse interval questionnaires were mailed to the spouses to be self-administered, or were completed in La Jolla, California, if the spouse accompanied the participant to the physical examination site. Analysis of the spouse data is not included in this report.

Since some study subjects refused to participate in 1982 and other participants were new to the study, Baseline questionnaires were administered to these new participants and their spouses. The same procedures used at Baseline were used to administer the Baseline questionnaires in the homes of these individuals.

The elements of each questionnaire are identified in Table B-1 of Appendix B. Questionnaire development and administration and scheduling of participants were conducted by the National Opinion Research Center (NORC), a social science research center at the University of Chicago.

QUESTIONNAIRE DEVELOPMENT

The goal of questionnaire development was to maintain to the maximum extent possible the question wordings, context, and procedures that were used in the 1982 Baseline study. The largest task of questionnaire development was asking for interval histories on crucial questionnaire items to update the information provided by the 1982 Baseline questionnaires. For the participant interval questionnaire, new questions were also developed on risk factors for skin cancer, since the Baseline Morbidity Report[1-3] found Ranch Hands to have an excess of nonmelanoma skin cancer. Because the chemical constituents of Herbicide Orange had not previously been associated with skin cancer in the literature, no questions had been included in the Baseline participant questionnaire to collect information on risk factors for this condition.

New questions were added to determine personality type, since Type A behavior is associated with coronary heart disease.[4] The Jenkins Activity Scale was administered to collect these data. Enhancements were also made to improve data collection for birth defects, smoking habits, and drinking habits. A copy of the participant interval questionnaire is provided in Appendix B.

An information sheet containing a computer-generated summary of key respondent answers to the Baseline survey was used to provide bounded recall for participants. Even when given a precise "starting date," respondents frequently repeat information given earlier, neglect to report new information because they thought they had previously reported it, and otherwise misplace events in time or forget them completely. The best means of preventing such errors is through the use of bounded recall, in which the respondent is reminded of information he has already reported and new information is sought with reference to an updated information sheet. Among the data elements included were date of birth, highest educational degree, military status at last interview, marital status at last interview, and name of spouse.

The questionnaire was pretested on 8 ineligible individuals who had been interviewed during Baseline, and on 10 men who participated in the pretest examination.

INTERVIEWER TRAINING

Twelve interviewers were recruited and trained by NORC's field management and Chicago office staffs in May 1985 to administer the interval questionnaires. The onsite NORC interview staff was not informed of the exposure status of any study participant either before or after contract completion. The site supervisor reported to the Project Director in Chicago on a weekly basis, and quarterly visits were made to the site by the Director. The site supervisor observed a sample of interviews, at least one per interviewer per week, and reviewed and edited interview questionnaires before shipping them to Chicago for further processing.

In early 1985, personal interviewers were recruited to conduct Baseline interviews for new participants in their homes. The interviewers were trained in the Chicago NORC office, using questionnaires and procedures established for the Baseline survey. They were supervised by an assistant survey director in the NORC office, who edited each completed questionnaire and talked with each interviewer weekly.

TELEPHONE SURVEY

The telephone survey of uncontacted Comparisons was intended to gather data on the general health status of the 7,963 replacement candidates for the active Comparison group. The sample consisted of men who served in C-130 units in Southeast Asia between 1962 and 1971, but who did not participate actively in the Baseline phase of the study. A total of 7,411 cases (93%) was completed by NORC computer-assisted telephone interviewers. The telephone survey was conducted prior to the scheduling of the physical examinations.

The key question asked was, "Compared to other people your age, would you say that your health is...excellent, good, fair, poor?" Other questions asked about current medications, severity of illness or injury during the last 6 months, and income. Locating and refusal conversion algorithms similar to the Baseline data collection efforts were used.

The data from the telephone survey of uncontacted Comparisons were used to select a replacement whose self-reported health status matched that of the noncompliant Comparison. If a willing replacement was not found by this method, the perception of health status variable was dichotomized into excellent/good versus fair/poor, and a new replacement was selected from the Comparison set. If this second attempt at identifying a suitable replacement failed, no replacement was made. The selection procedure is provided in Figure 3-1. In this example, the first randomly ordered Comparison was contacted but refused to participate. In the second attempt, the Comparison was deceased. The third Comparison volunteered to participate in the morbidity study.

SCHEDULING OF PARTICIPANTS

NORC recruited and trained four schedulers to perform the initial contacts with study subjects. Their training included background information on the details and purpose of the study, simulation of the actual scheduling of calls, documentation of results, and conversion of refusals. An initial letter was sent by the Air Force to each study subject, informing him of the upcoming interval physical examination. The NORC scheduler then followed this letter with a call to attempt to schedule the participant.

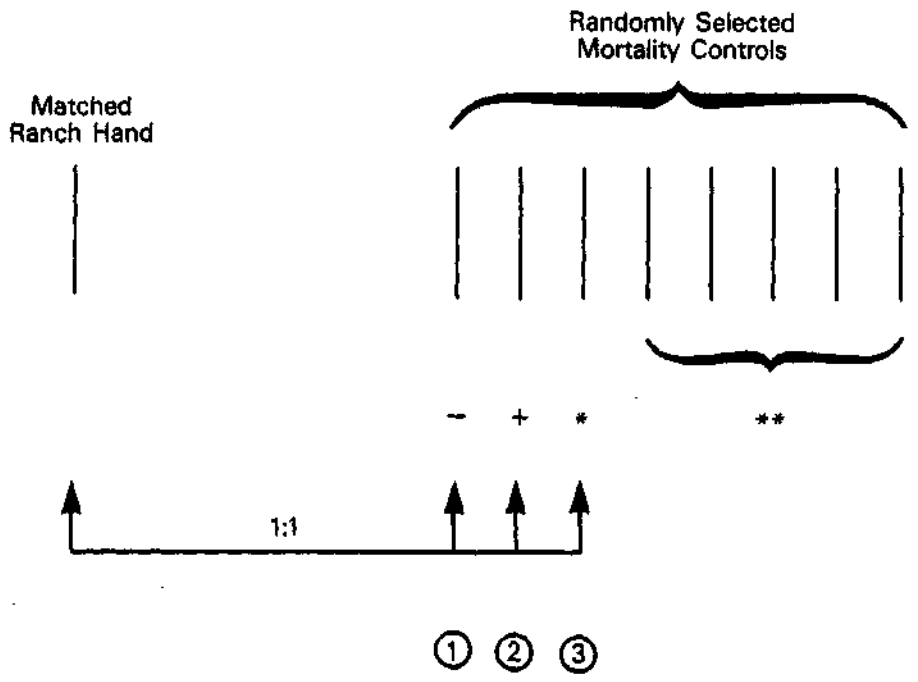
Refusals occurred at a number of steps in the scheduling process. A team of conversion specialists was assigned to contact refusing study subjects and attempt conversions. Help in conversion was also received from individuals in the U.S. Air Force School of Aerospace Medicine and the Ranch Hand Association. Many more participants were scheduled, but due to "no-shows" at the examination site, and passive refusals who rescheduled frequently, the final figure stood at 2,309.

The Baseline interviewer contacted the potential study participant by telephone for scheduling the in-home interview. Toward the end of the physical examination phase, the Baseline questionnaire was administered at the examination site by one of the interviewers who had been trained in administering that questionnaire. Of the 106 participant Baseline questionnaires administered during the first followup, 21 had to be conducted at the examination site.

The supervisor of the Baseline interviewers conducted the locating efforts for new and interval participants. Procedures similar to those used in 1982 were followed: a postal search, followed by a local telephone directory search, a motor vehicle registration search, and personal locating efforts in the area of last known residence when appropriate. The Air Force also provided locating support through its records.

DATA COLLECTION

Upon arrival at the Scripps Clinic and Research Foundation (SCRF), the participant received a schedule including the time and place for the interval interview, and a race-matched interviewer was appointed to conduct the



– Unwilling
+ Deceased
* Volunteered
** Replacement Candidates

Figure 3-1.
Selection Procedure for the Questionnaire, Physical Examination, and Followup Study

interview. Because of scheduling problems and the unavailability of a Black interviewer, 65 of the 143 Black study participants were interviewed by whites.

As in all of the personal interviews for the AFHS, interviewers were required to ask questions exactly as written, were not allowed to interpret questions or inject personal commentary, and were not allowed to skip between sections of the questionnaire. They were also instructed to probe "don't know" answers at least once. During the interview, medical record release forms were signed. The respondent was also asked to give the current name and address for each former spouse listed in the questionnaire, so that spouse questionnaires could be mailed to these individuals.

The spouse interval survey was mailed to current spouses at the time the study subject was at the SCRF. Two NORC Chicago telephone interviewers were trained to prompt refusing spouses to return the questionnaire, or to administer the spouse interview by telephone as part of the refusal conversion effort. If the spouse also traveled to La Jolla, the questionnaire was completed under the supervision of a site interviewer. Of the 1,898 completed spouse interval questionnaires, 1,066 were returned by mail, 348 were completed by telephone, and 484 were completed in La Jolla.

DATA PROCESSING

All completed interviews were sent to the NORC Chicago office following editing by the site supervisor, who retrieved missing data from study subjects while they were still onsite; any further retrieval of critical items was conducted from the Chicago office through telephone contacts. Critical items were those for which missing data were unacceptable.

The questionnaires were coded for data entry by a staff of five coders who received a week of training on the various AFHS instruments. Data entry was programmed to provide value and range checks as the data were being entered, to perform logic checks and arithmetic checks, to flag important missing items, and to verify the key entry of 10 percent of each questionnaire. Then the data were run through an automated cleaning program to detect a wide range of data errors that were corrected by pulling the hard copy questionnaires and reviewing each situation on a case-by-case basis. No changes were ever made in the hard copy data; corrections were entered into the data tape, and the tape was run against the cleaning program until no errors were detected.

CHAPTER 3

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CHAPTER 4

PHYSICAL EXAMINATION METHODOLOGY

The first followup examination was provided to four categories of individuals: those who had taken the Baseline questionnaire and Baseline physical examination; those who had been invited to the Baseline events but chose not to participate, only took the questionnaire, or were unlocatable; those Comparisons who had not been invited previously, but who were selected as replacements for Baseline Comparisons noncompliant to this followup examination; and the six newly identified Ranch Hands. As noted in the Baseline Report, all potential study participants were verified as eligible for the AFHS following a detailed review of military personnel records. Replacement individuals were carefully selected, by matching data on the self-perception of health from the noncompliant Comparison (obtained from the telephone survey) with those of the replacement candidate (see Chapter 3 for details).

The followup examination differed logistically from the Baseline examination in one significant way: All structured interval questionnaires were administered at the examination site as contrasted to the in-home interviews conducted at Baseline. The followup examination consisted of the following major elements:

- Interval Questionnaire
- Combat Experience Questionnaire
- Review-of-Systems Questionnaire
- Psychological Testing
- Physical Examination
- Specialized Testing, e.g., Doppler Arterial Studies
- Laboratory Testing
- Psychological and Medical Outbriefings.

Details of the above examination elements were carefully prescribed by the Air Force and set forth as contractual requirements. Clinical innovations or variations were neither desired nor authorized; all proposed examination procedural changes were reviewed in detail by Air Force technical and contractual personnel. An important objective of the technical review was to ensure that bias was not created by any procedural change. The requirement to maintain blind examinations was particularly stringent: The clinical staff was prohibited from knowing or seeking information as to the group identity (Ranch Hand, Comparison) of any participant. At the end of the examination, each participant was asked to note on the critique form whether such information was sought by any member of the clinical or paramedical staff.

EXAMINATION CONTENT

Examination content was designed by the Air Force to emphasize detection of medical endpoints suspected of being associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. In addition, findings in the Baseline examination were used by the Air Force to direct changes in the followup examination (e.g., abnormal pulses at Baseline suggested the need for Doppler measurements at the followup). The general content of the physical examination and psychological test battery is shown in Table 4-1, and the complete laboratory test series is displayed in Table 4-2.

Quality control requirements for both laboratory testing and clinical procedures were extensive. Although details are provided in Chapter 6, the following categories provide an overview of the extent of the quality emphasis. For laboratory testing, single reagent lots and control standards were used when practical, duplicate specimens were routinely and blindly retested, testing overlaps were mandatory when test reagents required change, and fast initial response cumulative statistical techniques (FIR CUSUM) were used to detect rapidly any subtle test drift over time. In addition, 50 specimens from the Baseline serum bank were retested to assess the comparability of laboratory methods. The SCRF clinical team was carefully instructed to assure clinical quality. The quality control elements included: a pretest of the examination process; detailed clinical inspection techniques by SCRF, Science Applications International Corporation (SAIC), and Air Force physicians and personnel; preprinted mark-sense examination forms; clinical quality assurance meetings to detect and correct problems; and blindness of exposure status at the examination. In addition, participant rapport-building techniques were added to boost participation in future followup studies, such as participant critique forms and recreational opportunities afforded to the accompanying family members.

CONDUCT OF EXAMINATIONS

All examinations were conducted at SCRF, La Jolla, California, from May 1985 to March 1986. Except for weeks with national holidays, two groups of participants, averaging about 32 per group, were examined weekly. Midway through the study, NORC recruiters noted that a number of participants refused the examination because of weekday business commitments or because of single-parent responsibilities. Consequently, two special weekend examinations were arranged late in the examination cycle, and many of the former refusals were then able to attend. The examination was identical to the regular 2 1/2-day process, except that it was compressed into 2 days by reducing the number of participants in a group.

The logistics effort required in contacting, transporting, and examining 2,309 study members was formidable. Preexamination contacts consisted of the telephone health survey, telephone recruitment to the examination if necessary, and calls by either the NORC scheduling specialists or by the travel agent to arrange transportation and determine whether special requirements existed (e.g., wheelchair assistance, weekend examination schedule). Once scheduling was reasonably firm, the SAIC logistics coordinator sent each participant a detailed information package outlining dietary requirements, inbriefing schedules, important telephone numbers, a request for medical records, and local maps designating examination-site eating and recreational facilities.

TABLE 4-1.

Elements of the Followup Physical Examination

Elements	Remarks
General Physical Examination	Internist
Neurological Examination	Neurologist
Dermatological Examination	Dermatologist
Electrocardiogram	Resting, 4-Hour Fasting and Nicotine Abstinence
Doppler Peripheral Arterial Blood Flow Studies	4-Hour Nicotine Abstinence
Chest X Ray	
Immunological Studies	50% Random Sample
Skin Test Studies	75% Sample
Psychological Evaluation: Minnesota Multiphasic Personality Inventory (MMPI) Cornell Medical Index Halstead-Reitan Battery	
Patient Outbriefing and Discussion of Individual Results	Medical Diagnostician, Internist, and Ph.D. Psychologist

TABLE 4-2.

Laboratory Test Procedures of the Followup Physical Examination

Clinical Laboratory	
Fasting Glucose	2-Hour Postprandial Glucose
Blood Urea Nitrogen (BUN)	Creative Phosphokinase (CPK)
Cholesterol	Total Bilirubin
HDL Cholesterol	Direct Bilirubin
Triglyceride	Total Protein
Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Protein Electrophoresis
Serum Glutamic-Pyruvic Transaminase (SGPT)	Routine Urinalysis
Gamma-Glutamyl Transpeptidase (GGTP)	T_3 % Uptake
Alkaline Phosphatase	T_4
Lactic Dehydrogenase (LDH)	Testosterone
Thyroid Stimulating Hormone (TSH)	Hepatitis B Surface Antigen
Initial Cortisol	Hepatitis B Surface Antibody
2-Hour Cortisol	Follicle Stimulating Hormone (FSH)
Prothrombin Time	Rapid Plasma Reagin (RPR)
Quantitative Immunoglobulins	Porphyrins (Mayo Clinic)
Complete Blood Count (CBC)	Sedimentation Rate
Leuteinizing Hormone (LH)	

Immunological Laboratory
Cell Surface (Phenotype) Analyses
Lymphocyte Mitogen Stimulation Assays
Mixed Lymphocyte Culture (MLC)
Natural Killer Cell Assay by Specific Cellular Cytotoxicity Using K-562 Target Cells
Natural Killer Cell Assay (Using Interferon) by Specific Cellular Cytotoxicity Using K-562 Target Cells

The logistical flow of the entire examination process was complex. Figures 4-1 and 4-2 outline participant flow for the first 2 examination days. As depicted in these figures, each group of participants (generally containing equal numbers of Ranch Hands and Comparisons) was transported early in the morning to SCRF on the first 2 days in a fasting state; tobacco, alcohol, and coffee abstinence were also required. Following initial inbriefing and blood draw on the first day, each participant was randomly assigned to the examination group or to the psychological testing group. On the second day, these groups were reversed. After randomization, each member was given an individualized 3-day schedule outlining his medical, interviewing, and laboratory appointments. The schedule carefully noted the specific required periods of fasting and tobacco abstinence (see Figures 4-1 and 4-2 for generalized periods in relation to ECG and Doppler testing). Each individual was reminded of the fact that all aspects of the examination were strictly voluntary, and that refusals would be honored without question. Both general and specific consent forms (e.g., skin biopsy), approved by the Air Force, were explained in detail.

In contrast to the Baseline examination, great reliance was placed upon each individual to find the appropriate clinic area at his scheduled time. This approach had great appeal to this self-reliant population as evidenced by critique feedback. Throughout the examination day, generous time was provided for waiting-room activities, i.e., renewal of past friendships, discussions of the Vietnam War, consumption of refreshments when permitted, and completion of paperwork. Day 3 of the examination was largely spent in finishing up the specialty examinations and receiving the outbriefings from a psychologist and medical diagnostician. Only upon completion of these important debriefings were the participants paid their stipend, reimbursed for travel expenses, and transported to the airport.

As noted previously, the SCRF clinical team was hand-picked for participation in this project. In total, 15 board-certified physicians in internal medicine, neurology, and dermatology participated in the general, specialty, and diagnostic examination. To reduce observer variability, turnover in the clinical or paramedical staffs was minimized during the 9 months of examinations. One SCRF physician served as the Project Medical Director, responsible for the scheduling, conduct, and quality control of the examinations. All examining physicians were introduced to the mark-sense examination forms during the pretest examination. The layout of the form was designed to parallel the flow of the clinical examination so as to minimize recording errors. Because data transcription was not permitted, each physician was responsible for filling in the bubbled form. To a large extent, these mark-sense forms and subsequent quality control were the primary reason for a remarkably clean data set. Two examples of the mark-sense forms are presented as Figures 4-3 and 4-4; a complete set of forms is provided in Appendix C.

For the first followup, the special testing included Doppler tests, delayed hypersensitivity skin tests, and immunological tests. Doppler measurements were obtained on all participants by highly experienced technicians; results were recorded and Polaroid photographs were taken of representative oscilloscope displays. As previously noted, considerable emphasis was placed upon tobacco abstinence prior to Doppler evaluations. Skin tests for four antigens were administered in a standardized manner: Candida (1:1,000 weight/volume, 0.1 ml intradermal), mumps (2 complement-fixing units), Trichophyton (1:1,000 weight/volume, 0.1 ml intradermal), and

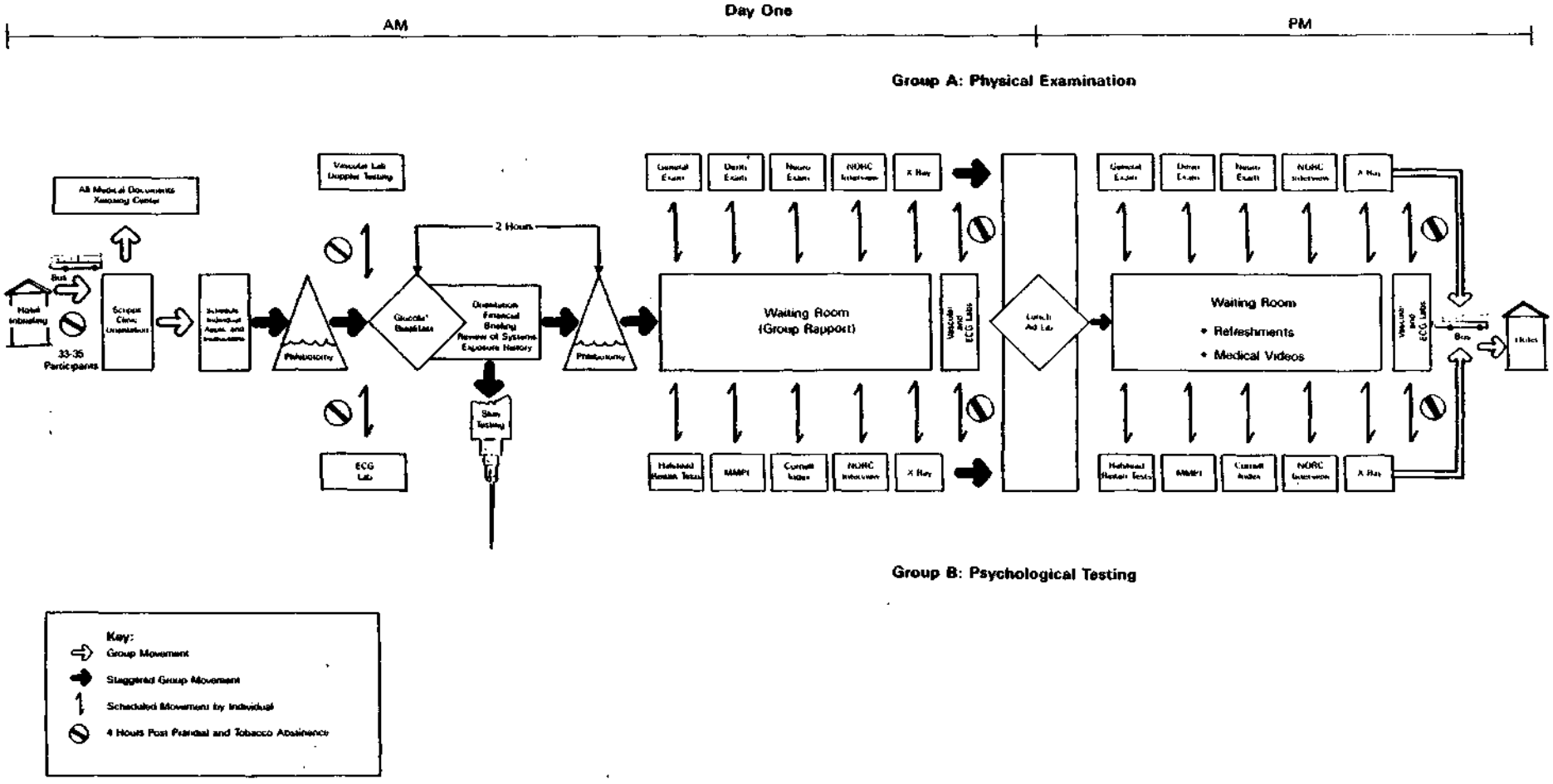

Figure 4-1.
Flow Diagram of Day One Followup Interview and Physical Examination

CHAPTER 5

STUDY SELECTION AND PARTICIPATION BIAS

INTRODUCTION AND BASELINE SUMMARY

The Protocol

During the design phase, the authors of the Protocol anticipated that loss to followup would pose the greatest threat to the validity of the study. In particular, they expected differential compliance with relatively more Ranch Hands self-selecting themselves into the study than Comparisons and with health differences of unknown character between noncompliant Ranch Hands and noncompliant Comparisons. As a partial correction, the study design specified that noncompliant Comparisons would be replaced by Comparisons having the same values of the matching variables and the same health perception. In this way, the replacement Comparisons would serve as surrogates for those Comparisons who refused to participate. This, in turn, would tend to reduce the bias due to noncompliance in the Comparison group and would have the added advantage of maintaining this group's sample size.

The Comparison in each randomized matched set who happened to be first asked to participate in the Baseline questionnaire and physical examination was identified as the Original Comparison for his respective Ranch Hand (in accordance with the Protocol). If the Original Comparison was noncompliant, that is, he refused to take the Baseline questionnaire or physical examination, his replacement was called a replacement Comparison. Replacement Comparisons were so distinguished to satisfy the Protocol requirement that they be contrasted with the noncompliant Comparisons, also called refusals, they replaced. No corresponding replacement strategy for the Ranch Hands was possible since all Ranch Hands had been identified and invited to participate.

The Protocol further specified that the replacements would be statistically compared with the noncompliant Original Comparisons to determine the extent to which the replacement strategy was being realized. The statistical contrast of replacements and refusals was to be based on responses to a noncompliance telephone questionnaire administered to refusals and to their potential replacements. This questionnaire assessed self-perception of health, days lost from work due to illness, and medication use, and was to serve as the basis for the health matching called for in the Protocol. Although the Protocol was not explicit on this point, it implied that the decision to include or exclude the replacements from the study would be based only on this contrast.

The Baseline Replacement Operation

The health-matching questions (identical to the noncompliance questionnaire) were, in fact, not administered to any potential replacement

Comparison before selection at Baseline, although questions regarding self-perception of health, medication use, and work loss were asked as part of the Baseline questionnaire after entry into the study. The noncompliance telephone questionnaire was offered to noncompliant study participants, but only 79 completed the telephone questionnaire, and of these only 57 were actually replaced. Replacements were, therefore, not health matched to refusals at Baseline. Rather, they were matched only on the basic matching variables: date of birth, race, and occupation. The statistical contrast of refusals and their replacements was not performed at Baseline.

During the scheduling operation at Baseline, two untoward events occurred that led to the identification of two additional categories of Comparisons, shifted Comparisons and Air Force-interviewed replacements. First, 212 of the Original Comparisons were discovered to be ineligible for participation in the study due to errors in the data base regarding their unit of assignment in Southeast Asia. These men had not served in Southeast Asia but, due to a duplication of codes, were mistakenly included in the Comparison population. They were deleted from the study.

This resulted in another Comparison in each previously randomized match set being first asked to participate in the study. These new Original Comparisons were figuratively called "shifted" Comparisons, labeled S in the Baseline Report, to describe the effective movement of these Comparisons in each matched set to fill the space left by the removed ineligible Original Comparison. The eligible Original Comparisons were labeled O in the Baseline report. Shifted Comparisons are more accurately referred to here as shifted Original Comparisons to emphasize that they are not replacement Comparisons and that they are the legitimate Original Comparisons for their respective Ranch Hands. Shifted Original Comparisons are not replacement Comparisons because their invitation to participate in the study was not the result of a previous refusal of another Comparison in their respective matched sets. Shifted Original Comparisons were identified to reflect concern that the process by which Comparisons were determined ineligible may not have distributed ineligible Comparisons uniformly.

Second, 30 replacement Comparisons were interviewed by Air Force staff rather than by the contractor. These replacements were labeled A. All other replacement Comparisons, labeled R, were simply called "replacements."

The removal of ineligible Comparisons from the study caused a pause in the scheduling operation that delayed the scheduling of the shifted Original and replacement Comparisons relative to that of the Original Comparisons. This scheduling delay is apparent in Figures V-3 and V-4 in the Baseline Report. Some study investigators speculated that this scheduling slip might cause shifted Original Comparisons and replacement Comparisons to self-select differently from Original Comparisons. Statistical analyses in Chapter V of the Baseline Report and further unpublished analyses following the release of the Baseline Report investigated the effect of this scheduling problem.

The Baseline Selection Bias Analyses

Since replacements were not health matched at Baseline to their corresponding noncompliant Comparisons and since differential scheduling opportunity may have created self-selection biases, statistical contrasts of the various Comparison groups were done at Baseline. In particular, the Comparisons labeled O, S, R, and A were contrasted on the basis of self-perception of health, medication use, work loss, and five clinical variables.

The results of these analyses suggested to some investigators that shifted Original Comparisons were not statistically distinguishable from Original Comparisons and that shifted Original Comparisons were not statistically different from replacements, but that replacement Comparisons appeared to be statistically different from Original Comparisons. The 30 Air Force-interviewed replacement Comparisons were not statistically distinguishable from other replacement Comparisons and were not investigated further as a group. Since opinions differed among Air Force principal investigators and statisticians, a management decision was reached to use only the Original Comparisons in the primary analyses and to contrast Ranch Hands with all Comparisons in the appendix of the Baseline Report. The reader is referred to Chapter V of the Baseline Report for additional detail. In retrospect, the concern with statistical distinguishability between replacement Comparisons and Original Comparisons is difficult to justify, since the only valid question regarding the replacements is their similarity to the refusals whom they replaced.

The Baseline Compliance Bias Analyses

Telephone questionnaire data obtained from the 57 noncompliant Comparisons, who were replaced, were not analyzed in the Baseline Report. Instead, compliance bias was analyzed by contrasting partially compliant with fully compliant participants, with adjustment for group (Ranch Hands, O, S, R, A). These analyses were based on data from the Baseline questionnaire regarding self-perception of health, medication use, work loss, anger, anxiety, erosion, depression, liver ailments, miscarriages, and acne. Results suggested that partially compliant participants were statistically different from fully compliant participants for some of these variables. Based on these results, calculations were presented to suggest that the noncompliance bias could produce an error in relative risk of 25 percent, either overestimating or underestimating the risk, and a spurious mean shift of up to 8 percent in either direction.

THE FIRST FOLLOWUP SCHEDULING AND REPLACEMENT OPERATION

Matching of replacements to noncompliant Comparisons on the basis of health status was initiated with the first followup scheduling operation. This was accomplished by administering a short telephone questionnaire to all previously uncontacted Comparisons and then using their health status responses to select from among the Comparisons in a matched set the first one who was similar to the refusal regarding self-perception of health. In addition, NORC was required to schedule replacements within 5 working days of a confirmed refusal. These features were intended to correct the described Baseline scheduling deficiencies and to bring the study into Protocol compliance regarding health matching of replacements.

To further minimize the possibility of scheduling bias, the entire study population was partitioned into 79 groups; these groups were then randomly scheduled for an examination time. In this way, no single group would be favored a priori for a certain scheduling period. The groupings, consisting of approximately 32 participants, corresponded to the examination groups established at Baseline. Group integrity was maintained to enhance study compliance and comradery. Study participants were given the option to remain with their group or to reschedule their examination at a time more convenient to them.

FIRST FOLLOWUP COMPLIANCE

Eighty-five percent (1,016/1,191) of the Ranch Hands and 81 percent (955/1,176) of the Original Comparisons participated in the first followup examination and questionnaire process. Of 288 replacements, 267, or 93 percent, chose to attend the first followup examination; additionally, 71 new replacements participated in the followup, yielding a total sample size of 338 replacements at followup. These counts and others are summarized in Table 5-1. In Table 5-1 and subsequently in this report, the shifted Original Comparisons were combined with the Original Comparisons, and the Air Force replacements were combined with the replacement Comparisons.

TABLE 5-1.

Baseline Versus First Followup Sample Sizes

	Group		
		Comparison	
Participation	Ranch Hand	Original	Replacement
Baseline Only	74	64	21
Baseline and Followup	971	872	267
Followup Only	45	83	71

Although fully compliant at Baseline, 74 Ranch Hands, 64 Original Comparisons, and 21 replacement Comparisons chose not to participate in the first followup examination. In the interim, 10 of the 74 Ranch Hands and 16 of the 85 Comparisons died. An additional 5 of the 74 Ranch Hands and 14 of the 85 Comparisons were unlocatable during the scheduling operation. There were 56 of 59 remaining Ranch Hands and 50 of 55 remaining Comparisons who refused to participate in the first followup, although they were alive and locatable during scheduling, and responded to the noncompliance telephone questionnaire, giving their reported health status and reason for nonparticipation. The 3 remaining Ranch Hands and 5 Comparisons refused to participate in the telephone survey. Reasons for nonparticipation given in the telephone survey are summarized in Table 5-2. The totals in Table 5-2 do not correspond to Table 5-1 because some participants gave more than one reason for nonparticipation.

Of the 56 living locatable Ranch Hands and the 50 Comparisons who took the noncompliance telephone questionnaire, only 35 Ranch Hands and 42 Comparisons responded to the question regarding health status. The reported health status of these 77 nonparticipants is summarized in Table 5-3.

TABLE 5-2.

Reasons for Nonparticipation in the First Followup of 56 Ranch Hands and 50 Comparisons Who Were Fully Compliant at Baseline*

Reason	Group			
	Ranch Hand		Comparison	
	Number	Percent	Number	Percent
Fear of Physical	0	0	2	4
Job Commitment	13	17	9	16
Dissatisfaction with USAF	10	13	9	16
No Time or Interest	7	9	6	11
Travel Distance, Family	13	17	12	21
Confidentiality	0	0	1	2
Health Reasons	8	11	3	5
Passive Refusal	11	15	6	11
Dissatisfaction with Baseline	5	7	2	4
Financial Hardship	3	4	0	0
Other	5	7	7	12
Total	75		57	

*Some participants gave more than one reason for nonparticipation.

TABLE 5-3.

Reported Health Status of 35 Ranch Hands and 42 Comparisons Fully Compliant at Baseline and Noncompliant at First Followup

Reported Health Status	Group			
	Ranch Hand		Comparison	
	Number	Percent	Number	Percent
Excellent	5	14	10	24
Good	22	63	22	52
Fair	6	17	8	19
Poor	2	6	2	5
Total	35		42	

p=0.72

Among the individuals responding to the health status question, there was no statistically significant difference between noncompliant Ranch Hands and Comparisons regarding reported health (p=0.72).

Further detail regarding the 45 Ranch Hands, 83 Originals, and 71 replacements newly examined at followup is shown in Table 5-4, which gives the Baseline status of these participants. Taking the questionnaire but not the physical examination at Baseline were 39 of the 45 Ranch Hands newly examined at followup. Five of the 45 Ranch Hands who were identified too late to be invited at Baseline were simply described as having had "no action" taken.

TABLE 5-4.

Baseline Status of Newly Examined Participants

	Group		
		Comparisons	
Baseline Status	Ranch Hand	Original	Replacement
Interview Only, Refused Physical Examination	39	61	32
No Interview, No Physical Examination	0	10	11
Unlocatable	0	1	3
No Action	5	11	16
Proxy	1	0	0
New to Study	0	0	9
Total	45	83	71

Of the 71 newly examined replacements, 43 (32+11) were either partially compliant at Baseline or were at least contacted at Baseline and, therefore, identified as replacements, although not health matched to a noncompliant Comparison. The remaining 28 newly examined replacements were not previously contacted. Of these, 14 were health-matched replacements and 2 were replacements added to the study in August 1985 after completion of the Baseline physical examination. Thus, of the 71 replacements who took the physical examination for the first time at followup, only 14 were new health-matched replacements. All 71 replacements may be regarded as new to the study, even though 43 had been previously contacted at Baseline and knew that they were potential study participants. The 28 replacements who had not been previously contacted may be regarded as new in a more restrictive sense since they did not know of their potential involvement in this study before they were recruited for the first followup examination. This set of 71 replacement Comparisons and the subset of 28 are distinguished from each other using

the unrestricted and restricted definitions of "new" to provide data regarding changes in replacement self-selection, an issue explored later in this chapter.

FACTORS KNOWN OR SUSPECTED TO INFLUENCE STUDY PARTICIPATION

A multitude of factors may be considered to influence self-selection. These may be broadly classified as health, logistic, operational, publicity, or demographic factors. The Baseline Report contains a list of specific factors within each of these categories. For example, health factors are thought to include self-perception of health as well as demonstrable health indicators, such as medication use and work days lost due to illness or injury. Logistic factors are thought to include distance to the examination site, reluctance to spend time away from family or job, income, and occupation. Demographic factors might include flying status, age, race, or military duty status (active, retired, separated). Operational factors include any aspect of study operation that may cause differential compliance, such as differential treatment of participants during scheduling, physical examination, interview, or debriefing. Publicity factors have to do with national attitudes and media presentations regarding the Agent Orange issue, the Vietnam war, veteran health care, or health care in general. Additionally, these considerations may affect people differently and, in particular, may influence Ranch Hands differently than Comparisons.

The decision to volunteer for this study is admittedly complex, making statistical assessment of compliance bias difficult and necessarily crude in that many of the factors contributing to self-selection cannot be measured directly. Instead, compliance bias was investigated at first followup, as in the Baseline Report. Specifically, it was investigated with respect to self-perception of health, medication use, daily aspirin use, work days lost due to illness or injury, and income in comparing partially compliant with fully compliant participants. In other selection bias assessments, such as statistical contrasts of Original and shifted Original Comparisons, these same factors and 26 variables taken from the physical examination and psychometric testing were analyzed.

THE TELEPHONE SURVEY

In April 1985, all previously uncontacted living Comparisons were identified for telephone contact to assess their current health. This health status information was necessary for the matching of replacements to noncompliant Comparisons. From a total of 9,982 available Comparisons, 7,963 were included in the telephone survey. The 2,019 nonselected Comparisons included 488 deceased, as of 1 August 1985, and 1,531 who had been previously contacted. The group of 1,531 previously contacted Comparisons comprised all Comparisons who were fully compliant, partially compliant, or noncompliant at Baseline.

The survey questionnaire is shown in Appendix D. In brief, it queried the respondent regarding self-perception of health (excellent, good, fair, poor), current prescribed medication use (yes, no), work days lost due to illness or injury, special health care needs (wheelchair, nurse, or other special equipment), and income (less than $20,000, $20,000 to $40,000, or more than $40,000). If the respondent indicated that he was taking

prescribed medication, he was asked to identify the illness for which the medication was prescribed. If work days were lost due to illness or injury, the respondent was asked to identify the causing illness or injury. If special health care or equipment was needed, he was asked to specify the illness or condition requiring the special care. He was further asked to distinguish conditions requiring special care from those that were previously identified in response to the medication and days lost from work questions. The telephone interview was accomplished via CATI.

Of the 7,963 cases fielded, 7,411 telephone surveys were actually completed. The nature of the 552 noncompletions is summarized in Table 5-5.

TABLE 5-5.

Summary of Reasons for Noncompleted Telephone Interviews

Reason	Number	Percent of 7,963
Deceased	26	0.3
Active Refusal	93	1.2
Passive Refusal	242	3.0
Unlocatable	190	2.4
Ineligible	1	0.0
Total	552	6.9

Several questionnaires that could not be administered by telephone were accomplished by mail; these numbered 540 out of the 7,411 completed. Summaries of the responses to each of the five questions are shown in Table 5-6.

Of the 1,271 respondents who reported that they had lost work days due to illness or injury, 550 (43%) lost 1 to 5 days, 197 (15%) lost between 6 and 10 days, and 524 (41%) lost more than 10 days. The maximum number of days reported lost was 965. The 56 respondents who reported more than 180 days lost misinterpreted the question; it referred only to the past 6 months.

The telephone interviewer reported whether the respondent was friendly, cooperative but not interested, impatient, or hostile. The association between the interviewer's remark and the self-reported health of the respondent was investigated. The results are displayed in Table 5-7. The association between the interviewer's remark and reported health status is statistically significant ($p=0.02$), with hostile repondents reporting poorer health than friendly, cooperative, or impatient respondents.

Other analyses of these data, not shown here, demonstrated significant associations between health perception and income ($p=0.001$), rank ($p=0.001$), age ($p=0.001$), medication use ($p=0.001$), and need for special health care ($p=0.001$). Positive health perception increased with income and rank and

TABLE 5-6.

Summary of Results to the Telephone Questionnaire

Self-Assessment of Health Compared to Others Same Age

Response	Number	Percent
Excellent	2,882	38.89
Good	3,306	44.61
Fair	972	13.11
Poor	245	3.31
Do Not Know	3	0.04
Missing	3	0.04
Total	7,411	100.00

Taking Medication for Current Illness

Response	Number	Percent
Yes	2,129	28.73
No	5,277	71.20
Refused	1	0.01
Missing	4	0.05
Total	7,411	100.00

Illness or Injury Absence From Job During Last 6 Months

Response	Number	Percent
Yes	1,271	17.15
No	6,135	82.78
Refused	3	0.04
Missing	2	0.03
Total	7,411	100.00

TABLE 5-6. (continued)

Summary of Results to the Telephone Questionnaire

Need Assistance in Daily Activities

Response	Number	Percent
Yes	114	1.54
No	7,291	98.38
Refused	4	0.05
Missing	2	0.03
Total	7,411	100.00

Earned Income From Any Job During 1984

Response	Number	Percent
Yes	6,636	89.54
No	755	10.19
Refused	17	0.23
Missing	3	0.04
Total	7,411	100.00

Income Level

Response	Number	Percent
Less than $20,000	2,015	27.19
$20,000-$40,000	3,034	40.94
More than $40,000	1,411	19.04
Not Applicable	774	10.44
Refused	161	2.17
Do Not Know	9	0.12
Missing	7	0.10
Total	7,411	100.00

TABLE 5-7.

Contrast of Interviewer's Remark from Telephone Interviews and Reported Health Status

Remark	Reported Health Status									
	Excellent		Good		Fair		Poor		Total	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Friendly	2,209	39	2,476	44	730	13	191	3	5,606	76
Cooperative	622	38	755	46	229	14	44	3	1,650	22
Impatient	42	40	48	45	10	9	6	6	106	1
Hostile	9	21	27	63	3	7	4	9	43	0
Total	2,882	39	3,306	45	972	13	245	3	7,405	

p=0.02

decreased with age, medication use, and special health care. Further, there was no significant association between health perception and the duration of the telephone interview (p=0.17) or the time of day of the interview (p=0.98). There was no significant health-by-duration-by-time of day interaction (p=0.77).

These data were also used to assess the self-reported health of 773 Original Comparisons (excluding shifted Original Comparisons) fully compliant at Baseline relative to the reported health of the 7,411 previously uncontacted Comparisons who completed the telephone survey. The self-reported health status of the Original Comparisons from the Baseline questionnaire was contrasted with that of the previously uncontacted Comparisons on a three-category scale (excellent, good, fair/poor) with an adjustment for date of birth (born during or before 1942, born after 1942). The results are displayed in Table 5-8. Previously uncontacted Comparisons who completed the survey are indicated by T (telephone); Original Comparisons are labeled O. Data are missing for 12 Original Comparisons and 16 telephone-surveyed Comparisons.

There was no statistically significant difference between these groups regarding health perception after adjustment for age (p=0.14), and this equivalence did not change with age (p=0.80). Additionally, there was a statistically significant age effect (p=0.001), as expected. These results suggested that the Original Comparisons were representative of the entire Comparison cohort with respect to health perception.

TABLE 5-8.

Self-Reported Health of Previously Uncontacted Comparisons, in 1986, Versus Self-Reported Health Status of Original Comparisons at Baseline

Age	Group*	Health Perception: Excellent Number	Excellent Percent	Good Number	Good Percent	Fair/Poor Number	Fair/Poor Percent	Total
Born >1942	T	1,847	39	2,003	43	837	18	4,687
	0	203	39	239	46	83	16	525
Born ≤1942	T	1,034	38	1,298	48	376	14	2,708
	0	91	39	120	51	25	11	236

*T = previously uncontacted Comparisons
0 = Original Comparisons.

REPLACEMENT COMPARISONS VERSUS THE NONCOMPLIANT COMPARISONS THEY REPLACED

Baseline Replacement

These analyses are refinements of the analyses in Chapter V of the Baseline Report. Of 288 Comparisons replaced at Baseline, only 57 responded to the short noncompliance telephone questionnaire shown in the appendix. These 57 comprised 38 Original Comparisons and 19 replacements. As in the followup telephone survey, the short noncompliance telephone questionnaire queried respondents on health status, work days lost due to illness, medication use, and income level. In accordance with the Protocol, replacements were statistically contrasted with the noncompliant Comparisons they replaced based on their reported health status (excellent, good, fair, poor), medication use (yes, no), and income level (less than $20,000, $20,000 to $40,000, more than $40,000). This contrast, with adjustment for group membership (Original, replacement) of the noncompliant Comparison, is shown in Table 5-9.

There was no significant difference between the reported health patterns in the upper and lower panels of Table 5-9. When these two tables were merged, no statistically significant difference was found between the health status of noncompliant Comparisons and their non-health-matched replacements ($p=0.99$). It is noteworthy that 53 percent of Original and replacement noncompliant Comparisons were matched, by chance, perfectly to their replacements on the basis of reported health status. Only 7 percent (4/57) were mismatched by two categories and one replacement was mismatched by three categories.

These same groups were contrasted on medication use; the results are shown in Table 5-10.

TABLE 5-9.

Noncompliant Original Comparisons and Replacement Comparisons Versus Their Baseline Replacements: Reported Health Status at Baseline

Group	Health Status	Health Status of Replacements: Excellent	Good	Fair	Poor	Total
Noncompliant Original Comparison	Excellent	13	4	2	0	19
	Good	9	7	0	0	16
	Fair	1	1	0	0	2
	Poor	1	0	0	0	1
Total		24	12	2	0	38
Noncompliant Replacement	Excellent	7	5	0	0	12
	Good	3	3	0	0	6
	Fair	1	0	0	0	1
	Poor	0	0	0	0	0
Total		11	8	0	0	19

TABLE 5-10.

Noncompliant Original Comparisons and Replacement Comparisons Versus Their Baseline Replacements: Medication Use at Baseline

Group	Medication Use	Medication Use of Replacements: Yes	No	Total
Noncompliant Original Comparison	Yes	0	4	4
	No	3	31	34
Total		3	35	38
Noncompliant Replacement	Yes	0	1	1
	No	1	17	18
Total		1	18	19

Due to sparseness these data were not analyzed. It is interesting to note, however, that there was 82 percent agreement in the upper panel of Table 5-9 (31/38) and 89 percent in the lower panel (17/19), with 84 percent agreement in the combined table (48/57), close to expected within group percentages of 83 and 90 percent, respectively, due purely to chance.

Work loss was not analyzed due to slight differences between the way the work loss question was worded in the noncompliance telephone and telephone survey questionnaires.

The contrast regarding income level is shown in Table 5-11.

TABLE 5-11.

Noncompliant Original Comparisons and Replacement Comparisons Versus Their Baseline Replacements: Income at Baseline

Group	Income Level	Income Level of Replacements (in thousands) <$20	$20-$40	>$40	Total
Noncompliant Original Comparison	<$20	1	3	0	4
	$20-$40	6	6	3	15
	>$40	0	7	6	13
Total		7	16	9	32*
Noncompliant Replacement	<$20	0	0	2	2
	$20-$40	1	7	0	8
	>$40	1	3	5	9
Total		2	10	7	19

*Six noncompliant Original Comparisons were unwilling to respond.

The patterns of income matching in the first and second panels of Table 5-11 were not significantly different ($p>0.10$). In the combined table, replacements reported significantly lower income than the Comparisons they replaced ($p<0.05$) although 49 percent (25/51) were perfectly categorically matched.

These analyses suggested that the Baseline replacements were very similar to the noncompliant Comparisons they replaced regarding reported health status, medication use, and income. These analyses were also pertinent to the question of whether there was selection bias due to noncompliance in the Comparison group. The predominantly negative findings suggested that there was little or no Comparison selection bias. These

results suggested that the upper-bound bias calculations reported in Chapter V of the Baseline Report are overestimates of reality. However, lack of clinical data for the noncompliant Comparisons precluded refining those Baseline bias calculations at this time. Accordingly, the Baseline selection bias calculations may be viewed as crude bounds to an unknown bias that must await future data for proper recalculation.

First Followup Replacement

Replacements were matched to noncompliant Comparisons at first followup on the basis of the matching variables--date of birth, race, and occupation--and self-reported health status (excellent, good, fair, poor), as recorded in the telephone survey. This was accomplished by recording the self-reported health status of the noncompliant Comparison during the attempt to schedule and matching that status against those of the other Comparisons in the same matched set. A Comparison in a matched set was considered to replace a noncompliant Comparison if he had the same health status as that recorded for the noncompliant Comparison during the attempt to schedule him. If no willing Comparison reporting the same health status could be found in the matched set, health status was dichotomized to excellent or good versus fair or poor. A willing Comparison with the same health status as the refusal on the dichotomized scale was then accepted as a replacement. If no willing Comparison could be found using the dichotomized scale, attempts to find a replacement were terminated.

During this process, 14 Comparisons were health matched to noncompliant Comparisons. The results are summarized in Table 5-12.

TABLE 5-12.

Health Status of Refusals and Their Matched Replacements

Replacement's Health	Refusal's Health				
	Excellent	Good	Fair	Poor	Total
Excellent	1	2	0	0	3
Good	5	6	0	0	11
Fair	0	0	0	0	0
Poor	0	0	0	0	0
Total	6	8	0	0	14

All refusals reported good or excellent health. This implied that bias due to noncompliance in the Comparison group could possibly bias the study away from finding an herbicide effect. The inclusion of health-matched replacements tended to correct for this by replacing healthy noncompliant Comparisons with healthy replacement Comparisons. The relatively small number of new health-matched replacements minimized the actual effect of this bias "correction," however.

SCHEDULING AT FIRST FOLLOWUP

The schedulers were required to find and schedule a willing health-matched replacement within 5 working days of a confirmed refusal to correct scheduling differences experienced at Baseline. This constraint proved impractical to implement since Comparisons would vacillate, forcing a series of repeated telephone calls. Rather than terminate the process at 5 days, as required by the contract, the schedulers continued their recruiting attempts, sometimes for several months. Hence, new health-matched replacements were brought into the study much later than other participants.

The percent completing the physical examination by calendar date is plotted in Figure 5-1 for all Ranch Hands, Original Comparisons, and all Comparisons.

The corresponding plot for Ranch Hands, Original Comparisons, old replacements, and the 28 restricted new replacement Comparisons is shown in Figure 5-2.

Additionally, schedulers experienced reticence and vacillation with other Comparisons being scheduled for the first time. In particular, as a group, the 71 unrestricted new replacement Comparisons were also scheduled later than other participants. Figure 5-3 shows the percent of Ranch Hands, Original Comparisons, "old" Comparisons, and the 71 unrestricted newly examined replacement Comparisons completing the physical examination by calendar date.

During the scheduling for the 1987 followup examination, schedulers will attempt to schedule health-matched replacements within 15 working days of a refusal.

NEW REPLACEMENTS VERSUS OLD REPLACEMENTS

Another statistical issue of concern is the homogeneity of the replacement Comparisons. The validity of the study might be compromised if, for example, newly admitted replacements had self-selected themselves into the study differently than previously admitted replacements. This kind of difference may occur due to changes in public opinion regarding the Agent Orange issue, the national political climate, changes in national opinion regarding health care, changes in the location of the examination site, or a combination of these and other factors. This issue was addressed by comparing new with old replacements on a variety of endpoints with adjustment for the matching variables. Blacks were deleted from the analyses.

Two separate series of analyses were performed, one for each of the two kinds of new replacements (unrestricted and restricted) defined earlier. First, unrestricted new replacements were identified as the 71 replacements who were examined for the first time at first followup, regardless of their compliance at Baseline. Second, analyses were restricted to the 28 replacements who were examined for the first time and who had never been contacted before the first followup; these were called restricted new Comparisons. In each of the two series of new replacement analyses, all replacements not satisfying the definition of "new" are included by referring to them as "old" replacements. All "old" replacements were at least contacted at Baseline and were fully compliant at first followup.

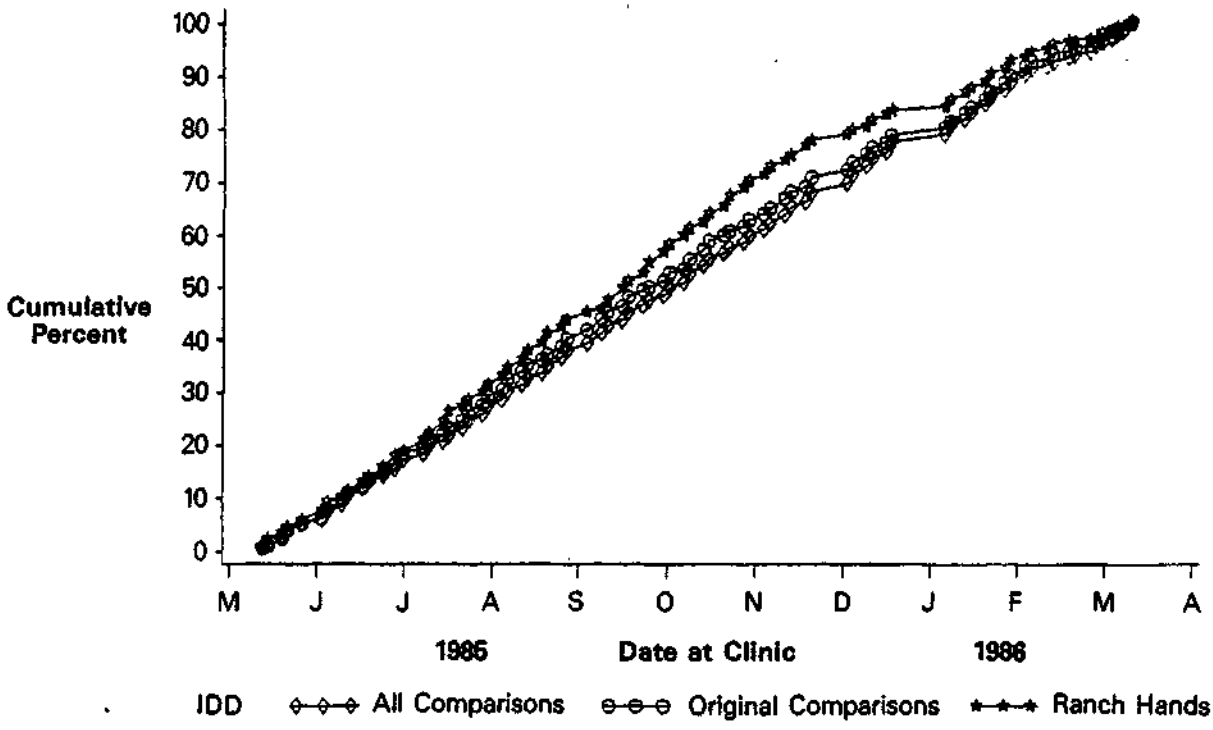

Figure 5-1.
Percent Completed Physical Examination by Calendar Date for All Comparisons

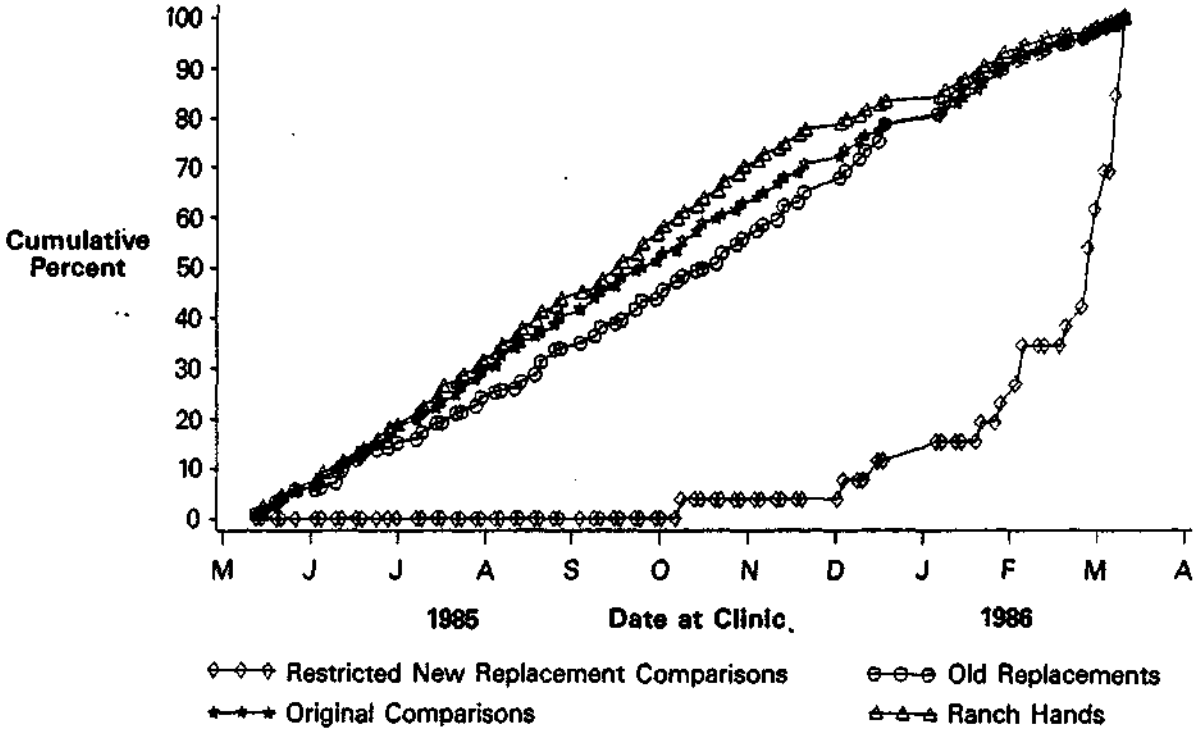

Figure 5-2.
Percent Completed Physical by Calendar Date

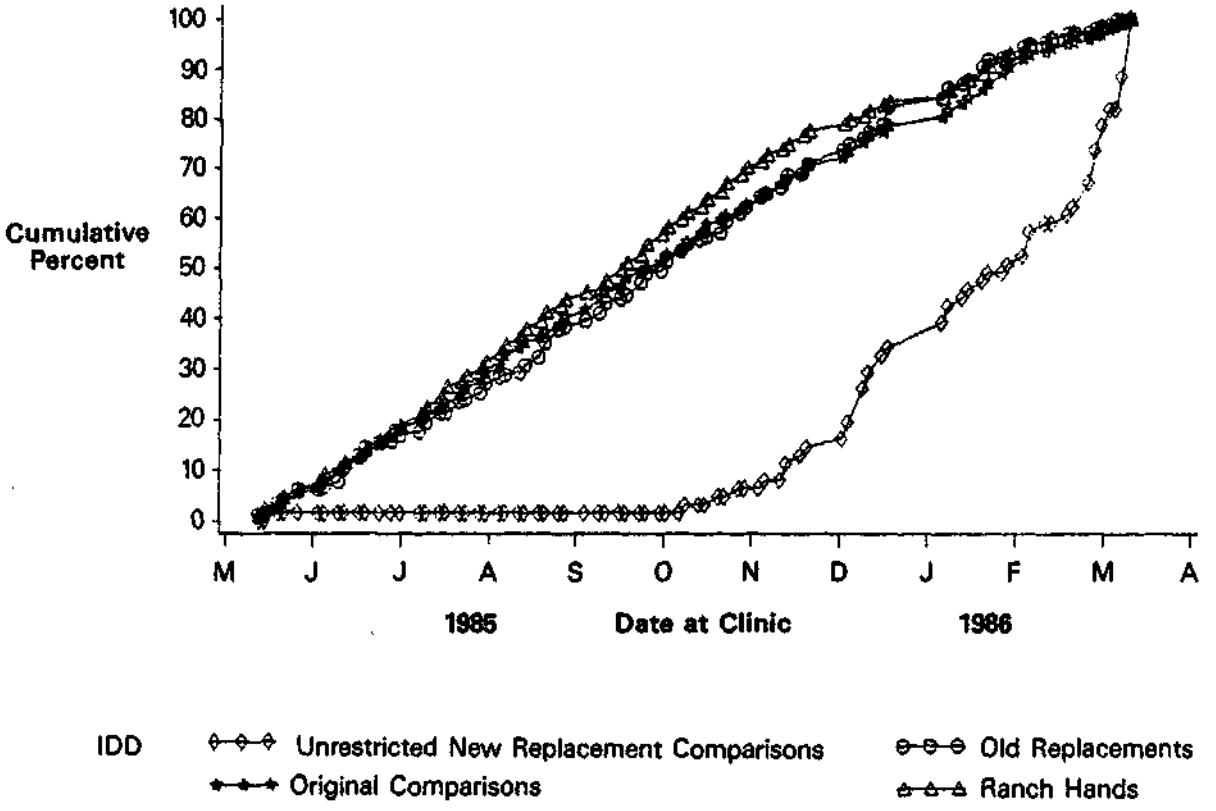

Figure 5-3.
Percent Completed Physical Examination by Calendar Date for Unrestricted New and Old Replacement Comparisons

In each of the two series of analyses, new and old replacement Comparisons were contrasted on health perception (excellent, good, fair, or poor), medication use (yes, no), work loss (yes, no), and daily use of aspirin (yes, no). Blacks were deleted from all analyses. New and old replacements were then contrasted on 20 clinical determinations from the first followup examination. Table 5-13 shows two cross-classifications of 313 nonblack replacements, from a total of 338 replacements fully compliant at first followup, by group (old, new) and reported health status.

In the unrestricted sense, the reported health status of new and old replacements differed significantly ($p=0.04$), with new replacements reporting more fair or poor health than old replacements. In the restricted sense, the difference between new and old replacements was statistically significant ($p=0.001$), with new replacements tending to declare themselves of fair or poor health more often than old replacements.

The same groups were contrasted on medication use; the results are shown in Table 5-14. The difference between old and new Comparisons under the unrestricted definition was not statistically significant (p=0.16) as regards medication use. The difference between old and new Comparisons under the restricted definition was, however, statistically significant (p=0.003). This difference was due to the higher reported medication use of the 26 non-black new replacements not previously contacted.

New and old replacements were contrasted on work loss due to illness; the results are shown in Table 5-15.

TABLE 5-13.

Reported Health Status of Nonblack New and Old Replacements, According to Two Definitions of "New"

	Unrestricted				Restricted			
	Old		New		Old		New	
Health	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Excellent	142	56	30	49	161	56	11	42
Good	91	36	20	33	103	36	8	31
Fair/Poor	19	8	11	18	23	8	7	27
Total	252		61		287		26	
	p=0.04				p=0.001			

TABLE 5-14.

Reported Medication Use of Nonblack New and Old Replacements, According to Two Definitions of "New"

	Unrestricted				Restricted			
	Old		New		Old		New	
Medication	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Yes	30	12	12	20	33	11	9	35
No	222	88	49	80	254	89	17	65
Total	252		61		287		26	
	p=0.16				p=0.003			

TABLE 5-15.

Reported Work Loss of Nonblack New and Old Replacements, According to Two Definitions of "New"

	Unrestricted				Restricted			
	Old		New		Old		New	
Work Loss	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Yes	47	19	12	20	54	19	5	19
No	205	81	49	80	233	81	21	81
Total	252		61		287		26	
	p=0.99				p=0.99			

The difference between new and old replacements regarding work loss under the unrestricted or restricted definition was not statistically significant (p=0.99 and p=0.99, respectively).

Results of a similar contrast on daily aspirin usage are shown in Table 5-16. The difference between new and old replacements regarding daily use of aspirin under the unrestricted or the restricted definition was not statistically significant (p=0.99 and p=0.75, respectively).

It is noteworthy that the differences for general health and medication use did not occur for work loss and daily aspirin usage, suggesting that some participants may have over-reported when asked less specific questions about their health.

New and old replacement Comparisons were also compared on 20 clinical and psychometric variables measured during the physical examination and psychological testing. These 20 variables are a subset from 26 selected from among an entire collection of nearly 200 endpoints in this study by requiring near statistical independence within and between organ systems. Variables selection was accomplished by screening the correlation matrices of variables as an entire set and separately within each organ system, including examining partial correlations between single variables and linear combinations of other variables within organ systems. Identified first were 10 variables with pairwise correlations less than 0.10 in absolute value. This was followed by identification of 16 additional variables with pairwise correlations between 0.10 and 0.20 in absolute value, making a total of 26 variables. These variable selection screens were accomplished on Baseline data for 1,154 nonblack fully compliant Comparisons subsequent to publication of the Baseline Report. The complete set of 26 dependent variables selected as

TABLE 5-16.

Reported Daily Aspirin Usage of Nonblack New and Old Replacements, According to Two Definitions of "New"

	Unrestricted				Restricted			
	Old		New		Old		New	
Aspirin Usage	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Yes	182	73	44	72	206	72	20	77
No	69	27	17	28	80	28	6	23
Total	251		61		286		26	
	p=0.99				p=0.75			

nearly statistically independent is shown in Table 5-17. The Baseline correlation matrix of these 26 variables as determined on the entire Comparison data set is shown in Table D-1 of Appendix D. It is recognized that relative statistical independence of these variables does not imply biological independence of these variables.

These 26 variables were intended to serve as the basis for statistical contrasts of Original Comparisons, shifted Original Comparisons, and replacement Comparisons in the decision regarding the inclusion of shifted Original Comparisons and replacement Comparisons in the primary analyses. Generically, the analyses first compared two groups on each of the 26 variables with adjustment for rank (officer, enlisted), age at Baseline (40 or under, over 40), occupation (officer flyer, officer nonflying, enlisted flyer, enlisted groundcrew), and race (Black, nonblack). Blacks were deleted from the analysis. The total number of significant differences on the first set of 10 dependent variables was used as the basis for a decision regarding group difference. These 10 analyses were assumed to be 10 independent repetitions of a Bernoulli trial with probability of 0.05 of success under the null hypothesis that there were no group differences for any of the 10 variables. The probability of observing three or more successes in 10 independent repetitions of a Bernoulli trial, with probability of 0.05 of success, is 0.012. The entire set of 26 analyses was then assessed to test the hypothesis of group equality. The probability of 4 or more successes in 26 independent repetitions of a Bernoulli trial, with probability of 0.05 of success, is 0.039. These 2 critical values, both probabilities below 0.05, were used to assess the analyses on the 10 and on the 26 selected variables.

TABLE 5-17. Twenty-Six Dependent Variables Selected as Nearly Statistically Independent With the Use of Baseline Data

Variables Having Pairwise Absolute Correlations Less Than 0.10

Total Bilirubin (TBILI)
Diastolic Blood Pressure (DBP)
White Blood Cell Count (WBC)
Skin Index (SKIN)
MMPI Depression Scale (MMPID)
Blood Urea Nitrogen (BUN)
Urine Specific Gravity (USG)
Pulse Index (PULSE)
Nerve Conduction Velocity Above the Elbow (NCVE)
Semen Count (SEMEN)

Variables Having Pairwise Absolute Correlations Greater Than 0.10 and Less Than 0.20

Red Blood Cell Count (RBC)
FEV1/FVC (PULM)
Glucose (GLUC)
Electrocardiogram (ECG)
Platelet Count (PLAT)
Full IQ (IQ)
Central Nervous System Index (CNS)
Nerve Conduction Velocity Above the Ankle (NCVA)
Cholesterol (CHOL)
Alkaline Phosphatase (ALKPHOS)
Coproporphyrins (COPRO)
Delta-Aminolevulinic Acid (ALA)
Thyroid T_4 (T4)
Testosterone (TEST)
Sedimentation Rate (SED)
Gamma-Glutamyl Transpeptidase (GGTP)

The statistical issue of how to account for the many interactions in the 26 separate analyses was not resolved during or since the first application of this method. Only the group main effect was regarded as the basis for determining whether a particular analysis was a success.

At first followup, only 20 of the 26 variables were measured. The six variables not measured were the two-nerve conduction velocities (NCVE, NCVA), semen count (SEMEN), FEV1/FVC (PULM), full IQ (IQ), and delta-aminolevulinic acid (ALA). New and old replacements were contrasted on each of the remaining 20 variables via the general linear model and log-linear model. The variables--skin index (SKIN), pulse index (PULSE), electrocardiogram (ECG), and central nervous system index (CNS)--were analyzed as dichotomous variables, with each being scored abnormal if any of its components were abnormal. All others were analyzed as continuous variables. The correlation matrix of the 20 variables, based on 1,210 nonblack Comparisons fully compliant at first followup, on first followup data is shown in Table D-2 of Appendix D.

The results of these analyses contrasting new versus old replacements with "new" following the unrestrictive definition and Blacks removed from the analyses are shown in Table 5-18. There were 61 nonblack new replacements and 251 nonblack old replacements. In some analyses, the dependent variable was transformed to better approximate normality. Unadjusted means are presented when there is a significant interaction involving group.

The probability of observing 2 or more successes in 8 independent repetitions of a Bernoulli trial, with probability of 0.05 of success, is 0.057. In view of the results for the first 8 dependent variables in Table 5-18, new and old replacements appeared to be statistically indistinguishable. The probability of observing 3 or more successes in 20 independent repetitions of a Bernoulli trial, with probability 0.05 of success, is 0.075; the probability of 4 or more is 0.016. Recognizing the slight correlations between the dependent variables in the lower panel of Table 5-18, and the results of the analyses, new and old replacements again appeared to be statistically indistinguishable.

The same analyses were conducted to contrast new and old replacement Comparisons, with "new" defined in the restrictive sense. The results are shown in Table 5-19, with the same notations as Table 5-18.

The same binominal critical values, 2 for the first panel and 4 for the entire set of 20 analyses, and the results shown in Table 5-18 indicated that there was no statistical difference between the 26 nonblack new replacements and the 287 nonblack old replacements.

The negative findings shown in Tables 5-18 and 5-19 suggested very strongly that there has been no change in the way replacements self-select for entry into this study.

ORIGINAL COMPARISONS VERSUS SHIFTED ORIGINAL COMPARISONS

The removal of ineligible Comparisons early in the Baseline scheduling operation resulted in the exclusion of approximately 18 percent of all Comparisons from the study. Since some of these ineligibles had been randomized as Original Comparisons, some previously randomized Comparisons were allocated to the positions vacated by the removed original Comparisons and, thus, were referred to as shifted Original Comparisons.

TABLE 5-18.

Summary Results of Unrestricted New Versus Old Nonblack Replacements Contrasted on 20 Variables

Variable (Transformation)	Replacement Group Means* (Percent Abnormal) Old	New	p-Value	Significant Interactions
Variables With Absolute Pairwise Correlations Less Than 0.10				
TBILI (LOG)	0.76	0.76	NS	
DBP (SQRT)	79.17	79.51	NS	
WBC (LOG)	7.06	7.13	NS	
SKIN	(54.0)	(49.2)	NS	
MMPID (LOG)	56.21	57.19	NS	
BUN (SQRT)	14.15	13.79	NS	
USG	1.014	1.014	NS	
PULSE	(16.7)	(11.5)		GRP*OCC, GRP*AGE
Variables With Absolute Pairwise Correlation Between 0.10 and 0.20				
RBC	5.00	5.00		GRP*OCC*AGE
GLUC (LOG)	109.31	101.33	NS	
ECG	(15.5)	(13.1)	NS	
PLAT (SQRT)	269.5	275.0	NS	
CNS	(2.8)	(5.0)	NS	
CHOL (SQRT)	212.7	208.8	NS	
ALKPHOS (LOG)	87.9	87.10		GRP*OCC
COPRO (SQRT)	116.9	122.6	0.03	
T4	7.51	7.94	NS	
TEST (SQRT)	601.4	605.3	NS	
SED (LOG)	4.17	4.93		GRP*OCC*AGE
GGTP (LOG)	31.06	29.77		GRP*AGE

*All means are expressed in original units.

NS: Not significant (p>0.05)
LOG: Analysis performed on logarithmic scale.
SQRT: Analysis performed on square root scale.

GRP: Group
OCC: Occupation
AGE: Birth year (Age)

TABLE 5-19.

Summary Results of Restricted New Versus Old
Nonblack Replacements Contrasted on 20 Variables

Variable (Transformation)	Replacement Group Means* (Percent Abnormal) Old	New	p-Value	Significant Interactions
Variables With Absolute Pairwise Correlations Less Than 0.10				
TBILI (LOG)	0.76	0.75	NS	
DBP (SQRT)	79.44	76.98	NS	
WBC (LOG)	7.01	7.91	NS	
SKIN	(52.3)	(61.5)	NS	
MMPID (LOG)	56.11	59.73	NS	
BUN (SQRT)	14.02	14.75	NS	
USG	1.014	1.013	NS	
PULSE	(15.3)	(19.2)	NS	
Dependent Variables With Absolute Pairwise Correlation Between 0.10 and 0.20				
RBC	5.01	4.90	NS	
GLUC (LOG)	108.8	95.86	0.007	
ECG	(14.3)	(23.1)	.	GRP*AGE
PLAT (SQRT)	270.5	271.56	NS	
CNS	(2.8)	(7.7)	NS	
CHOL (SQRT)	212.5	205.6	NS	
ALKPHOS (LOG)	87.75	87.72	NS	
COPRO (SQRT)	117.8	120.5	NS	
T4	7.56	8.00	NS	
TEST (SQRT)	601.2	612.6	NS	
SED (LOG)	4.15	6.37	0.03	
GGTP (LOG)	31.23	26.41	NS	

*All means are expressed in original units.

NS: Not significant (p>0.05).
LOG: Analysis performed on logarithmic scale.
SQRT: Analysis performed on square root scale.

Fully compliant Original and shifted Original Comparisons were compared in the Baseline Report with respect to reported health status, medication use, and work loss. Group differences for health status were significant ($p=0.001$) but were not so for medication use or for work loss; the shifted Original Comparisons tended to report themselves in poorer health than the Original Comparisons but were statistically equivalent to the Originals regarding medication use and work loss.

Fully compliant Original and shifted Original Comparisons were contrasted at first followup on reported health status, work loss, medication use, and daily use of aspirin. As in the Baseline Report, these analyses were done for only nonblack Comparisons.

The results of the contrast of Original and shifted Original Comparisons on reported health status are shown in Table 5-20. Here, health status is evaluated on a three-category scale (excellent, good, fair/poor).

The group difference between Original and shifted Original nonblack Comparisons regarding reported health status was not significant ($p=0.30$).

The results of the contrast of Original versus shifted Original Comparisons on medication use are shown in Table 5-21. The group difference between Original and shifted Original nonblack Comparisons regarding medication use was not significant ($p=0.68$).

The results of the contrast on work loss are shown in Table 5-22. The group difference between nonblack Original and shifted Original Comparisons regarding work loss was not significant ($p=0.82$).

The results of the contrast on daily aspirin usage are shown in Table 5-23. The group difference between Original and shifted Original nonblack Comparisons regarding daily aspirin usage was not significant ($p=0.98$).

Fully compliant Original and shifted Original nonblack Comparisons were also contrasted on each of the full set of 26 nearly uncorrelated variables shown in Table 5-17 on Baseline data. The results are shown in Table 5-24.

Sedimentation rate (SED) was analyzed as a categorical variable with values low (0-1), medium (2-3), and high (3-4). The percents of Original Comparisons within these categories were 35.8, 33.1, and 31.1 percent, respectively; the shifted Original Comparison percents were 30.8, 36.3, and 32.9, respectively. The probability of observing 3 or more successes in 10 independent repetitions of a Bernoulli trial, with a probability of 0.05 of success, is 0.0115. The probability of observing 2 or more is 0.0861. Based on these critical values and the results shown in the upper panel of Table 5-24, there appeared to be no statistical difference between Original Comparisons and shifted Original Comparisons.

The probability of observing 4 or more successes in 26 independent repetitions of a Bernoulli trial is 0.039. The probability of observing at most 2 successes in 26 independent repetitions of a Bernoulli trial, with probability 0.05 of success, is 0.86. Based on these critical values and the known slight correlation of the 16 dependent variables in the second panel of Table 5-19, these results suggested that Original and shifted Original Comparisons are not statistically distinguishable.

TABLE 5-20.

Reported Health Status of Fully Compliant Original and Shifted Original Nonblack Comparisons: First Followup

Reported Health	Original Comparison Group				Total	p-Value
	Original		Shifted Original			
	Number	Percent	Number	Percent		
Excellent	387	52	76	51	463	0.30
Good	307	41	68	45	375	
Fair/Poor	53	7	6	4	59	
Total	747		150		897	

TABLE 5-21.

Medication Use of Fully Compliant Original and Shifted Original Nonblack Comparisons: First Followup

Medication Use	Original Comparison Group				Total	p-Value
	Original		Shifted Original			
	Number	Percent	Number	Percent		
Yes	102	14	23	15	125	0.68
No	645	86	127	85	772	
Total	747		150		897	

TABLE 5-22.

Work Loss of Fully Compliant Original and Shifted Original Nonblack Comparisons: First Followup

	Original Comparison Group					
	Original		Shifted Original			
Work Loss	Number	Percent	Number	Percent	Total	p-Value
No	631	83	116	82	747	0.82
Yes	125	17	25	18	150	
Total	756		141		897	

TABLE 5-23.

Daily Aspirin Use of Fully Compliant Original and Shifted Original Nonblack Comparisons: First Followup

	Original Comparison Group					
	Original		Shifted Original			
Daily Aspirin Use	Number	Percent	Number	Percent	Total	p-Value
Yes	529	71	107	71	636	0.98
No	218	29	43	29	261	
Total	747		150		897	

TABLE 5-24.

Summary Results of Original Versus Shifted
Original Nonblack Comparisons on 26 Variables at Baseline

Variable (Transformation)	Original Comparison Group Means* (Percent Abnormal) Original	Shifted Original	p-Value	Significant Interactions
Variables With Absolute Pairwise Correlations Less Than 0.10				
TBILI	0.61	0.61		GRP*OCC*AGE
DBP	80.46	78.95	NS	
WBC	7.52	7.18	NS	
SKIN	(37.5)	(43.8)	NS	
MMPID	56.25	58.40	NS	
BUN	14.26	13.76	NS	
USG	1.0209	1.0205	NS	
PULSE	(10.7)	(8.9)	NS	
NCVE	56.26	55.88	NS	
SEMEN (LOG)	77.4	72.8	NS	
Variables With Absolute Pairwise Correlation Between 0.10 and 0.20				
RBC	5.20	5.18	NS	
PULM	0.80	0.81	NS	
GLUC (LOG)	97.4	94.5	NS	
ECG	(27.6)	(26.7)	NS	
PLAT	270.6	269.9	NS	
IQ	108.6	108.4	NS	
CNS	(23.7)	(31.5)	0.02	
NCVA	48.17	47.59	0.01	
CHOL	220.7	213.1	NS	
ALKPHOS	7.84	7.60	NS	
COPRO (LOG)	31.1	30.4	NS	
ALA	2,497.0	2,505.3	NS	
T4	8.42	8.35	NS	
TEST	634.6	634.3	NS	
SED	given in text		NS	
GGTP (LOG)	38.43	35.53	NS	

*All means are expressed in original units.

Taken together, the results displayed in Table 5-24 very strongly suggested that Original and shifted Original Comparisons did not differ statistically at Baseline.

These analyses were repeated on the 20 available variables at the first followup. The results are shown in Table 5-25.

The results in the first and second panels of Table 5-25 and the binomial critical values given above suggested that no statistical difference was present between the Original and shifted Original Comparisons.

A single multivariate linear regression analysis was done on the 20 dependent variables shown in Table 5-25; no significant interactions involving group (Original, shifted Original) were noted and the group effect was not significant ($p=0.28$). Taken together, these analyses strongly suggested that there was also no statistical difference between Original and shifted Original Comparisons at first followup.

PARTIALLY COMPLIANT VERSUS FULLY COMPLIANT PARTICIPANTS

Ideally, compliance bias should be assessed by comparing the health of noncompliant and fully compliant participants with adjustment for group (Ranch Hand, Comparison) and the matching variables. The only information available on the noncompliant participants, however, is their responses to the health status questions, if they were willing to answer them, during the telephone conversation in which they refused to participate in the study. Noncompliant Comparisons were contrasted with their Baseline replacements (see noncompliance telephone questionnaire data, Tables 5-9 to 5-12). In addition, as in the Baseline Report, selection bias was studied by contrasting partially compliant with fully compliant participants with adjustment for group (Ranch Hand, Comparison). Taking the Baseline questionnaire at followup but refusing to take the physical examination or followup questionnaire were 9 Ranch Hands and 30 Comparisons who were either nonlocatable or noncompliant at Baseline. These 39 men were the only partially compliant participants at first followup. Their Baseline compliance is summarized in Table 5-26.

One of these individuals, a Ranch Hand with no interview, no physical, and no telephone interview, was Black. The label "no action" indicates that these individuals were not contacted because the Baseline contract expired. Individuals labeled "new Comparisons" were added to the study after the Baseline examination but before start of the first followup.

Data from these 39 partially compliant participants were statistically compared with similar data from fully compliant participants with adjustment for group (Ranch Hand, Comparison). This is shown in Table 5-27. Endpoints evaluated were reported health, medication use, and work loss. These analyses are similar to those reported in Table V-15 of the Baseline Report. Reported health status was collapsed to two categories (excellent, good/fair/poor) due to sparse data. One Black participant, a Ranch Hand, was deleted from these analyses.

The health versus compliance association in these data was of borderline statistical significance ($p=0.08$), with partially compliant participants tending to report themselves in better health than fully compliant

TABLE 5-25.

Summary Results of Original Versus Shifted Original
Nonblack Comparisons on 20 Variables:
First Followup

Variable (Transformation)	Original Comparison Group Means* (Percent Abnormal) Original	Shifted Original	p-Value	Significant Interactions
Variables With Absolute Pairwise Correlations Less Than 0.10				
TBILI (LOG)	0.75	0.73		GRP*OCC*AGE
DBP (SQRT)	80.0	79.60	NS	
WBC (LOG)	6.88	6.92		GRP*AGE
SKIN	(49.7)	(42.1)	NS	
MMPID (LOG)	56.2	55.1	NS	
BUN (SQRT)	14.8	14.04	NS	
USG	1.015	1.015	NS	
PULSE	(16.7)	(16.4)	NS	
Variables With Absolute Pairwise Correlation Between 0.10 and 0.20				
RBC	4.97	4.95	NS	
GLUC (LOG)	111.8	111.6	NS	
ECG	(15.3)	(11.9)	NS	
PLAT (SQRT)	263.2	271.9	NS	
CNS	(2.6)	(2.3)	NS	
CHOL (SQRT)	219.5	214.1	NS	
ALKPHOS (LOG)	89.76	85.53	NS	
COPRO (SQRT)	115.4	114.9	NS	
T4	7.58	7.58	NS	
TEST (SQRT)	576.6	559.0		GRP*OCC, GRP*AGE
SED (LOG)	5.11	4.91	NS	
GGTP (LOG)	32.39	29.77	NS	

*All means are expressed in original units.

TABLE 5-26.

Baseline Compliance Status of 39 Partially Compliant Participants: First Followup

Baseline Compliance	Group	
	Ranch Hand	Comparison
No Interview, No Physical, No Telephone Interview	3	23
No Interview, No Physical, Telephone Interview	2	1
New Comparison	0	3
No Action	4	3
Total	9	30

TABLE 5-27.

Reported Health of Partially Compliant Versus Fully Compliant Nonblack Participants

Compliance Status	Reported Health	Group				
		Ranch Hands		Comparisons		
		Number	Percent	Number	Percent	Total
Full	Excellent	473	43	635	57	1,108
	Good/Fair/Poor	482	46	575	54	1,057
Total		955		1,210		2,165
Partial	Excellent	5	20	20	80	25
	Good/Fair/Poor	3	23	10	77	13
Total		8		30		38

participants; 66 percent of partially compliant participants reported excellent health while only 51 percent of fully compliant participants reported excellent health. This association did not change with group ($p=0.91$).

The data on medication use and compliance status demonstrated no association ($p=0.57$), and this equivalence did not change with group ($p=0.79$). These data are shown in Table 5-28.

As shown in Table 5-29, the work loss-by-compliance association in these data was significant ($p=0.03$), with 84 percent of fully compliant participants reporting work loss and 95 percent of partially compliant participants reporting work loss.

These data are sparse and are not considered supportive or nonsupportive of the compliance bias calculations presented in the Baseline Report. The conclusions of the Baseline Report regarding the potential effects of compliance bias should be regarded as conservative overestimates, but worthy of consideration in inference formulations until more data become available.

CONCLUSIONS

These predominantly negative findings suggest that there has been no change in the way replacements self-select for entry into this study and, due to the obvious scheduling differences between new and old replacements, that no additional bias has been introduced at followup by scheduling differences. These data also strongly suggest that shifted Original Comparisons are not statistically distinguishable from Original Comparisons, either at Baseline or at first followup. This interpretation is also equivalent to the conclusion that no additional bias was introduced by scheduling differences between Original Comparisons and shifted Original Comparisons at Baseline. Available data on noncompliant Comparisons and their replacements suggest that, although replacements were not health-matched to refusals at Baseline, they are remarkably similar to refusals with respect to reported health, medication use, and income level. This result also supports a conclusion that there has been little, if any, selection bias due to nonparticipation in the Comparison group. This conclusion supports the use of the total Comparison group for all of the main analyses in the body of this report. Data regarding the few partially compliant participants at first followup are not sufficient to confirm or deny compliance bias calculations published in the Baseline Report.

TABLE 5-28.

Medication Use of Partially Compliant Versus Fully Compliant Nonblack Participants

		Group				
		Ranch Hand		Comparison		
Compliance Status	Medication Use	Number	Percent	Number	Percent	Total
Full	Yes	123	42	167	58	290
	No	832	44	1,043	56	1,875
Total		955		1,210		2,165
Partial	Yes	1	25	3	75	4
	No	7	21	27	79	34
Total		8		30		38

TABLE 5-29.

Work Loss of Partially Compliant Versus Fully Compliant Nonblack Participants

		Group				
		Ranch Hand		Comparison		
Compliance Status	Work Loss	Number	Percent	Number	Percent	Total
Full	Yes	796	44	1,010	56	1,806
	No	155	44	200	56	355
Total		951		1,210		2,161
Partial	Yes	8	22	28	78	36
	No	0	0	2	100	2
Total		8		30		38

CHAPTER 6

QUALITY CONTROL

During the first AFHS followup, stringent adherence to quality assurance (QA) was planned for and upheld throughout the study, from project initiation to final product delivery and acceptance by the Air Force. A quality program plan was developed for this study cycle, outlining all contract activities requiring periodic and/or systematic QA and quality control (QC) monitoring.

The purpose of this chapter is to provide an overview of the specific QA measures developed and used by the project team, specifically in the areas of administrative QC; questionnaire, physical, and psychological examination QC; laboratory QC measures; data base management QA; and statistical QC.

ADMINISTRATIVE QUALITY ASSURANCE

In recognition of the magnitude, complexity, and importance of the AFHS, a Quality Review Committee (QRC) was established at the initiation of the third-year followup for the purpose of providing general oversight to the AFHS QA Program and advice on the appropriateness of program management and QC actions. The QRC was composed of senior corporate personnel from the prime contractor. These independent reviewers remained separate from the project management staff. The QRC met formally each quarter to review recent study progress and any issues that either had an impact on study quality or were perceived as a potential problem.

Assisting the QRC in day-to-day oversight responsibilities was a QA officer responsible for reviewing procedures, performance, and work products from all task managers and key project staff. As part of the monitoring function, the QA officer received exception reports from project task managers whenever an incident occurred that appeared to affect study quality. Monthly reports were also prepared for the Air Force, documenting project compliance with project QA criteria and noting any instances of non-compliance.

An additional measure of corporate QC was implemented through independent QA audits of individual project tasks. Members of the QRC determined first-hand whether QA procedures for a particular task were being conducted, whether procedures were appropriate for the task, and whether QA was complete for all aspects of each task.

The remainder of this chapter comprises specific QA procedures followed for the individual tasks.

QUESTIONNAIRE QUALITY CONTROL

NORC used both onsite and home-office QA procedures to produce a comprehensive data set. All AFHS questionnaires were pretested to evaluate

their completion time and participant acceptability before they were used at the SCRF. Onsite QC procedures included weekly observation and rating of each interviewer, editing of every questionnaire at the completion of the interview, and monitoring of participant evaluations. The Air Force also continuously conducted QA observations of all onsite activities. QC of data processing included manually editing each questionnaire, including a 100-percent verification of critical items for each questionnaire, computerized cleaning (with both single item and interitem review for range and consistency), identifying outliers, and reviewing the actual questionnaire copy to reconcile or correct detected errors.

All telephone surveys were monitored for quality and accuracy of interviewer performance by NORC supervisors. The telephone survey supervisor monitored 3 percent of each interviewer's calls to assure an appropriate presentation and an accurate transcription of responses. An additional 5 percent of the participants were recontacted after the interview to evaluate interviewer performance and validate that the correct respondent had been contacted.

NORC recruited and trained interviewers according to the detailed procedures described in Chapter 3. A minimum number of interviewers was selected to reduce interviewer variability. Additionally, these individuals were blinded to the participants' exposure status to avoid any bias. Interviewers were required to ask questions exactly as recorded, and in the order in which they appeared. No personal interpretation was allowed.

An onsite field manager closely supervised each interviewer's work regularly, observing individual interviews weekly during the examination schedule. The field manager reported directly to the NORC Project Director weekly, and was reviewed by the Project Director during quarterly site visits, to ensure direct accountability by the home office and the field manager for promptly resolving any issues.

Specifically, interviewers were checked for accuracy in questionnaire skip patterns, probing, circling of the correct code, control of the interview, voice quality, reading, and use of associated documents. When called for, the onsite manager gave immediate retraining after each observation and documented the content of this training. At weekly meetings, held with all interviewers, the field manager used generalizations from individual interviewer performance observations to train an entire group of interviewers.

The NORC field manager also monitored participant evaluations of the study closely and used the information gathered to plan and implement retraining. The manager and staff edited each completed questionnaire before it was shipped to Chicago, attempting to retrieve missing data while the study participant was at the physical examination site. Missing or ambiguous data were also retrieved by telephone when necessary.

Spouse fertility data were obtained independently of the participant interview by sending the mail questionnaire while the study participant was at the examination site, and by having a group meeting for wives who accompanied their spouses to the clinic site, where they could complete their questionnaires in private. The Assistant Survey Director in Chicago supervised and edited all interviews conducted at home with participants and spouses.

Once the participant and spouse questionnaires were received in Chicago, they were edited for completeness by a coding supervisor and staff dedicated to the AFHS for the entire project. Resolution of inconsistencies was accomplished by staff members, who standardized all responses prior to keypunching. Questionnaires were then coded, and a 10-percent recode was done on open-ended items. When a batch failed the 10-percent recode, the entire batch was recoded and the coding staff was retrained. One hundred percent quality control was accomplished by the Air Force.

During data entry, range validity checks were performed and 10 percent of the most important items in each questionnaire was verified. Data were then passed through a computer program that checked for inter- and intra-column errors. When errors were detected, the questionnaires were reviewed and the errors corrected. The process continued until no errors were detected by the cleaning program. Then, frequencies were reviewed and any anomalies or errors previously undetected were corrected by reviewing the questionnaires on a case-by-case basis. All corrections were entered into the data tape, but no changes were made to the data recorded in the questionnaires. QA reports were generated monthly, detailing the summary statistics on the number of questionnaires reviewed, the number and types of transcriptions failing QC checks, and the average number of coding errors per batch processed.

PHYSICAL EXAMINATION QUALITY CONTROL

QC was emphasized in the physical examination, as this data source provided most of the medical information for clinical and epidemiological analyses.

Initial concern for a high-quality physical examination was addressed by a stringent SCRF selection process for all personnel who were to directly interact with the participants. Each staff member was hand-selected for the AFHS on the basis of expertise, experience, and a commitment to remain with the study throughout the examination cycle. Further, the Air Force Technical Team reviewed the credentials of all key staff members and approved their participation in the study.

A complete pretest physical examination, interview, psychological test, and laboratory workup was done for 10 volunteers several weeks before the scheduled start of the study. Refresher training was given to the dermatologists to enhance their skill in diagnosing chloracne, techniques for detecting specific heart sounds were reviewed with the internists, and diagnosticians were reminded of the need to review Baseline examination data as they formulated all diagnoses. Further, all aspects of patient contact were reviewed: the initial inbriefing of the participants, the logistics of transportation and patient flow within the clinic, and the final outbriefing by the diagnostician.

During the examinations, refinements continued whenever operational problems were detected by the SCRF staff and the Air Force onsite monitor, or when participants identified areas requiring improvement. Both of these types of information were addressed during the weekly clinical QA meeting of key SCRF staff, chaired by the SCRF Medical Project Director and attended by an Air Force representative. In addition, written critique forms submitted by all participants were reviewed in detail at the SCRF weekly meetings,

providing additional insight to both temporary shortcomings of the entire logistic process as well as the numerous strong points of the programs.

Following examination of each participant group, all physical examination forms were reviewed by the SCRF staff for omissions, incomplete examinations, and inconsistencies. The examiners or technicians were quickly contacted to correct the data. Special effort was made to complete this review while the participants were at the examination site. In all cases of data correction, a complete audit trail was maintained. Finally, all mark-sense physical examination forms were read by an optical scanner to ensure total continuity and sensibility of the final examination contents. (This subject is discussed in more detail in the Data Management Quality Control section of this chapter.)

Compliance with all aspects of the physical examination was monitored daily by the Air Force onsite monitor and the SCRF Medical Project Director. Additional periodic inspections were conducted by the SCRF Chief of Medicine and the SAIC Principal Investigator. All such clinical reviews were done unobtrusively, and with the full consent of the participant; suggestions or corrections to the examination procedure were always discussed privately with the attending physician. These inspections emphasized aspects of clinical techniques, sequencing and completeness of the clinical data with respect to the examination forms, and the total blindness of the examinations. Of particular note were the detailed daily log entries of the five Air Force monitors. These entries ensured continuity of knowledge (the monitors rotated approximately every 2 weeks) by documenting examination procedural changes and recording events requiring followup by either the Air Force or the prime contractor.

Establishment of rapport with each study participant was a primary goal of all organizations involved in this study. Although "rapport building" may not be a traditional QA parameter in most research studies, it is paramount in the AFHS because maintaining the satisfaction of participants encourages them to continue in the study, and thus a significant reduction in future statistical power or bias, or both, is avoided. Every staff member, therefore, from the initial telephone recruiter to the nurse coordinator and the Project Manager, emphasized courtesy, empathy, assistance, and personalized treatment of each participant.

LABORATORY QUALITY CONTROL

Before the study was begun, specific QC laboratory procedures were designed, developed, and implemented to rapidly detect problems related to test/assay performance, validity of reagents, analysis of data, and reporting of results. All laboratory assays for the study were done with state-of-the-art laboratory equipment and techniques. Laboratory facilities all had the equivalent of National Institutes of Health Biosafety Level 2 (BSL-2) approval ratings and were certified by the College of American Pathology (CAP).

Hematology assays were performed on Coulter S Plus® equipment; sedimentation rate determinations were performed using the large-tube Westergren method. The Dupont Automated Chemical Analyzer® (ACA) was used to perform the biochemical assays; radioimmunoassays (RIA) were done with standard test kits; and porphyrin was assayed by high-performance liquid

chromatography at the Mayo Clinic in Rochester, Minnesota. Hepatitis B tests were performed using Abbott kits, and manually performed electrophoresis and monospecific antibodies were used for immunologlobulin assays. Blood-cell counts were performed with standard microscopy, and Clinitek, a reflectance spectometry urinalysis, was used for all urinalyses. All other assays were done using industry-approved equipment and techniques.

All laboratory operations were controlled with the use of an integrated medical laboratory management information system that incorporated direct device to data base interfaces for automated testing equipment, and data entry for manual tests was performed by the laboratory technologists. An automated audit trail and a set of comments for technologist entries were kept for each test so that any QC results could be retraced.

Procedural QC included using instrumentation and reagents from one lot number throughout the study. Strict standards of calibration for all automated laboratory equipment were maintained at all times.

Trilevel or bilevel controls were used as the primary means for monitoring the quality of all tests. On every group of participant samples, one control (low, medium, or high) was run at the start, after every ninth sample, and at the end of each test run. Each trilevel control was used before repeating it in the run, when more than 18 experimental samples were analyzed. In addition, split aliquots were made from every tenth patient sample and were analyzed separately to measure test reproducibility.

All QC data were analyzed and summarized in formal QC reports generated weekly. QC data were subjected to independent statistical analysis to produce and analyze time-dependent trends. For all equipment malfunctions or other exceptions, a formal QC exception report was prepared by the responsible individual and forwarded to the QA officer and the project management team.

An additional measure of quality control introduced during the study was the CUSUM tests run with trilevel controls.[1] In particular, the fast initial response cumulative sum (FIR CUSUM) QC technique was used. It has an advantage in detecting long-term subtle drift that could have substantial adverse analytical consequences.[2] FIR is a special case of the CUSUM QC scheme that increases the overall effectiveness of the QC procedure. Unlike QC procedures using standard control charts, which compare each observation to designated limits, these tests utilize the cumulative sum of deviations from a target value.

CUSUM statistics were accumulated for each of the trilevels to quickly detect instrument calibration problems as identified by excessive drift. If an out-of-control situation was indicated, the graph showed when the change first occurred. Coefficient of variation (CV) standards were established before the study for each test. All adjacent patient samples were reanalyzed after the equipment was thoroughly checked and fresh controls were run.

FIR CUSUM generally has been applied to QC in industry, particularly in high-volume, high-precision applications. To our knowledge, FIR CUSUM has not generally been applied in a biomedical setting. According to SCRF laboratory personnel, this procedure proved so successful in the AFHS that most of the SCRF clinical laboratory will begin using it in the near future.

As the examination portion of this study ended, all laboratory outliers were analyzed for logical validity by an independent clinician. All out-of-range test results were examined and scored as clinically explainable, clinically possible, or clinically unexplained.

Quality Control Procedures for the Immunology Laboratory

The QC procedures for the Cellular Immunology section of the AFHS were structured to rapidly detect any problems in four major test parameters: (1) assay performance, (2) reagent validity, (3) data analysis, and (4) results reporting. The QC measures were detailed in the Quality Procedures Plan and documented before testing started. Compliance was monitored daily by the Cellular Immunology laboratory supervisor. Key aspects of the program included instrument and equipment calibration and maintenance, assay controls, accuracy and precision determination, and system failure checks.

QC measures followed in all Cellular Immunology assays included:

- Blood sample from a normal, healthy control individual with each group of AFHS patient samples
- Duplicate testing of one random patient sample in each assay
- Quadruplicate testing of each patient sample for each variable in each of the functional assays (e.g., PHA stimulation, natural killer cell effector/target ratios)
- Parallel testing and monitoring reactivity of various lots of reagents when appropriate
- Verification of patient and specimen identification by at least two individuals before final reporting to the data base
- Note codes attached to any data point with a detected deviation from normal due to procedural setup error, assay malfunction, equipment malfunction, or assay technical error
- Review of all final assay reports by the Cellular Immunology laboratory supervisor prior to entry into the data base.

QC for each functional assay including phytohemagglutinin (PHA), pokeweed, mixed lymphocyte culture (MLC), and natural killer cell consisted of monitoring assay controls, duplicate sample reproducibility, and any trends in reagent reactivity. Assay precision was determined by calculating the CV of the quadruplicates for each variable tested. Also, a mean value of the CV for each assay was calculated. Individual CV's of 15 percent or less were the target values for the stimulated samples in the mitogen and natural killer cell assays. The Student's t-test was applied to duplicates to determine if there was a significant difference in sampling for the functional assays. Critical t-values at the 0.05 significance level were used to determine if duplicate sample results varied significantly. Grubbs' statistical test[3] was used to identify any statistically significant outlier. This test was applied only to samples whose CV's were greater than 20 percent at a p-value of 0.01. The mitogen stimulation (PHA, pokeweed) effect was

followed by daily evaluation of the radioactive counts in counts per minute (cpm) for each mitogen. When counts fell below expected values, suggesting that reagent deterioration had occurred, new aliquots were used.

QC measures for the cell surface marker assays were calculation of T_4+T_8/T_{11} cell ratios, evaluation of flow cytometer computer outputs (cytograms and histograms), and duplicate sample testing. T_4+T_8/T_{11} cellular ratios should approximate the value 1.0 for a normal population. Validity of cytogram and histogram distributions generated by the flow cytometer was confirmed by the Cellular Immunology laboratory supervisor for each sample analyzed. The percent positive cells for each surface marker was determined in the duplicates and viewed graphically using a microcomputer program. Any significant differences between duplicates were noted and followed for abnormal trends.

On completion of this followup effort, the entire cellular immunology data base was reviewed by the Air Force team, laboratory staff, and consultants. Comments attached to the data points were also reviewed. Any data point that appeared unusual was reviewed and identified as an unexplained outlier. Unexplained outliers were deleted from the data base as errors of an unknown nature. This review was conducted without knowledge of exposure status.

DATA MANAGEMENT QUALITY CONTROL

Overview of Quality Control Procedures

The QC program for the data management activity consisted of multiple checks at all steps of the examination, data collection, and data processing cycle. Data QC procedures for data collection, conversion, and integration were developed before the clinical examinations began. Pretesting of all forms, procedures, and logistic arrangements was conducted 3 weeks before the examinations actually began. Additionally, during the first 2 months of the clinical examinations, all data collection activities were intensely scrutinized to detect and correct procedural deficiencies.

QC activities also included automated QC techniques applied to laboratory data, clinical evaluations of all laboratory outliers, review of all physical examination findings by an independent diagnostician, and automated and manual data quality checking of hard copy against transcribed computer files for all questionnaire, physical examination, and medical coding data streams.

Five interwoven layers of QC were instituted to ensure data integrity. Efforts focused on (1) data processing system design, (2) design and administration of all exams or questionnaires, (3) data completeness checks, (4) data validation techniques, and (5) quality control of medical records coding. In some cases, the QC procedures about to be described were implemented throughout the data management task rather than assigned to a particular activity. These comprehensive QC procedures will be mentioned where appropriate throughout the remainder of this section.

Data Processing System Design

For each data stream, standards were set to establish data element format (character or numeric), data element naming conventions, data element text labels, numeric codes for qualitative responses and results, QC range checks for continuous data elements, and QC validity checks for categorical data. A data dictionary provided detailed information on each data element.

A systems integration approach was applied to the design and implementation of data collection procedures and techniques so that data emanating from the various study sources (physical examination, questionnaire, laboratory) were consistent in file format and structure. This was necessary to ensure that all data could be integrated into a single data base management system for analysis. Figure 6-1 provides an overview of the QC activities used in the data base management process.

Forms and questionnaires were carefully designed to ensure that all required data elements would be collected according to the Study Protocol. The design of these instruments was such that they reflected the order in which the examination itself would be administered and provided for the sequential recoding of information to streamline remaining data management activities.

Completed medical records and questionnaires were converted from hard copy to machine-readable images using customized data-entry systems or state-of-the-art optical mark reading equipment. Verification procedures were performed to ensure that a uniquely identified participant record existed within each data file, and that the appropriate number of responses for each applicable field was provided. Data files were then verified against original data sheets and corrected as necessary.

Data files were then subjected to validity checks. Any potentially conflicting results as well as any data values falling at the extremes of expected ranges were manually reviewed. Extreme values were reverified against the original raw data copies and either corrected or documented as valid results. Potentially conflicting results were returned to the examiners for review. These results were then documented as correctly recorded, corrected, or flagged for exclusion from analysis because of unresolvable examiner errors or omissions.

Once the edits were completed and the data reverified, the "cleaned" files or tapes were transferred to the data analysis center for final inspection and integration into the study data base. For this QC measure, each data file was loaded into a Statistical Analysis System (SAS®) data set, and descriptive analyses were run. The validation, correction, transmission, and analysis QC procedures were repeated as necessary to ensure that all extreme or suspicious values had been validated.

Design and Administration of Physical and Psychological Examination Forms

As mentioned, the examination forms were designed to solicit all required data such that recording time was minimized, comprehension was enhanced, and data input could occur with a minimum of transcription errors. Optical Mark Recognition (OMR) technologies were selected to eliminate the risk of transcription errors and were applied to all psychological tests.

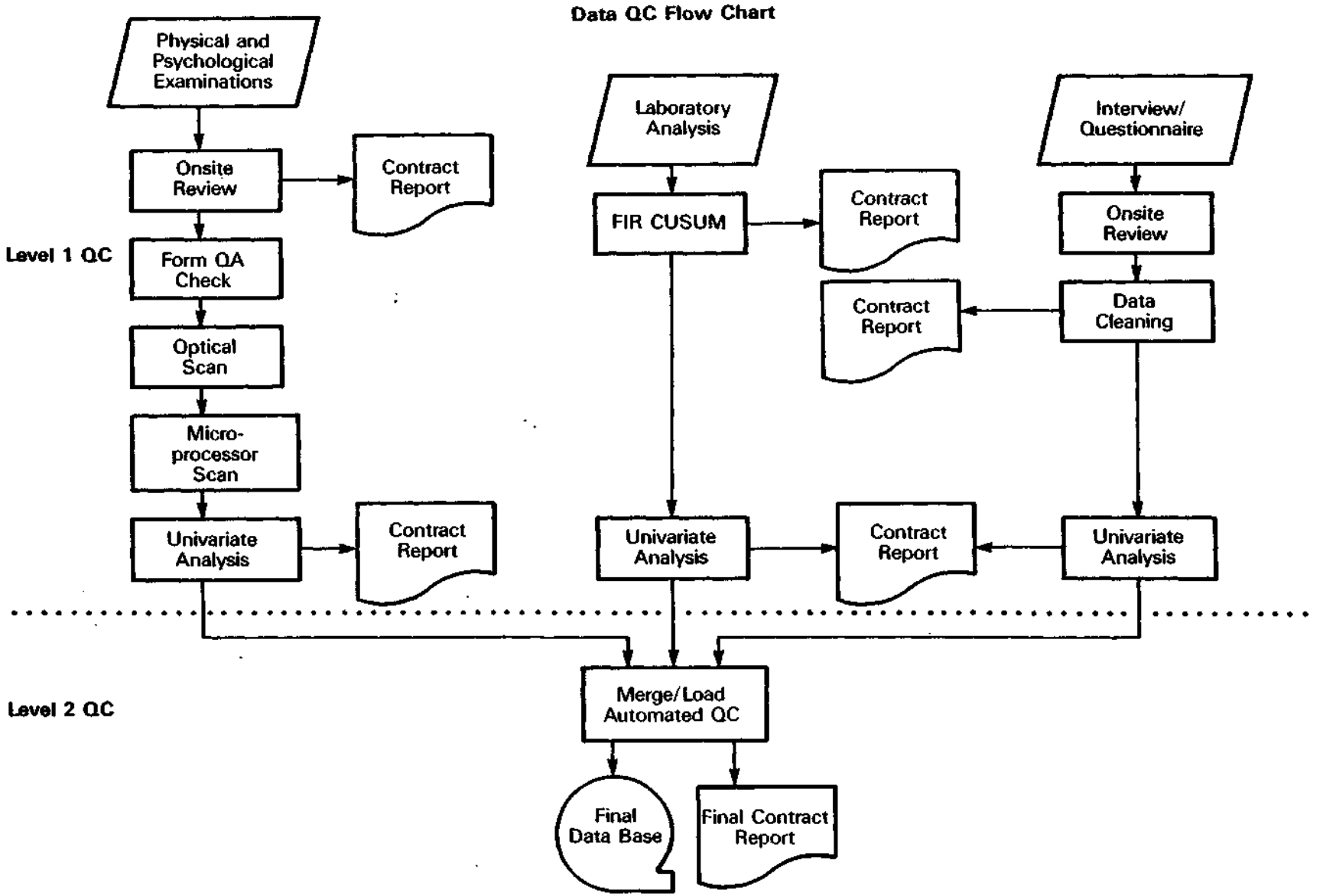

Figure 6-1.
Two Levels of Quality Control Applied to All Collected Data Prior to Statistical Analysis

Customized mark-sense forms were also developed and OMR technology was used to achieve these same objectives for segments of the physical examination and the self-administered questionnaires. The use of mark-sense forms allowed the creation of computerized data files directly from the raw data recorded on these forms.

QC procedures for all data collection instruments began with a review of all forms immediately as they were completed. Any forms containing missing examination results were returned to the examining physician for completion before the participants left the site. Any questionable results or "hard-to-diagnose" conditions (such as heart sounds or peripheral pulses) were verified by the diagnostician at the outbriefing. All examination forms were signed by the examining physician, and the examiner identification number was coded in the data base so that interexaminer variation could be analyzed. Detailed QC records were maintained, which indicated the examining physician and the type of deficiency detected. Deficiency reports were reviewed by the study coordinator to detect any patterns of physician data entry error. A final level of QC audit was accomplished by Air Force statisticians, who conducted a detailed screening of the data and checked for errors.

Data Completeness Checks

Customized programming of the OMR allowed for the identification of those forms (and their corresponding data records) with missing responses, as well as those with multiple responses to questions that required a single response. The OMR scanner was programmed to reject forms that failed completeness and multiple response checks and to output a control code for each rejected form. The control code identified the location of the first three verification checks failed for a given form.

When a raw data form was rejected, the reason for the rejection was determined and the exact data element was corrected by comparing the rejected raw data form to the values recorded in the data record created by the scanner. A customized set of rejection and resolution codes was developed for the study to describe all the reasons for a form's rejection and any subsequent reasons for changing a data value. Various codes identified values recovered from light marks, missing marks explained by examiner comments, and missing comment flags resolved by the presence or absence of text in the comment areas. These codes ensured data completeness by accounting for all questionable or missing responses. (See examples of mark-sense forms in Figures 4-3 and 4-4.)

Some of the rejected forms did not contain actual data errors but rather anomalies created in using mark-sense cards for data collection. For instance, incompletely erased responses and responses marked with too little carbon or graphite were incorrectly counted or missed, respectively, by the scanner. Examiners also tended to clearly mark responses for abnormal findings while bypassing or lightly marking responses for expected or desired findings. Failure of the form to provide the correct number of expected responses always resulted in rejection. These technology-based errors were resolved, as were the anticipated, more traditional errors.

The rejection code, data location code, resolution code, data inspector's initials, and correct data value were directly posted to a

participant's data record. This innovative technique not only effectively maintained a comprehensive audit trail of all record manipulations, it also provided a mechanism for measuring the frequency of specific errors.

Careful monitoring identified trends where individual data values were missed as well as the frequency with which individual examiners incorrectly marked their examination forms. Statistics were compiled on out-of-range results and data omissions that had been accepted in the previous QC audits. The results were monitored to detect trends, possible bias situations, and other data quality problems. This information was reviewed and relayed to examiners and internal auditors to assist in preventing or correcting chronic, but avoidable, problems.

Data Validation Techniques

QC activities also included data validation techniques. As mentioned earlier, data files were examined in a series of verification and validation procedures developed to check the results within each participant's record for logical consistency and abnormal findings. Any records noted to have ambiguous findings, incongruent observations, extreme results, or nonobvious errors or omissions were listed and submitted for review to a physician.

Again, clinical judgments were made by the auditing physician in assigning a validation code for each extreme or questionable data result. The validation codes allowed for indicating that data were deciphered from examiner comments or from related findings from another specialty area, or were accurately recorded and logically consistent with other findings for the participant. Data points that could not be definitively validated or recovered through clinical judgment and consultation with the original examiner were assigned codes noting missing or invalid data values. These unrecoverable data points were excluded from subsequent analysis.

Medical Records Coding Quality Control

Upon completion of the NORC data processing, all AFHS questionnaires were forwarded to SAIC for the medical coding of reported conditions. The International Classification of Diseases, 9th Revision, Clinical Modification (morbidity); International Classification of Diseases, 9th Revision (mortality); Systematized Nomenclature of Medicine (anatomic site); and American Hospital Formulary Service (medications) coding schemes were used, suitably modified. Each questionnaire was coded by two coders working independently. The results of the two coders were forwarded to the USAF for 100-percent QA/QC and final adjudication. The information from the physical examination was coded similarly.

After the coding data were adjudicated, they were returned to SAIC for data entry. The coding sheets were batched, key entered, verified, and corrected. The corrections were also verified. The key entry and verification functions were performed by various operators. Five percent, or 100 records of each batch (whichever was larger), was randomly selected and subjected to manual reverification. An error rate of greater than 1 percent of this sample mandated reverification of the entire batch. In this final QA/QC check, the automated files were reviewed and compared to the hard copy by trained medical record coders, all of whom satisfied the minimum requirement of Accredited Record Technician or Registered Record Administrator eligibility.

A manual tracking system was used to retrieve medical records. A chronological log was maintained to track participant requests for authorization to obtain medical record(s), receipt of the authorizations, requests for records from the provider, and receipt of the records from the provider. Identifying information in these logs included participant name, case number, date of action, condition(s) to be verified, dependent name (if appropriate), and type of medical provider (Federal/non-Federal).

Due to the intricacies of obtaining medical records from Federal facilities, this task ultimately became the responsibility of the Air Force.

STATISTICAL ANALYSIS QUALITY CONTROL

Specific QC measures were developed for activities falling within the statistical analysis task: construction of data bases for the statistical analysis of each clinical chapter, the statistical analysis itself, and the production of statistical reports to serve as the basis for the clinical chapters.

Each specialized statistical data base was constructed by defining and locating each variable within the many subparts of the composite followup data base. Lists of variables and their data sources were submitted to the Air Force for approval. Although the data had been subjected to QC procedures during collection, statistical checks for outliers and other improbable values were conducted; anomalies identified by the statisticians were discussed with those responsible for the data collection, i.e., either NORC or SCRF.

QA largely depended on regular communication and general agreement among statisticians. Several meetings and consultations among the Air Force team, the Principal Investigator, the SAIC statisticians, and the University of Chicago staff members were held in conjunction with the development of the data analysis plan. During the course of the analysis there were frequent telephone conversations. Any problems arising in the statistical analysis were resolved by team discussion. The software was checked by comparing results from analyses on the same variable by different programs (for example, BMDP®-LR [logistic regression] and BMDP®-4F [log-linear model] will give the same results for dichotomous variables when the program options are chosen properly). The statisticians frequently checked that the number of observations used in an analysis was correct, and peer review ensured that the program code was appropriate for the chosen procedure. The analyses were conducted in accordance with the data analysis plan which was reviewed extensively. Throughout the study, duplicate data bases were maintained by the USAF and SAIC. Upon completion of the analyses, SAIC delivered all analysis software and SAS data sets for each clinical area to the USAF for final review and archiving.

All tables and statistical results were checked against the computer output from which they were derived, and all statistical statements in the text were checked for consistency with the results given in the tables. Additionally, drafts of chapters in the report were reviewed by the USAF and SAIC investigators, and the QRC.

CHAPTER 6

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CHAPTER 7

STATISTICAL METHODS

This chapter summarizes the key statistical elements of the study design, the statistical analysis issues, and the specific statistical methods used in the analysis. Additional details may be found in the USAF Study Protocol.

The primary focus of the statistical analysis was a contrast of health status of the Ranch Hand and Comparison groups. Assessments were made of the proportions of participants with abnormal findings and of mean levels of key laboratory measurements. The analyses encompassed both simple contrasts between the two groups and more complex methods, in which adjustment was made for important covariates.

In addition to these analyses, the possibility of an increasing response of medical problems with herbicide dose was explored, since if indeed there were an effect, more problems would be expected among the more heavily exposed. Although exact dosage information is not available, an exposure index was developed for the exposed population (the Ranch Hands) that approximates the potential herbicide exposure of each individual, incorporating information such as the occupation of the individual, his period of duty in the spraying operation, and the numbers of barrels per day of herbicide used during that period. Details on the exposure index are given in Chapter 8. Dose-response analyses were conducted for the Ranch Hands only, using this exposure index as a surrogate measure of dose.

Interpretation of the results of the exposure index analyses, however, depends critically on the accuracy of the exposure index, which presently can be regarded as only fair. (Improved dosage information will be obtained for future studies from recently developed serum dioxin assay techniques.) Thus, the analyses of overall group differences between the Ranch Hands and the Comparisons are given primary emphasis, and the exposure index analyses merely supplement them.

STATISTICAL STUDY DESIGN

An overt herbicide effect would be characterized by more symptoms, signs, abnormal laboratory tests, syndromes, or diseases in the Ranch Hand group than in the Comparison group. If the disease(s) were fatal, increased mortality might also be observed. A subclinical herbicide effect would be detected as an increase in abnormal findings on the physical examination (particularly laboratory tests) that may or may not also be associated with symptom reporting or increased mortality. Thus, the basic objective of the statistical analysis is to test for differences between the Ranch Hand (exposed) group and the Comparison (nonexposed) group.

In general, two types of data are used in the analysis. First, there are subjective data on symptoms reported by the participant in the questionnaire and in the review-of-systems section of the physical examination. Second, there are objective data, which include medical findings or signs identified during the physical examination, or by reviews of laboratory results, medical records, and death certificates.

Symptoms reported by the study participants are subjective by definition, and are subject to influences that could result in erroneous conclusions. An association found between reported symptoms and herbicide exposure must be subjected to further confirmation, as the observations may result from over- or under-reporting bias and may not be indicative of a true herbicide effect. On the other hand, the medical findings data do not suffer from the same degree of participant influence.

The medical findings and medical records review were conducted by highly trained individuals employed for the duration of the data collection and assessment phases of the study. They were held to stringent QC standards, as described in Chapter 6, to ensure that these data were as objective and accurate as possible.

Incorporated in the study design is a feature that attempts to check for and correct symptom-reporting errors. A key component is a reported symptom verification process conducted by reviewing participant medical records and findings from the physical examination. In the retrospective morbidity portion of the study, the participant is questioned on past illnesses and medical conditions. With the participant's consent, an effort is made to obtain the medical records to verify the reported condition and, thus, to substantiate any unverified conditions. In addition, the study design includes verification of negative responses to determine unreported conditions. The medical record review process is time intensive and only a portion of the data was available for analysis in this study. Over-reporting was assessed by comparing the reported illness rates with the results of the physical examination and medical record review. Similarly, the assessment and correction of under-reporting requires the review of medical records to identify unreported illnesses. Obviously, this under-reporting assessment is restricted to conditions for which medical care was obtained or that were identifiable at the physical examination.

STATISTICAL ISSUES

In conducting the statistical analysis of the data in this study, there are a number of underlying issues. Except for bias, which is the topic of Chapter 5, these issues are discussed in this section. However, based upon the results of the bias analysis presented in Chapter 5, all statistical analyses in the clinical chapters use the contrast of Ranch Hands versus the total Comparison group. For the purposes of completeness and cross-reference to the Baseline report, identical analyses using the contrast of the Ranch Hands versus the Original Comparisons have been conducted, and these results are presented in the form of summary tables in each chapter appendix.

Intervening Variables

When comparing any two groups of individuals, the exact proportion of diseased individuals in each group is usually found to differ. The purpose of classical statistical hypothesis testing is to determine whether the observed difference in disease rates could be due to chance alone. If the observed difference is not attributable to chance, the two groups are considered representative of two truly different populations.

If a statistically significant difference is found between the Ranch Hand group and the Comparison group, results from more rigorous statistical procedures must be examined and the medical context considered before the possibility of a causal relationship between disease and group (exposure) can be entertained. Alternatively, the absence of a statistically significant difference between groups does not exclude the possibility of a true causal relationship between exposure and disease. Thus, group associations, whether significant or not, should be examined with adjustment for other variables called intervening variables (explanatory variables, risk factors, or covariates) that may account for, or mask, a true effect. For example, the two groups might differ with respect to age or racial composition, each of which may affect the outcome of the study. To protect against this, the technique of matching was used: The Ranch Hands and Comparisons were matched on age, race, and military occupation.

Since it is not feasible to perfectly match a Comparison to an exposed individual with respect to all important explanatory variables, statistical procedures may be used to adjust for such explanatory variables so that valid interpretations can be made of apparent group differences. Thus, it was necessary to identify and collect data on suspected explanatory variables. Unfortunately, there is no way to ensure that all important intervening variables are taken into account. The best method that can be achieved is to incorporate all known covariates in the data collection and analysis.

In most studies, covariates are variables measured prior to exposure. However, in the AFHS, except for the matching variables and historical data related to events prior to service in Southeast Asia, most covariate values were obtained at the Baseline or first followup interview and physical examination, which occurred 10 to 20 years following exposure. These covariates can generally be referred to as time-dependent covariates. They can elucidate the causal path between exposure and a particular disease; however, they are in a sense both dependent and independent variables, and therefore, analyses involving such covariates require careful interpretation.

Besides covariates, both confounding variables and interactions must also be considered. A confounding variable is an intervening variable associated with both disease and exposure. (This is in contrast with a covariate that is associated only with disease.) Adjustments must be made for confounding variables to avoid a biased estimate of the group-disease relationship. An interaction exists when the effect of one variable varies across the levels of another variable. For example, the group difference might be large in one occupation group and negligible in another. Incorporating interactions in the analysis allows for the identification of subpopulations at increased or decreased risk.

Power

Conducting a statistical test using a Type I error, also called alpha level, of 0.05 (α =0.05) means that, on the average, in 5 cases out of 100, a false conclusion that an association (herbicide effect) exists would be made when in reality, there is no association. The other possible inference error (called a Type II error) is that of failing to detect an association when it actually exists. The probability of a Type II error (β) for a statistical test is 1 minus the power of the test. The power of the test is the probability that the test will reject the hypothesis of no herbicide effect when an effect does in fact exist. The power of a test depends on the group sample sizes, the disease prevalence rate, and the true group difference measured in terms of relative risk.

Table 7-1 contains the approximate sample size required to detect specific relative risks with an approximate power of 0.8 (β =0.2) using an alpha level of 0.05 for a two-sided test and assuming equal Ranch Hand and Comparison group sizes and unpaired analyses. Relative risk is the ratio of the disease prevalence rate of the Ranch Hand and Comparison groups. Conditions or diseases with comparison population prevalence rates and exposed group relative risks corresponding to those below the heavy black line on the table can be detected with an approximate 0.8 probability with the sample sizes used in this study.

Table 7-2 provides the same information for continuous variables in terms of percentage mean shift and variability, assuming unpaired testing of a normally distributed variable and equal sample sizes.

In the first followup of the AFHS, 1,016 Ranch Hands participated in the physical examination. In this size group, the chance of identifying zero cases of a disease with a prevalence of 1/500 or less is greater than 10 percent. Table 7-3 contains the probability of encountering no cases of disease states for cumulative prevalence rates of 1/200, 1/500, 1/1,000, 1/2,000, 1/5,000, and 1/10,000.

Multiple Endpoints and Comparisons

In developing the Protocol for the AFHS, previous animal and epidemiologic studies, case reports, and veterans' concerns were reviewed to delineate the possible effects of exposure. The conclusion was reached that a comprehensive evaluation was needed due to the lack of an easily identifiable symptom complex in individual patients. Consequently, the morbidity study is very broad in scope, involving the collection and analysis of data related to general health indices as well as specific organ systems and clinical disease categories.

The large number of endpoints under consideration presents a difficult problem in the assessment of Type I error rates. More than 150 dependent variables were tested, not to mention tests for interaction and multiple contrasts among the low, medium, and high exposure-level categories in the exposure index analyses. Furthermore, the dependent variables were correlated to varying degrees, and this makes it even more difficult to assess the attained significance levels. To allow for multiple endpoints, Bonferroni's inequality,[1] which requires significance at the α /K level where K is the number of endpoints considered, may be used, but this procedure

TABLE 7-1.

Required Sample Sizes To Detect Group Differences
in Two-Sample Testing Assuming Equal Sample Sizes*
(Relative Risk Calculations)

Occurrence Rate of Disease in Control Population	Relative Risk (Multiplicative Factor of Occurrence Rate for Exposed Group)										
	1.25	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00
1/10,000	2,822,082	783,901	235,164	78,384	43,544	29,391	21,944	17,415	14,393	12,243	10,640
1/5,000	1,410,882	391,901	117,564	39,184	21,766	14,690	10,968	8,703	7,193	6,118	5,317
1/1,000	281,922	78,301	23,484	7,824	4,344	2,930	2,187	1,735	1,433	1,218	1,058
1/500	140,802	39,101	11,724	3,904	2,166	1,460	1,089	863	713	606	526
1/100	27,906	7,741	2,316	768	424	284	211	167	137	116	100
1/50	13,794	3,821	1,140	376	206	137	101	79	65	54	47

*This study has unequal sample sizes; therefore, the tabled values are understated. The similar table in the Baseline Morbidity Report, 24 February 1984, is in error because tabulated sample sizes were only one-half of their correct values.

TABLE 7-2.

Required Sample Sizes To Detect Group Differences in Two-Sample Testing Assuming Equal Sample Sizes* (Mean Shift Calculations)

Mean shift	Variability (σ/μ)				
	0.05	0.10	0.25	0.50	0.75
0.5%	1,568	6,272	39,200	156,800	352,800
1.0%	392	1,568	9,800	39,200	88,200
1.5%	175	697	4,356	17,423	39,200
2.0%	98	392	2,450	9,800	22,050
2.5%	63	251	1,568	6,272	14,112
5.0%	16	63	392	1,568	3,528
7.5%	7	28	175	697	1,568
10.0%	4	16	98	392	882

*This study has unequal sample sizes; therefore, the tabled values are understated. The similar table in the Baseline Morbidity Report, 24 February 1984, is in error because tabulated sample sizes were only one-half of their correct values.

TABLE 7-3.

Probability of Zero Cases as a Function of Prevalence

Disease Prevalence	Probability of Finding Zero Cases in a Group of 1,016 Participants
1/10,000	0.903
1/5,000	0.816
1/2,000	0.602
1/1,000	0.362
1/500	0.131
1/200	0.006

becomes increasingly more conservative as the correlation among the endpoints increases. For the analysis results in this report, an alpha level of 0.05 was used for each dependent variable. In addition, group contrasts in strata defined by levels of a covariate involving in a group-by-covariate interaction were assessed by an alpha level of 0.05. The same was true for exposure level strata.

In light of the multiple-endpoints problem, extreme caution in the interpretation of statistical results was required. A first consideration was the strength of the association in terms of the significance of the relative risk or difference in group means. All associations with p-values of 0.10 or less were examined and are described in this report. Then, careful consideration was given to the pattern of statistically significant results. Were only a few sporadic endpoints statistically significant, or was significance achieved on a number of endpoints indicating the same organ system failure? Were the significant results all in the same direction, and did they make biological and clinical sense? Did they confirm previous studies, or were they new findings?

Paired Versus Unpaired Analyses

Matching subjects in a study design on selected variables improves the comparability of the groups to be compared and, depending on the relationship of the matching variables to the study objective, the matching can be used explicitly in the analysis. In this study, the Comparison group was matched to the exposed group on age (to the nearest month of birth), race (Black, nonblack), and occupational category (officer-pilot, officer-navigator, officer-nonflyer, enlisted flyer, enlisted groundcrew). The matching was exact for occupational category, nearly exact for race (three mismatches occurred because of recording errors), and very close with respect to age (69% of the mortality population was matched to the nearest month of birth and more than 95% to the nearest year of birth).

The general approach in this report, however, was to conduct unpaired analyses using all available data, based on stratification and/or covariate adjustment. In an unpaired analysis, the matching still serves to improve

the comparability of the two groups, and precision is usually gained from the stratification and covariate adjustment.

Mortality and Morbidity Data

The AFHS incorporated both mortality and morbidity endpoints. The mortality data have been, and will continue to be, subjected to separate analysis. Interpretation of the morbidity analyses must be made in the light of the mortality results, particularly as the study continues and the number of deaths increases. Differential mortality in the two groups could obviously have an important impact on contrasts of physical examination findings in the surviving cohorts. This issue was examined in the analysis of selected diseases, for example, cancer.

Cutpoints

The variables in this study were discrete, categorical, or continuous. Many served primarily as dependent variables, and when in the continuous form, powerful analyses were possible. In other settings, particularly when log-linear or logistic regression models were fitted, it is often necessary to dichotomize or discretize the continuous variables. Discretization, by establishing suitable nonoverlapping intervals or cutpoints, was often the result of a judgment requiring both statistical and clinical input.

In general, cutpoint decisions considered the form of the variable, distribution of the variable, established values (e.g., cholesterol, normal-abnormal, as specified by a given technique in a given laboratory), scientific values set by precedence (e.g., systolic and diastolic normal threshold 140/90), and error induction by another variable (e.g., use of the blood pressure threshold in obese-armed individuals). The approach to the selection of appropriate cutpoints was to select all cutpoints on a case-by-case basis and, where indicated, use the norms of the SCRF laboratory.

Exclusions

Due to medical considerations, certain subjects were excluded from the analyses of selected clinical categories. The exclusions were generally defined in the Baseline study and are identified in the clinical chapters of this report. Other exclusions were the result of missing data.

OVERVIEW OF STATISTICAL PROCEDURES

This section summarizes the basic statistical approach used in the data analysis of the first followup of the AFHS. The approach consisted of four parts: (1) preliminary analysis of the dependent variables and covariates to check for data anomalies and to obtain a general overview of the data, (2) core analyses to carefully determine any possible effect of herbicide exposure, (3) analysis of the exposure index to investigate the dose-response relationship for the Ranch Hand group only, and (4) longitudinal analysis to examine changes over time. A summary of the statistical techniques utilized is provided in Table 7-4. This basic approach was utilized in the analyses for each clinical category.

TABLE 7-4.

Summary of Statistical Procedures

Chi-Square Contingency Table Test

The chi-square test of independence[2] is calculated for a contingency table by the following formula:

$$\chi^2 = \Sigma(f_o - f_e)^2/f_e$$

where the sum is taken over all cells of the contingency table and

f_o=observed frequency in a cell

f_e=expected frequency under the hypothesis of independence.

Large values indicate deviations from the null hypothesis and are tested for significance by comparing the calculated χ^2 to the tables of the chi-square distribution.

Fisher's Exact Test

Fisher's exact test[2] is a randomization test of the hypothesis of independence for a 2x2 contingency table. This technique is useful for small samples and sparse cells. This is a permutation test based on the exact probability of observing the particular set of frequencies.

General Linear Model Analysis

The form of the general linear model[1] for two independent variables is:

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon$$

where

Y = dependent variable (continuous)

α = level of Y at $X_1 = 0$ and $X_2 = 0$, i.e., the intercept

X_1, X_2 = measured value of the first and second independent variables, respectively, which may be continuous or discrete

β_1, β_2 = coefficient indicating linear association between Y and X_1, Y and X_2, respectively

β_{12} = coefficient reflecting the linear interaction of X_1 and X_2

ε = error term.

This model assumes that the error terms are independent and normally distributed with a mean of 0 and a constant variance. Extension to multiple independent variables and interaction terms is immediate.

TABLE 7-4. (continued)

Summary of Statistical Procedures

Linear regression, multiple regression, analysis of variance, and analysis of covariance are all examples of general linear model analysis.

Kolmogorov-Smirnov Distribution Test

The Kolmogorov-Smirnov (K-S) test[3] is a nonparametric procedure which assesses differences between the distribution of two samples. Specifically, the K-S procedure tests the hypothesis that populations π_1 and π_2 are identical and is designed to detect all possible deviations from this hypothesis. The assumptions of the K-S test are that the observations from the two samples are mutually independent and that both sets of observations are samples from the same distribution.

Logistic Regression Analysis

The logistic regression model[2,4] enables a dichotomous dependent variable to be modeled in a regression framework with continuous and/or discrete independent variables. For two risk factors, such as group and age, the logistic regression model would be:

$$\text{logit } P = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon$$

where

P = probability of disease for an individual with risk factors X_1 and X_2

logit P = ln (P/1-P), i.e., the log odds for disease

X_1 = first risk factor, e.g., group

X_2 = second risk factor, e.g., age.

The parameters are interpreted as follows:

α = log odds for the disease when both factors are at a 0 level

β_1 = coefficient indicating the group effect adjusted for age

β_2 = coefficient indicating the age effect adjusted for group

β_{12} = coefficient indicating the interaction between group and age

ε = error term.

In the absence of an interaction ($\beta_{12} = 0$), $\exp(\beta_1)$ reflects the adjusted odds ratio for individuals in Group 1 ($X_1 = 1$) relative to

Group 0 ($X_1 = 0$). If the probability of disease is small, the odds ratio will be approximately equal to the relative risk.

Homogeneity of the odds ratios across different strata was assessed by the method of Breslow and Day.[5]

Throughout this report the adjusted odds ratios are referred to as adjusted relative risks. Correspondingly, in the absence of covariates (i.e., unadjusted analysis) the odds ratios are referred to as estimated relative risks.

Proportional Odds Model

The proportional odds model[6] allows for the analysis of an ordered outcome variable. The model assumes that the odds of falling below a certain level rather than above it for individuals at different levels of an independent variable $\underline{X}$ are in constant ratio. For example, if the response takes one of the four values "excellent," "good," "fair," or "poor," and $\underline{X}$ is a simple indicator variable designating group (Ranch Hand versus Comparison), then the proportional odds model states that the odds for responding "excellent" versus "good," "fair," or "poor" in the Ranch Hand group are a multiple, $\exp(\beta)$, of the corresponding odds in the Comparison group. Likewise, the odds for responding "excellent" or "good" versus "fair" or "poor" in the Ranch Hand group are the same multiple, $\exp(\beta)$, of the corresponding odds in the Comparison group, as are the odds for responding "excellent," "good," or "fair" versus "poor" in the two groups. Thus, the model is appropriate whenever one frequency distribution is "shifted left" relative to another distribution. Incorporation of other variables into $\underline{X}$ allows the estimation of proportional odds ratios adjusted for covariates.

Let the ordered response Y take values in the range 1 to K, and let $\pi_i(\underline{X})$, i=1,...,K, denote the probability of responding at level i for an individual with covariate vector $\underline{X}$. Let $\kappa_j(\underline{X})$ be the odds that $Y \leq j$ given $\underline{X}$, i.e.,

$$\kappa_j(\underline{X}) = \frac{\pi_1(\underline{X}) + \pi_2(\underline{X}) + \ldots + \pi_j(\underline{X})}{\pi_{j+1}(\underline{X}) + \pi_{j+2}(\underline{X}) + \ldots + \pi_k(\underline{X})}, \quad j=1,\ldots K-1$$

The proportional odds model specifies that

$\kappa_j(\underline{X}) = \kappa_j \exp(\beta'\underline{X})$, for constant κ_j

Thus the ratio of odds for individuals at covariate levels $\underline{X}_1$ and $\underline{X}_2$ is

$$\frac{\kappa_j(\underline{X}_1)}{\kappa_j(\underline{X}_2)} = \exp\{\beta'(\underline{X}_1 - \underline{X}_2)\}$$

and depends only on $\underline{X}_1 - \underline{X}_2$ and not on j.

Log-linear Analysis

Log-linear analysis[2] is a statistical technique for analyzing cross-classified data or contingency tables. A saturated log-linear model for a three-way table is:

$$\ln(Z_{ijk}) = U_o + U_{1(i)} + U_{2(j)} + U_{3(k)} + U_{12(ij)} + U_{23(j,k)} + U_{13(ik)} + U_{123(ijk)}$$

where

Z_{ijk} = expected cell count

$U_{1(i)}$ = specific one-factor effect

$U_{12(ij)}$ = specific two-factor effect or interaction

$U_{123(ijk)}$ = three-factor effect or interaction.

The simplest models are obtained by including only the significant U-terms. Adjusted relative risks are derived from the estimated U-terms from an adequately fitting model.

McNemar's Test

McNemar's test[4] effectively considers discordant pairs in which only the Ranch Hand or only the Comparison member in each pair experiences the abnormality. Using a chi-square approximation with continuity correction, the following statistic is used to test whether the off-diagonal entries are evenly divided:

$$\chi^2 = \frac{(|b-c|-1)^2}{b+c}$$

Where b and c are the number of pairs in which only the Ranch Hand is abnormal or only the Comparison is abnormal, respectively. This test is compared to a chi-squared distribution with one degree of freedom.

TABLE 7-4. (continued)

Summary of Statistical Procedures

Test for Linear Trend

For a kx2 contingency table in which the k groups fall into a natural order, Armitage[7] developed a test for a linear trend in the proportions. Let P_i denote the proportion of individuals in the ith row possessing some attribute (e.g., proportion of individuals with abnormal values at each of the three exposure level categories). A score, X_i, is assigned to each of the k levels of the row variable, and the regression coefficient, $\hat{\beta}$, of P_i on X_i is estimated. The regression coefficient is estimated in the usual way except that P_i is weighted by the sample size, n_i, in each row. $\hat{\beta}/SE(\hat{\beta})$ provides a normal deviate for testing the null hypotheses of $\beta = 0$.

Preliminary Analysis

The preliminary analysis included the calculation of basic descriptive measures for the dependent and independent variables (covariates), for each group (Ranch Hand and Comparison). The descriptive measures included frequency distributions, histograms, mean, median, standard deviation, and range. These analyses provided an overview of each variable and the relationship of the Ranch Hand group to the Comparison group. In addition, the preliminary analysis provided insight for the construction of composite variables, the plausibility of normal/abnormal limits and cutpoints, and the choice of possible transformations to enhance the normality of the distribution of continuous dependent variables.

Another purpose of the preliminary analysis was to examine the relationship between the covariates and the dependent variables and the relationships between and among the covariates. To accomplish this, cross tabulations of discrete variables were constructed and analyzed by the chi-square, or Fisher's exact test. For continuous variables, simple t-tests of group differences were done and product-moment correlation coefficients were computed. The preliminary analyses were accomplished with the use of the SAS®. Selected covariate tables are presented in the clinical chapters for illustration.

Core Analysis

The core analysis consisted of a series of steps taken to ascertain whether or not the data indicated a significant difference between the Ranch Hand and Comparison groups for each dependent variable.

Both unadjusted and adjusted analyses were performed and are presented for each clinical chapter. Unadjusted analyses are simple contrasts between the Ranch Hand and Comparison groups of the mean values, or proportion with abnormal values, of each dependent variable, by t-tests, one-way analysis of variance, Fisher's exact test, or chi-square tests, as appropriate. Adjusted analyses take into account important covariates in the assessment of possible group differences, i.e., the covariates are included in the general linear, logistic regression, proportional odds models, or log-linear models.

Continuous Dependent Variables

When the dependent variable was continuous, the general linear models (GLM) procedure of SAS® was used to fit a model of the dependent variable in terms of the group indicator (Ranch Hand or Comparison) and appropriate covariates, and interactions between covariates. The covariates could be continuous or categorical variables. If necessary, the dependent variable was transformed prior to analysis by a transformation (e.g., logarithm) to enhance normality of its distribution.[8] When a "best" model was fitted, according to the strategy outlined below, the test for significance of the group difference was then done on the adjusted group means, provided there were no significant interactions between the group indicator and any of the covariates. Group differences in the presence of interactions were assessed using stratification by different levels of the covariate(s) involved in the interaction or estimation of group differences at selected covariate levels using the best model identified.

For some non-normally distributed dependent variables, the Kolmogorov-Smirnov[3] (K-S) test of significant differences between the distributions of the variables in the two study groups was conducted. The K-S test is a nonparametric test for the equality of two distributions designed to detect broad classes of alternatives.

Categorical Dependent Variables

Discrete dependent variables were analyzed by methods parallel to those used for continuous variables. For dichotomous variables, logistic regression was carried out by the program BMDP®-LR; for this analysis, the covariates could be either continuous or discrete. For polychotomous dependent variables, where the number of categories was three or more, log-linear modeling was performed by the use of the program BMDP®-4F, by incorporating the full (k)-factor interaction term involving the (k) covariates used in the model. For this type of analysis, all covariates had to be categorized. The models were fitted by the method of maximum likelihood.

To make the results parallel to those obtained by logistic regression, i.e., because of the distinction between dependent and independent variables, the marginals were fixed in the model,[9] effectively converting the log-linear model into a logit model. The significance of the relative risk for group was determined by examination of the appropriate model, as determined by the study, that includes all statistically significant effects and the group indicator or by examination of the significant interactions. Adjusted relative risks were derived from the coefficients of the appropriate model.

Modeling Strategy

In each clinical category, many covariates were considered for inclusion in the statistical models for adjusted group contrasts. The large number of such covariates and consequent interaction terms and the resulting difficulties of interpretation forced the adoption of a strategy for identifying a moderately simple model involving only significant effects. Interpretation of possible group differences was then made in the context of this simple model. A schematic representation of the generalized modeling strategy is provided in Appendix E.

An initial model including all two-factor interactions and all three-factor interactions involving group was examined. Global tests at the 0.15 level, or individual tests at the 0.05 level, were used to screen out unnecessary three-factor interactions. A hierarchical stepwise deletion strategy was then used, eliminating effects with $p>0.05$ (except the main group effect) and retaining lower order effects if involved in higher order interactions, to result in the simplest model. Interactions between covariates, if significant, were retained as effects.

The analysis was carried out by different statisticians, and there are necessarily subtle differences between them in presentation and approach. This, however, should not affect any of the final conclusions as to group differences. In some chapters, for instance, adjusted group means are presented, and in others the differences between the adjusted group means are

presented. In each case, the same conclusion may be drawn since the statistic of relevance is the difference between the adjusted group mean and the associated p-value. Further, if an interaction of group with a continuous covariate was found, two equally valid methods were used to illustrate how the interaction was arising. One method was to categorize the continuous covariate and describe the group differences within each (covariate-defined) stratum. Another technique was to present group differences for several selected values of the covariate. Further, in the presence of small frequencies of abnormalities, exposure index analyses were occasionally carried out using only the main effects model (i.e., using group and all the covariates but not including interaction terms).

It is recognized that, due to the large number of group-by-covariate interactions examined (up to 7 per dependent variable) for some 150 variables, some of the group-by-covariate interactions judged significant at the 0.05 level may be spurious, i.e., chance occurrences and not of biological relevance. This is analogous to the concept of Type I error for a two-sample adjusted contrast.

When several covariates are used in an adjusted analysis of the group contrast for a single dependent variable, and each group-by-covariate interaction is tested at the 0.05 level, the chance of finding at least one that is statistically significant is, of course, greater than 0.05; this is assuming that there is no group effect or group-by-covariate interaction. How much greater depends on the interrelatedness of the covariates and their association with the dependent variable.

For a study of this size, with many interrelated dependent variables being examined, it is not known how to estimate the number of group-by-covariate interactions that may be due to chance alone. However, this frequency clearly will be more than 5 percent. It is noted that this concept should be considered when significant group-by-covariate interactions are interpreted. Further, it is important that the size of the p-value associated with each group-by-covariate interaction be carefully weighed, as should be the pattern of the interaction findings for related dependent variables.

EXPOSURE INDEX ANALYSES

As described in Chapter 8, the exposure index was constructed to portray the level of dose of the herbicide for the Ranch Hand or exposed group only. Exposure index analyses were conducted on all dependent variables. The objective of the analyses was to determine if there was a difference in the levels of the dependent variable corresponding to the levels of the exposure index.

The exposure index was trichotomized as high, medium, and low, separately, for each of the three occupational groups: officer, enlisted flyer, enlisted groundcrew. Thus, separate analyses were conducted for each occupational cohort. Discrete dependent variables were evaluated using log-linear and logistic regression models, treating exposure level as a categorical variable (by means of two indicator variables) and adjusting for covariates. For continuous dependent variables, a general linear model was fit, adjusting for covariates and using two indicator variables to designate exposure level. Contrasts between medium and low, and between high and low exposure levels, were also examined.

LONGITUDINAL ANALYSES

General

Another objective of the AFHS is to observe the Ranch Hand population and the Comparison group carefully over time for the emergence, or deleterious rate change, of symptoms, signs, laboratory parameters, or frank disease. This followup objective is not without scientific and logistic challenge, considering mobile populations, problems of loss to study, changing laboratory methods and diagnostic criteria, and the diversity of many changing factors over a period encompassing numerous followup examinations. The following sections describe the statistical procedures used for both continuous and categorical longitudinal data.

Continuous Data

A repeated measurements analysis of variance procedure[10] was used to analyze the variables measured on a continuous scale. The model for the dependent variable (Y) measurement on the kth participant (π_k) in the ith group (α_i) at the jth time (β_j) is as follows:

$$Y_{ijk} = \mu + \alpha_i + \pi_{k(i)} + \beta_j + \alpha\beta_{ij} + \varepsilon_{ijk}$$

The sources of variation and associated degrees of freedom are given below:

Source	Degrees of Freedom*
Group (Ranch Hand vs. Comparison)	1
Subject/Group	2,108
Time (Baseline vs. Followup)	1
Group-by-Time	1
(Subject-by-Time)/Group	2,108

*Based on 971 Ranch Hands and 1,139 Comparisons.

The primary source of interest is the group-by-time interaction ($\alpha\beta_{ij}$). With measurements on each participant at only two times (Baseline and followup), a test on this interaction is equivalent to a test on the equality of mean differences (Baseline minus followup) between the Ranch Hand and Comparison groups.

Care must be taken in the interpretation of the main effect, time (β_j) (i.e., overall Baseline mean versus overall followup mean). This effect is totally confounded with laboratory differences, and with over 2,000 participants, "significant differences" come easily.

The source of variation due to group (α_i) reflects a difference between the overall Ranch Hand and Comparison means (averaged over both times). This source should complement the group difference findings at Baseline and at

followup, provided the group changes were consistent (no significant group-by-time interaction). All available participants were used at each Baseline and followup analysis, while only the participants with both measurements are included in the repeated measurement analysis.

Covariates were not used in these analyses. Generally, time-independent (e.g., year of birth) and time-dependent (e.g., smoking) covariates can be used. Only the time-dependent covariates would affect the primary source of interest, namely the group-by-time interaction. Hence, all of the previously considered time-independent covariates would affect only the main group effect, a source not of primary interest since it is being considered in the separate cross-sectional analyses.

Categorical Data

Frequently, data were collected as normal-abnormal, or continuous measurements were discretized into this binomial response. For each Ranch Hand and Comparison group, a Baseline versus followup 2x2 (normal-abnormal) table of frequencies was prepared (paired data):

Ranch Hand

Baseline \ Followup	Abnormal	Normal
Abnormal		✓
Normal	✓	

Comparison

Baseline \ Followup	Abnormal	Normal
Abnormal		X
Normal	X	

As with the McNemar test, only the Abnormal→Normal and Normal→Abnormal off-diagonal data were used in further contrasts. A conventional χ^2 test was used to test the null hypothesis of a comparable change pattern for the two groups (unpaired data).

Group \ Change Pattern	Normal-Abnormal	Abnormal-Normal
Ranch Hand	✓	✓
Comparison	X	X

This test is equivalent to testing no group-by-time-by-endpoint interaction in a matched pair analysis.[11]

CHAPTER 7

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CHAPTER 8

EXPOSURE INDEX

This chapter describes the development of the exposure index of the AFHS. Portions of this chapter are paraphrased from the Baseline Morbidity Report, 24 February 1984.

An increased incidence of adverse health effects at higher levels of exposure represents a classic increasing dose-response relationship. The potential relationship of clinical endpoints with herbicide exposure can be tested using an estimate of exposure, hereinafter called an exposure index, for each member of the Ranch Hand cohort of the AFHS. However, due to a variety of biomedical mechanisms, there can be exceptions to the hypothesis of a consistently increasing dose-response relationship.

An index of potential exposure to any of four TCDD-containing herbicides from fixed-wing spray missions was constructed for each Ranch Hand from the available historical data. The index serves as an estimate only, since the actual concentration of TCDD in the herbicides varied from lot to lot and individual assessments of actual body burden cannot be made. The four TCDD-containing herbicides used in the development of the index are Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green. The exposure index was designed to correlate as closely as possible with exposure and is not an exact measure of actual individual exposures. Although the index contains errors when used to assess the exposure of a specific individual, it provides some degree of useful inference for groups of similarly exposed individuals. In summary, the exposure index in the AFHS is a surrogate indicator of TCDD exposure.

The exposure index developed for the Baseline study and used in this report is defined in Table 8-1.

The exposure index for the ith subject, denoted E_i, is defined as the product of the TCDD weighting factor, the gallons of TCDD-containing herbicide sprayed in the Republic of Vietnam theater during the tour of the ith subject, and the inverse of the number of men sharing the subject's duties during the tour of the ith subject. Each of these factors is described below.

The TCDD weighting factor reflects the estimated relative concentration of TCDD in the herbicides sprayed. The estimated mean concentrations of TCDD in Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green are 2 parts per million (ppm), 33 ppm, 66 ppm, and 66 ppm, respectively. Archived samples of Herbicide Purple indicate a mean concentration of approximately 33 ppm, and samples of Herbicide Orange had a mean concentration of about 2 ppm. Since Herbicide Pink and Herbicide Green contained twice as much 2,4,5-T as Herbicide Purple, the mean concentration of TCDD in these two herbicides was approximately 66 ppm. Based on procurement records and dissemination information, a combination of Herbicide Green, Herbicide

TABLE 8-1.

Algorithm for Exposure Index

$$E_i = \left\{\begin{matrix}\text{TCDD} \\ \text{Weighting} \\ \text{Factor}\end{matrix}\right\} \times \left\{\begin{matrix}\text{Gallons of TCDD-} \\ \text{Containing Herbicide} \\ \text{Sprayed in the RVN} \\ \text{Theater During the} \\ \text{Tour of the ith Subject}\end{matrix}\right\} \times \left\{\frac{1}{\begin{matrix}\text{Number of Men with Subject's} \\ \text{Duties in the RVN Theater During} \\ \text{the Tour of the ith Subject}\end{matrix}}\right\}$$

where E_i = Exposure Index for the ith Subject

$$\text{TCDD Weighting Factor} = \begin{cases} 24.0 \text{ if before 1 July 1965} \\ 1.0 \text{ if on or after 1 July 1965} \end{cases}$$

Since prior to 1 July 1965 a combination of Herbicides Green, Pink, and Purple with a mean concentration of 48.0 ppm was sprayed, and after 1 July 1965 only Herbicide Orange with a mean concentration of 2 ppm was sprayed, the ratio is then 48:2 or 24:1.

Gallons of TCDD-Containing Herbicide Sprayed in the RVN Theater During the Tour of the ith Subject = Number of Gallons of Herbicides Orange, Green, Pink, and Purple Expressed in Herbicide Orange Equivalent Gallons Based on Mean Concentration of TCDD

Using the following:

Herbicide	Mean Concentration (ppm) of TCDD
Green	66
Orange	2
Pink	66
Purple	33

Number of Men with Subject's Duties in the RVN Theater During the Tour of the ith Subject = Number of Personnel in the Same Occupational Category

---

Source: Baseline Morbidity Report, 24 February 1984.

Pink, and Herbicide Purple was sprayed between January 1962 and 1965. The estimated mean concentration of TCDD for this time was 48.0 ppm, using available data on the number of gallons procured and sprayed.[1]

The Herbs Tape and other data sources[1] indicate that only Herbicide Orange was disseminated after 1 July 1965. Normalizing to Herbicide Orange, the weighting factor becomes 24.0 before 1 July 1965 and 1.0 after 1 July 1965.

Using the Herbs Tape, Contemporary Historical Evaluation and Combat Operations (CHECO) Reports, and quarterly operations reports, a table of gallons of TCDD-containing herbicide sprayed for each month of the operation was constructed. Gallons of Herbicides Purple, Pink, and Green were converted to Herbicide Orange equivalent gallons based on the TCDD weighting factor of 24.0. This information is provided in Table F-1 of Appendix F.

The dates and occupational category of each Ranch Hand's tour(s) in the Republic of Vietnam were obtained by a manual review of military records. The study design specified five occupational categories: (1) officer-pilot, (2) officer-navigator, (3) officer-nonflying, (4) enlisted flyer, and (5) enlisted groundcrew. Based on the review of the records, the Ranch Hand manning for each occupational category by month was compiled. This information is also presented in Table F-1 of Appendix F.

A numeric exposure index reflecting the effective number of gallons of Herbicide Orange to which each individual was potentially exposed was computed. For the purpose of analysis, the values were categorized as high, medium, or low for each occupational category. Only three occupational categories were used. The three officer categories were combined into one since pilots and navigators were exposed in the same manner and the officer-nonflying category, which included a relatively small number of participants, consisted of administrators whose exposure was considered to be essentially zero. The overall group of "nonexposed" Ranch Hands, estimated at approximately 2 percent of the Ranch Hand group, was analyzed in the low exposure category (see Table 8-2), conceivably leading to dilution of the exposure analyses and group contrasts. The exposure index categorizations developed for the Baseline study and used in this report are provided in Table 8-2, along with the frequencies of Ranch Hand participants by occupation and exposure level.

The current exposure index is not specific to job and, therefore, may underestimate exposure for those individuals whose jobs required routine handling of herbicide. For example, maintenance schedules for the aircraft herbicide spray tank required that an emergency dump valve be periodically greased, requiring entry into the tank. The current exposure index cannot distinguish between men who received such exposure and men who did not. The extent to which individuals are misclassified by the current exposure index is not known, precluding bias calculations at this time.

Because of the acknowledged imprecision of the exposure index, Air Force efforts are under way to develop new perspectives of exposure. One effort is the construction of a new questionnaire for the 459 enlisted groundcrew personnel that may permit more accurate exposure analyses within this category. Another approach is the measurement of serum dioxin levels.

TABLE 8-2.

Exposure Index Categorization of 1,016 Compliant Ranch Hands

Occupational Group	Exposure Category	Effective Herbicide Orange Gallons Corresponding to Exposure Category	Number of Ranch Hand Participants in Exposure Category
Officer	Low	<35,000	127
	Medium	35,000-70,000	130
	High	>70,000	123
Enlisted Flyer	Low	<50,000	55
	Medium	50,000-85,000	65
	High	>85,000	57
Enlisted Groundcrew	Low	<20,000	154
	Medium	20,000-27,000	163
	High	>27,000	142
Total			1,016

The Air Force currently is conducting a pilot study in conjunction with the laboratories of the Centers for Disease Control, Atlanta, Georgia, to determine levels of TCDD in serum and to establish the validity of exposure differential within the Ranch Hand and Comparison groups. This study is in accordance with the Study Protocol commitment to estimate dosage of TCDD as accurately as current technology permits. If successful, use of time-adjusted TCDD levels would permit more accurate exposure analyses within the Ranch Hand group. Perhaps of most importance, accurate TCDD levels within the Ranch Hand group could standardize exposure to a comparable baseline for all participants. Thus, the use of adjusted TCDD levels will place the exposure concepts on a firm scientific basis, and if herbicide effects exist, they can be discerned more accurately.

CHAPTER 8

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CHAPTER 9

GENERAL HEALTH

INTRODUCTION

The effects of heavy, acute exposure to TCDD have been demonstrated in a number of different organ systems. It is plausible, therefore, that chronic low-dose exposure to TCDD might induce subtle, interrelated effects that are not organ-system specific, but are manifest only in general terms, or affect the state of "well-being." However, it is difficult to measure overall health objectively, and for this reason general health outcomes, as defined by this study, should be judged in context with other more specific clinical endpoints. (It should be noted that "general health" outcomes have not traditionally been considered in other dioxin morbidity studies.)

Baseline Summary Results

Five general health variables were included in the Baseline examination: self-perception of health, appearance of illness or distress, relative age, sedimentation rate, and percent body fat. In the analysis of the 1982 Baseline examination data, a statistically significant difference was found between the Ranch Hand and Comparison groups in self-perception of health, with a greater percentage of Ranch Hands reporting their health as fair or poor than Comparisons. This was true in both the younger and older age groups ($p=0.017$ and $p=0.025$ for individuals 40 or less and more than 40 years of age, respectively). The relative risk of the Ranch Hand group was also somewhat greater in the younger subgroup than in the older subgroup (1.8 and 1.4, respectively). Since only 9 of 1,811 individuals were reported by the examining physician as appearing ill or distressed, this designation was apparently reserved for only very ill or distressed individuals. Nevertheless, 8 of the 9 individuals were Ranch Hands, the difference being of borderline significance ($p=0.056$). Conversely, more Ranch Hands than Comparisons were reported by the examiners as appearing younger than their actual ages (4.9% versus 2.5%, $p=0.029$). No overall differences in percent body fat or sedimentation rate were found, although a significant interaction between age, group, and sedimentation rate was noted; younger exposed group members had fewer sedimentation rate abnormalities than did their Comparisons, whereas no difference was found in participants more than 40 years old. No statistically significant dose-response relationships were detected in the Ranch Hand group.

Parameters of the 1985 General Health Assessment

Variables of the Baseline examination (self-perception of health, appearance of illness or distress, relative age, sedimentation rate, and percent body fat) were analyzed for the third year followup effort.

As an assessment of the general health status of each individual, three subjective measures were made as well as two more objective measures. During the health interview each study participant was asked, "Compared to other people your age, would you say that your health is excellent, good, fair, or poor?" This self-assessment of health is susceptible to varying degrees of conscious and subconscious bias. The examiner recorded the appearance of illness or distress (yes/no) and noted the appearance of the subject as younger than, older than, or the same as his stated age. To the degree that the examining physicians were kept blind to the study subject's group membership (Ranch Hand, Comparison), their assessments were less subject to bias.

The two objective measures were percent body fat, calculated from the body mass index, and the erythrocyte sedimentation rate. Although both variables are rather indirect measures of the general state of health, they are accepted indicators of poor health.

The adjusted statistical analyses below accounted for differences associated with age, race, and occupation. In the analysis of self-perception of health and sedimentation rate, adjustment was also made for personality score, determined from the Jenkins Activity Survey.[1] This is a continuous variable derived by means of a discriminant-function equation based on items that best discriminate men judged to be Type A from those judged as Type B. Positive scores reflected the Type A direction and negative scores the Type B direction. Table G-1 of Appendix G gives the distribution of the covariates in the Ranch Hand and Comparison groups. Age, race, and occupation were distributed similarly in the two groups (due to matching), and personality scores were also not significantly different.

Aside from the subjective nature and potential bias in the self-reported perception of health, no specific issues related to assessment methodology require further comment. No individuals were excluded from analysis, except those with missing data.

Chi-square tests and logistic regression models were applied to the categorical data. The sedimentation rate was normalized by logarithmic transformation. The proportional odds model was also used for ordinal data provided by the self-perception of health and relative age variables. Fisher's exact test was applied to the reporting of illness or distress by the examining physician because of the small number of cases who were classified as "ill." A two-sample t-test was used to assess differences in unadjusted group means, followed by multiple regression analysis to incorporate covariates, for percent body fat and sedimentation rate.

RESULTS AND DISCUSSION

Subjective Assessments

Self-Perception of Health

Each participant was asked to designate his health as excellent, good, fair, or poor. The frequency distributions of self-perception of health for each cohort are given in Table 9-1.

TABLE 9-1.

Unadjusted Analysis for Self-Perception of Health by Group

	Self-Perception of Health								
	Excellent		Good		Fair		Poor		
Group	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
Ranch Hand	490	48.2	434	42.7	74	7.3	18	1.8	1,016
Comparison	674	52.1	525	40.6	81	6.3	13	1.0	1,293
				p=0.14					

The summarized data in Table 9-1 show that a higher percentage of Ranch Hands perceived their health to be fair or poor (9.1%) than the Comparisons (7.3%), although this difference was not statistically significant (Est. RR: 1.25, 95% C.I.: [0.95,1.64], p=0.14). Of considerable interest is that the percentage of both groups perceiving their health as only fair or poor was lower than that reported at the Baseline examination 3 years earlier (20.4% and 15.9% for Ranch Hands and Comparisons, respectively). This shift was the opposite of that expected from an aging effect. The data collection technique was an in-home interview in 1982 versus an onsite clinic interview in 1985, but this was not judged to be the likely cause of the improvement in health perceptions for the 3-year period. Whatever the cause, the effects were similar in both groups.

A test of association between health perception (dichotomized as excellent/good and fair/poor) was performed with the covariates of age (born in or after 1942, born before 1942), race, occupation, and personality score (Jenkins score, trichotomized as low [less than -5], medium [between -5 and 5], and high [greater than 5]). These associations were examined both within the Ranch Hand and Comparison groups and pooled over the two groups. The findings were similar, and Table 9-2 shows the results after pooling.

These results indicated a significant effect of age, with a higher percentage of the older cohort than the younger cohort reporting their health as fair or poor, as well as a significant effect of occupation, with the percentage of enlisted personnel reporting fair or poor health nearly twice that of the officers. No significant associations were noted for race or personality score.

TABLE 9-2.

Association Between Self-Perception of Health and Age, Race, Occupation, and Personality Score in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Self-Perception of Health: Excellent/Good Number	Excellent/Good Percent	Fair/Poor Number	Fair/Poor Percent	Total	p-Value
Age	Born ≥1942	903	94.0	58	6.0	961	0.003
	Born <1942	1,220	90.5	128	9.5	1,348	
Race	Black	130	90.9	13	9.1	143	0.76
	Nonblack	1,993	92.0	173	8.0	2,166	
Occupation	Officer	819	94.8	45	5.2	864	
	Enlisted Flyer	347	89.7	40	10.3	387	<0.001
	Enlisted Groundcrew	957	90.4	101	9.6	1,058	
Personality Score	Low	827	92.2	70	7.8	897	
	Medium	716	91.2	69	8.8	785	0.61
	High	573	92.6	46	7.4	619	

Adjusted analyses of self-perception of health were done by logistic regression using the covariates of age, race, occupation, and personality type. (Self-perception of health was dichotomized and the covariates categorized as in Table 9-2.) These analyses revealed statistically significant age and occupation effects, as well as a significant group-by-occupation interaction (p=0.015). Exponentiation of linear combinations of relevant regression coefficients generated adjusted relative risks for each occupational stratum. These summary data are presented in Table 9-3.

TABLE 9-3.

Adjusted Relative Risks of Self-Perception of Health by Occupation

Occupation	Adj. Relative Risk (95% C.I.)	p-Value
Officer	0.78 (0.42,1.46)	0.441
Enlisted Flyer	0.75 (0.38,1.46)	0.395
Enlisted Groundcrew	1.90 (1.25,2.88)	0.003

These analyses showed significant group differences in the self-perception of health for the enlisted groundcrew category but not for the officers or enlisted flyers. This is perhaps more clearly seen in Table 9-4, which gives the frequency distribution of self-perception of health stratified by occupation.

Among officers and enlisted flyers, a lower percentage of Ranch Hands than Comparisons perceived their health as fair or poor. (These same Ranch Hands were also less likely to view their health as excellent.) In the enlisted groundcrew cohort, 12.7 percent of the Ranch Hands reported their health as fair or poor versus 7.2 percent of the Comparisons.

Because the logistic model does not account for the ordinal nature of the self-perception of health variable, a proportional odds model for ordinal responses was also fit to the data in Tables 9-1 and 9-4.

For the ordinal responses in Table 9-1, the proportional odds model yielded a statistically significant result (p=0.037), with poorer health estimated to be 1.18 times greater in the Ranch Hand group than in the Comparison group (95% C.I.: [1.01,1.39]). For the data in Table 9-4, a proportional odds model fit to each occupational stratum (adjusting for age) yielded p-values of 0.65 for officers, 0.43 for enlisted flyers, and 0.031 for enlisted groundcrew. Thus, only the enlisted groundcrew category reached statistical significance, with adjusted proportional odds of 1.30 (95% C.I.: [1.02,1.64]).

TABLE 9-4.

Frequency of Self-Perception of Health
by Occupation and Group

	Self-Perception of Health								
	Excellent		Good		Fair		Poor		
Occupation	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
Officer									
Ranch Hand	238	62.6	124	32.6	13	3.4	5	1.3	380
Comparison	314	64.9	143	29.6	23	4.8	4	0.8	484
Enlisted Flyer									
Ranch Hand	67	37.8	94	53.1	13	7.3	3	1.7	177
Comparison	94	44.8	92	43.8	19	9.0	5	2.4	210
Enlisted Groundcrew									
Ranch Hand	185	40.3	216	47.1	48	10.5	10	2.2	459
Comparison	266	44.4	290	48.4	39	6.5	4	0.7	599

Similar results were obtained when the analyses were performed on the 1,016 Ranch Hands and 955 Original Comparisons completing the third-year health interview. These results are provided in Table G-2 of Appendix G. In the unadjusted analysis, the estimated relative risk for fair or poor health versus excellent or good health reached statistical significance (Est. RR: 1.43, 95% C.I.: [1.03,2.00], p=0.042). In the adjusted analysis, group membership, age, and occupation effects were all statistically significant with an adjusted relative risk of 1.48 (95% C.I.: [1.05,2.07]). The group-by-occupation interaction, however, did not reach statistical significance (p=0.23). Nevertheless, little difference was seen in the officers and enlisted flyers, whereas among the enlisted groundcrew, 12.7 percent of the Ranch Hands versus 7.4 percent of the Original Comparisons reported their health as fair or poor.

Contrasts of the Ranch Hand and Original Comparison groups using the proportional odds model yielded only borderline significant results. For the unadjusted analysis applied to the overall data, the estimated proportional odds were 1.17 (95%. C.I.: [0.99,1.39], p=0.073). Stratifying by occupation and adjusting for age gave p-values of 0.76, 0.11, and 0.078 for the officers, enlisted flyers, and enlisted groundcrew, respectively. The adjusted proportional odds in the enlisted groundcrew cohort were 1.26 (95% C.I.: [0.97,1.62]).

Appearance of Illness or Distress

The recording of the appearance of acute ill health or physical distress at the examination was intended to capture significant subjective health data that might (though not likely) escape corroboration by other physical examination or laboratory data. In particular, examining physicians were requested to affirm the presence of acute distress when the sign of hippocratic facies was present, a sign not easily feigned by participants. Very few participants were diagnosed as being acutely ill; these data are summarized in Table 9-5.

TABLE 9-5.

Unadjusted Analysis for Appearance of Acute Illness or Distress by Group

	Acute Illness or Distress					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	p-Value*
Ranch Hand	4	0.4	1,010	99.6	1,014	0.53
Comparison	6	0.5	1,287	99.5	1,293	

*Fisher's exact test, 1-sided.

These data were too sparse to permit further meaningful analyses. Descriptively, it was noted that 9 of the 10 ill individuals were in the older age group; 9 of 10 were nonblack; and 2 were officers, 4 were enlisted flyers, and 4 were enlisted groundcrew. The 6 ill Comparison individuals were all Original Comparisons, as can be seen in Table G-3 of Appendix G.

Further, these results were in substantial contrast to the Baseline findings that revealed a marginally significant excess ($p=0.056$) of acute distress among the Ranch Hands.

Appearance of Relative Age

The examining physicians scored each participant as appearing younger, older, or the same as his chronological age. These data are presented in Table 9-6.

TABLE 9-6.

Unadjusted Analysis for Appearance of Relative Age by Group

	Appearance of Relative Age							
	Younger		Same		Older			
Group	Number	Percent	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	16	1.6	957	94.3	42	4.1	1,015	0.12
Comparison	9	0.7	1,233	95.4	51	3.9	1,293	

These frequency distributions showed that a slightly higher percentage of Ranch Hands than Comparisons appeared younger than their stated age, and almost equivalent percentages in both groups appeared older. Overall, there was no significant difference in the two distributions. The unadjusted findings in Table 9-6, however, did not confirm the significant tendency ($p=0.029$) at the 1982 Baseline examination for a higher percentage of the Ranch Hands than Comparisons to appear younger than their stated ages. Table 9-7 presents the association between each of the covariates and relative age (dichotomized as older looking versus the same or younger looking) after combining the Ranch Hand and Comparison groups.

As noted from this table, age and race were not significantly associated with the appearance of relative age, whereas occupation did reveal a significant association, with about 6 percent of the enlisted personnel appearing older than their stated ages compared to 1 percent of the officers.

An adjusted analysis using logistic regression with the covariates age, race, and occupation showed a significant effect due to occupation as well as a significant group-by-occupation interaction ($p=0.038$). Adjusted relative risks for each occupational stratum are given in Table 9-8.

The adjusted relative risk was greater than 1 for the officers, i.e., the odds of appearing older were greater in the Ranch Hand group than in the Comparison group, but the relative risk was less than 1 for the enlisted flyers. However, the associated confidence intervals were rather broad and did not rule out a relative risk of 1 in each case. Again, because the logistic regression model does not account for the ordinal nature of the dependent variable, a proportional odds model was applied to the enlisted flyer cohort (data in the officer and enlisted groundcrew strata did not fit the model properly). The estimated proportional odds for the enlisted flyer cohort were nonsignificant (estimated odds: 0.49, 95% C.I.: [0.22,1.11], $p=0.087$).

TABLE 9-7.

Association Between Appearance of Relative Age and Age, Race, and Occupation in the Combined Ranch Hand and Comparison Groups

		Appearance of Relative Age					
		Younger/Same		Older			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	914	95.2	46	4.8	960	0.14
	Born <1942	1,301	96.5	47	3.5	1,348	
Race	Black	138	96.5	5	3.5	143	0.91
	Nonblack	2,077	95.9	88	4.1	2,165	
Occupation	Officer	855	99.0	9	1.0	864	
	Enlisted Flyer	362	93.5	25	6.5	387	<0.001
	Enlisted Groundcrew	998	94.4	59	5.6	1,057	

TABLE 9-8.

Adjusted Relative Risks of Appearance of Relative Age by Occupation

Occupation	Adj. Relative Risk (95% C.I.)	p-Value
Officer	4.52 (0.94,21.9)	0.060
Enlisted Flyer	0.44 (0.23,1.27)	0.159
Enlisted Groundcrew	1.05 (0.62,1.78)	0.849

A contrast of the Ranch Hand group with the Original Comparisons gave similar results, as shown in Table G-4 of Appendix G. Overall, there was little difference, but the group-by-occupation interaction was of borderline significance in the adjusted analysis (p=0.052). Differences were largely confined to the enlisted flyers, where fewer Ranch Hands than Comparisons appeared older than their stated ages (Adj. RR: 0.47, 95% C.I.: [0.20,1.12], p=0.089) (see Table G-5 of Appendix G). A proportional odds model applied to the enlisted flyer stratum gave adjusted proportional odds of 0.45 (95% C.I.: [0.20,1.02], p=0.055).

Objective Assessments

Two objective but nonspecific indicators of general health, the erythrocyte sedimentation rate and percent body fat, were analyzed in both discrete and continuous forms. Because the sedimentation rate was a highly skewed variable, it was normalized by logarithmic transformation for the continuous analyses. The sedimentation rate dichotomy was set at 20 mm/hr or less (normal) and greater than 20 mm/hr (abnormal) by the large-tube Westergren method. Percent body fat was based on height and weight obtained during the examination and was calculated according to the following formula: Percent Body Fat = (Weight[kg]/Height[m]^2)(1.264) - 13.305. It is recognized that this formula will overstate the percent body fat for very muscular, large-boned men. Percent body fat was trichotomized into less than 10 percent (lean), 10 to 25 percent (normal), and greater than 25 percent (obese), consistent with the Baseline Report. Because of the sparseness of the lean category, it was often necessary to use a dichotomous variable of lean-normal versus obese.

Erythrocyte Sedimentation Rate

The unadjusted contrast of log sedimentation rate means revealed no significant group differences (mean±SE=1.620±0.026 in the Ranch Hand group versus 1.595±0.021 in the Comparison group, t=0.73, p=0.47). The geometric mean values were 5.05 and 4.93 for the Ranch Hand and Comparison groups, respectively. Tests of association of dichotomized sedimentation rate, with the covariates age, race, occupation, and personality score, pooled over both groups, were conducted; these summarized data are shown in Table 9-9.

These results showed significant effects of age, with older individuals having a higher frequency of abnormal sedimentation rates than younger individuals, and a significant effect of personality score, with Type B individuals (low personality score) having more sedimentation rate abnormalities. The effect of occupation was of borderline significance (p=0.080), with a slightly higher percentage of abnormal values among the enlisted flyers than among officers or enlisted groundcrew. There was no evidence of any association between race and abnormal sedimentation rate.

An analysis of the log sedimentation rate, adjusting for age, race, occupation, and personality score, detected significant effects for all of the covariates except race, as well as a significant age-by-personality score interaction. As in the unadjusted analysis, the adjusted analysis did not reveal any significant difference between the Ranch Hand and Comparison groups (p=0.412).

TABLE 9-9.

Association Between Sedimentation Rate and Age, Race, Occupation, and Personality Score in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Sedimentation Rate: Normal ≤20mm/hr Number	Normal ≤20mm/hr Percent	Abnormal >20mm/hr Number	Abnormal >20mm/hr Percent	Total	p-Value
Age	Born ≥1942	941	97.9	20	2.1	961	<0.001
	Born <1942	1,263	93.7	85	6.3	1,348	
Race	Black	136	95.1	7	4.9	143	0.999
	Nonblack	2,068	95.5	98	4.5	2,166	
Occupation	Officer	828	95.8	36	4.2	864	
	Enlisted Flyer	361	93.3	26	6.7	387	0.080
	Enlisted Groundcrew	1,015	95.9	43	4.1	1,058	
Personality Score	Low	843	94.0	54	6.0	897	
	Medium	758	96.6	27	3.4	785	0.026
	High	595	96.1	24	3.9	619	

However, in the dichotomous form, sedimentation rate abnormalities were significantly more prevalent in the Ranch Hands than Comparisons (Est. RR: 1.63, 95% C.I.: [1.12,2.38], p=0.013); these results are given in Table 9-10.

Logistic regression analysis found significant effects for age and personality score, and the adjusted relative risk of 1.68 (95% C.I.: [1.13,2.49], p=0.011), was very similar to the estimated relative risk of 1.63.

TABLE 9-10.

Unadjusted Analysis for Sedimentation Rate by Group

	Sedimentation Rate					
	Normal ≤20 mm/hr		Abnormal >20 mm/hr			
Group	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	957	94.2	59	5.8	1,016	0.013
Comparison	1,247	96.4	46	3.6	1,293	

The mean log sedimentation rate in the Original Comparisons was 1.636 plus or minus 0.025, not significantly different from the Ranch Hand mean (t=-0.45, p=0.65). The regression analysis yielded results very similar to those reported above, with little difference in the adjusted group means. Logistic regression analyses also gave similar results, with significantly more abnormalities in the Ranch Hand group (p=0.037).

In summary, there was no difference between groups based upon mean values of the sedimentation rate, unadjusted or adjusted, but both unadjusted and adjusted discrete analyses showed a significantly higher prevalence of sedimentation rate abnormalities in the Ranch Hand group. This finding was opposite to the Baseline findings in which Ranch Hands age 40 or less had significantly fewer sedimentation rate abnormalities than Comparisons, with no group difference in individuals over the age of 40.

Percent Body Fat

The mean percent body fat of Ranch Hands was significantly lower than that of Comparisons (21.10%±0.15 versus 21.54%±0.14, respectively; p=0.037). Because there were only a few values in the lean category (6 in the Ranch Hand group and 4 in the Comparison group), percent body fat was dichotomized into at most 25 percent (lean and normal) and more than 25 percent (obese) for tests of association between percent body fat and the covariates age, race, and occupation. The results are given in Table 9-11.

TABLE 9-11.

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

		Percent Body Fat					
		Lean/Normal ≤25%		Obese >25%			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	802	83.4	159	16.6	961	0.005
	Born <1942	1,060	78.7	287	21.3	1,347	
Race	Black	110	76.9	33	23.1	143	0.29
	Nonblack	1,752	80.9	413	19.1	2,165	
Occupation	Officer	719	83.3	144	16.7	863	
	Enlisted Flyer	314	81.1	73	18.9	387	0.023
	Enlisted Groundcrew	829	78.4	229	21.6	1,058	

These data demonstrated the significant effects of age, with a higher percentage of obesity in older men, and occupation, with a higher prevalence of obesity in enlisted personnel than in officers. Race was a noncontributory covariate. The covariate of smoking was unexplored.

An adjusted analysis of percent body fat, with the same covariates, also showed the significant effects of age, occupation, and an age-by-occupation interaction. The adjusted results showed a small, but significantly lower mean level of body fat in the Ranch Hand group (adjusted difference=-0.443± 0.210, p=0.035).

With percent body fat dichotomized into obese versus normal or lean, the percent obese was lower in the Ranch Hands than in the Comparisons (18.2% versus 20.2%), but the difference was not significant (Est. RR: 0.90, 95% C.I.: [0.71,1.08], p=0.25). Logistic regression analysis also failed to detect a significant group difference (Adj. RR: 0.87, 95% C.I.: [0.71,1.08], p=0.204).

Analysis of percent body fat in the Ranch Hands and Original Comparisons gave somewhat different results. The overall difference in means was significant as before: 21.10 plus or minus 0.15 in the Ranch Hand group versus 21.58 plus or minus 0.16 in the Original Comparison group (t=-2.15, p=0.032). However, the regression analysis detected a statistically significant group-by-race interaction (p=0.041). The adjusted difference in mean percent body fat (Ranch Hand versus Comparison) was greater in Black participants (-2.26%)

than in nonblack participants (-0.34%). Of the Original Comparisons (Table G-7 of Appendix G), 20.4 percent were obese, greater than, but not significantly different from, the percent obese in the Ranch Hand group (p=0.230). Logistic regression analyses again detected significant age and occupation effects, but it detected no significant interaction between these variables. There was no strong evidence of a group-by-race interaction (models including all two-factor interactions gave a Z-value of 1.19 for the group-by-race interaction). The group effect was not statistically significant (Adj. RR: 0.87, 95% C.I.: [0.70,1.09], p=0.242).

In summary, the unadjusted and adjusted tests of mean percent body fat showed a significantly lower value for Ranch Hands; correspondingly fewer Ranch Hands than Comparisons were obese, although this difference was not statistically significant. Few individuals were lean (less than 10 percent body fat). The 1982 Baseline examination found no difference in group means (p=0.67), or proportion of abnormalities (p=0.89). Further, analyses based solely upon the Original Comparison cohort found the difference in mean percent body fat between the Ranch Hand and Comparison groups to be greater in Blacks than nonblacks.

EXPOSURE INDEX ANALYSES

The exposure index, expressed in equivalent gallons of dioxin-containing herbicide potentially encountered by each Ranch Hand during his tour of duty in Vietnam, was categorized as low, medium, and high. Because it is not possible to assess the relative exposure between occupational groups, and since different cutoff values were used in the three occupational categories, separate analyses were performed within each occupational cohort. A detailed description of the exposure index is found in Chapter 8. Exposure analyses were performed on four of the five general health variables. Only four Ranch Hands were recorded as appearing ill or distressed (two were officers, both in the low-exposure category, and two were enlisted flyers, both in the high-exposure category). Further analysis was not done on this variable.

Self-Perception of Health

Table 9-12 presents dichotomized self-perception of health data by exposure level for the 1,016 Ranch Hands. While these unadjusted contrasts did not reach statistical significance within any of the occupational strata, the linear trend from low to high exposure in the officer cohort of the fair/poor category was of interest, and was subjected to further testing. Although the numbers were small at each exposure level, a test for linear trend led to a borderline significant increase of 2.5 plus or minus 1.3 percent per unit (step) increase in the exposure level category (p=0.064).

Logistic regression analyses adjusted for age (dichotomized), race, and personality score (trichotomized) did not detect any significant exposure level effects. The only significant covariate effect found was for age in the enlisted groundcrew cohort. The adjusted relative risk for each occupational stratum is given in Table 9-13.

TABLE 9-12.

Unadjusted Exposure Index Analysis of Self-Perception of Health by Occupation

Occupation	Exposure Index	Self-Perception of Health: Excellent/Good Number	Excellent/Good Percent	Fair/Poor Number	Fair/Poor Percent	Total	p-Value*
Officer	Low	124	97.6	3	2.4	127	
	Medium	124	95.4	6	4.6	130	0.17
	High	114	92.7	9	7.3	123	
Enlisted Flyer	Low	51	92.7	4	7.3	55	
	Medium	59	90.8	6	9.2	65	0.83
	High	51	89.5	6	10.5	57	
Enlisted Groundcrew	Low	134	87.0	20	13.0	154	
	Medium	146	89.6	17	10.4	163	0.51
	High	121	85.2	21	14.8	142	

*Chi-square tests, 2 d.f.

TABLE 9-13.

Adjusted Relative Risk of Self-Perception of Health by Occupation and Exposure Contrast

Occupation	Exposure Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Officer	Medium vs. Low	2.00 (0.49,8.15)	0.334
	High vs. Low	2.93 (0.76,11.3)	0.119
Enlisted Flyer	Medium vs. Low	1.30 (0.35,4.86)	0.700
	High vs. Low	1.50 (0.40,5.64)	0.549
Enlisted Groundcrew	Medium vs. Low	0.95 (0.47,1.92)	0.882
	High vs. Low	1.21 (0.62,2.35)	0.580

Appearance of Relative Age

The dichotomy of appearance of relative age was assessed for exposure effects in each occupational cohort. These unadjusted analyses, shown in Table 9-14, provided no evidence of a dose-response effect. As can be seen, the number of participants within each stratum appearing older than their stated ages was quite small. The adjusted analyses by logistic regression did not detect any significant exposure or covariate effects.

TABLE 9-14.
Unadjusted Exposure Index Analysis of Appearance of Relative Age by Occupation

		Relative Age					
		Younger/Same		Older			
Occupation	Exposure Index	Number	Percent	Number	Percent	Total	p-Value*
Officer	Low	125	98.4	2	1.6	127	
	Medium	127	97.7	3	2.3	130	0.89
	High	121	98.4	2	1.6	123	
Enlisted Flyer	Low	52	94.6	3	5.4	55	
	Medium	62	95.4	3	4.6	65	0.88
	High	55	96.5	2	3.5	57	
Enlisted Groundcrew	Low	146	94.8	8	5.2	154	
	Medium	151	93.2	11	6.8	162	0.82
	High	134	94.4	8	5.6	142	

*Chi-square tests, 2 d.f.

Erythrocyte Sedimentation Rate

The sedimentation rate was analyzed both continuously on a logarithmic scale and dichotomously (normal, abnormal). One-way analyses of variance were performed on the sedimentation rate means categorized by occupation and exposure level. These tests showed no significant differences in the officer and the enlisted flyer strata ($p=0.76$, $p=0.64$, respectively). In the enlisted groundcrew stratum the means were marginally different, with the mean sedimentation rate increasing with increasing exposure level, but the differences were not statistically significant ($p=0.12$). When these data were adjusted by an analysis of covariance for age, the difference in mean sedimentation rates in the enlisted groundcrew was less noteworthy ($p=0.33$). Age was positively associated with the mean sedimentation rate in all three occupational strata ($p<0.001$, $p=0.009$, and $p<0.001$, respectively). The adjusted tests are reflected in Table 9-15 (means and confidence limits have been transformed back to the original scale).

A categorical analysis of the sedimentation rate by exposure level for each occupational stratum was also conducted. Differing from the previous continuous analyses, the categorical contrasts revealed a significant exposure effect ($p=0.027$) in the enlisted flyer stratum, albeit with small numbers. These summarized data are shown in Table 9-16.

Adjustment for age, race, and personality score revealed a significant high versus low exposure contrast in the enlisted flyer stratum. The adjusted analysis is fully shown in Table 9-17.

TABLE 9-15.

Adjusted Mean Sedimentation Rates by Occupation

Occupation	Exposure Index, Adjusted Mean, mm/hr (95% C.I.) Low	Medium	High	p-Value
Officer	5.40 (4.71,6.19)	4.78 (4.17,5.47)	4.69 (4.09,5.37)	0.31
Enlisted Flyer	5.10 (4.11,6.33)	6.00 (4.91,7.32)	5.00 (4.04,6.19)	0.41
Enlisted Groundcrew	4.66 (4.10,5.29)	5.09 (4.49,5.77)	5.35 (4.69,6.12)	0.33

TABLE 9-16.

Unadjusted Exposure Index Analysis of Sedimentation Rate by Occupation

Occupation	Exposure Index	Sedimentation Rate: Normal ≤20mm/hr Number	Normal ≤20mm/hr Percent	Abnormal >20mm/hr Number	Abnormal >20mm/hr Percent	Total	p-Value*
Officer	Low	117	92.1	10	7.9	127	
	Medium	125	96.2	5	3.8	130	0.27
	High	119	95.9	5	4.1	123	
Enlisted Flyer	Low	53	96.4	2	3.6	55	
	Medium	62	95.4	3	4.6	65	0.027
	High	48	84.2	9	15.8	57	
Enlisted Groundcrew	Low	142	92.2	12	7.8	154	
	Medium	156	95.7	7	4.3	163	0.290
	High	136	95.8	6	4.2	142	

*Chi-square tests, 2 d.f.

TABLE 9-17.

Adjusted Relative Risk of Sedimentation Rate by Occupation and Exposure Contrast

Occupation	Exposure Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Officer	Medium vs. Low	0.47 (0.16,1.41)	0.177
	High vs. Low	0.50 (0.17,1.52)	0.226
Enlisted Flyer	Medium vs. Low	1.28 (0.21,7.96)	0.790
	High vs. Low	4.97 (1.02,24.2)	0.047
Enlisted Groundcrew	Medium vs. Low	0.76 (0.28,2.06)	0.592
	High vs. Low	0.54 (0.19,1.49)	0.234

Percent Body Fat

Exposure analyses of percent body fat were done using both linear models and logistic regression. One-way analyses of variance for means found no statistically significant exposure differences in the occupational cohorts. These statistics are presented in Table 9-18.

TABLE 9-18.

Unadjusted Means of Percent Body Fat by Occupation

	Exposure Index, Mean±SE			
Occupation	Low	Medium	High	p-Value
Officer	20.99±0.36	21.11±0.41	21.26±0.36	0.88
Enlisted Flyer	20.65±0.55	21.26±0.77	21.59±0.77	0.65
Enlisted Groundcrew	20.91±0.42	21.43±0.41	20.79±0.44	0.53

Linear models including age, race, and two-factor exposure level-by-covariate interactions found no significant difference in the adjusted exposure level means for percent body fat. The effect of age was significant in the officer cohort ($p=0.003$), and of borderline significance in the enlisted groundcrew stratum ($p=0.064$). Race was nonsignificant throughout all the tests.

The unadjusted categorical assessment of percent body fat, shown in Table 9-19, revealed no significant exposure effects. However, in the enlisted flyer stratum, a test for linear trend in the proportions gave a borderline significant result ($p=0.054$), with an estimated step increase of 6.8 plus or minus 3.6 percent per unit increase in exposure-level category. An adjusted analysis by logistic regression did not reveal significant exposure level effects but did detect significant effects of age in the officer and enlisted groundcrew categories.

In summary, detailed exposure analyses were performed on four of five dependent variables used to assess general health status. Only a very few of the tests approached statistical significance (multiple comparisons notwithstanding); of these, three associations suggested a trend of adverse effects from low to high exposure; but only one was statistically significant, and there was no consistency across occupational strata (health perception in officers, $p=0.064$; sedimentation rate in enlisted flyers, $p=0.027$; and percent body fat in enlisted flyers, $p=0.054$). These results were relatively comparable to the negative exposure findings in the Baseline Report.

TABLE 9-19.

Unadjusted Exposure Index Analysis of Percent Body Fat by Occupation

Occupation	Exposure Level	Percent Body Fat: Lean/Normal ≤25% Number	Lean/Normal ≤25% Percent	Obese ≤25% Number	Obese ≤25% Percent	Total	p-Value*
Officer	Low	104	81.9	23	18.1	127	
	Medium	110	84.6	20	15.4	130	0.76
	High	100	81.3	23	18.7	123	
Enlisted Flyer	Low	50	90.9	5	9.1	55	
	Medium	53	81.5	12	18.5	65	0.14
	High	44	77.2	13	22.8	57	
Enlisted Groundcrew	Low	126	81.8	28	18.2	154	
	Medium	131	80.4	32	19.6	163	0.88
	High	113	79.6	29	20.4	142	

*Chi-square tests, 2 d.f.

LONGITUDINAL ANALYSES

Two variables, self-perception of health and sedimentation rate, were prescribed to assess the longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables were analyzed in the discrete form. The four categories of perception of health were reduced to normal (excellent/good) and abnormal (fair/poor). The respective laboratory norms of 12 or less mm/hr and more than 12 mm/hr for the Baseline sedimentation rates, and 20 or less mm/hr and more than 20 mm/hr for the followup examination were used to categorize the sedimentation rate data into normal and abnormal groups. The off-diagonal data (normal to abnormal, abnormal to normal) from the two examinations were contrasted by group membership, a process equivalent to testing for a group-by-time-by-clinical endpoint interaction. The results of these tests, unadjusted for covariates, are given in Table 9-20.

These analyses showed an equivalence of the change in self-perception of health in the two groups between examinations, but a highly significant group difference in the change in sedimentation rate abnormalities. The latter was explained by the fact that the Baseline examination determined a significant excess of sedimentation rate abnormalities in the Comparisons whereas at the followup examination, the Ranch Hands had a significantly higher proportion of abnormalities. Perhaps as a related fact, it is recognized that the sedimentation rate laboratory test procedure changed to a more sensitive one at the followup examination.

TABLE 9-20.

Longitudinal Analysis of Self-Perception of Health and Sedimentation Rate: A Contrast of Baseline and First Followup Examination Abnormalities

Variable	Group	Baseline Examination	Followup Examination: Abnormal	Followup Examination: Normal	Odds Ratio (OR*)	p-Value (OR_{RH} vs. OR_C)
Self-Perception of Health	Ranch Hand	Abnormal	62	127	0.21	
		Normal	27	750		0.84
	Comparison	Abnormal	49	124	0.23	
		Normal	28	936		
Sedimentation Rate	Ranch Hand	Abnormal	17	16	2.44	
		Normal	39	899		0.002
	Comparison	Abnormal	14	37	0.73	
		Normal	27	1,061		

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

SUMMARY AND CONCLUSIONS

General physical health was evaluated by five measures, three of which were subjective (self-perception of health, appearance of distress, and appearance of relative age), and two of which were objective (percent body fat and sedimentation rate). Table 9-21 presents a summary of all the unadjusted and adjusted analyses of these five variables.

The Ranch Hands rated their health as fair or poor more often than the Comparisons (9.1% versus 7.3%, respectively), but this difference was not significant by categorical testing. However, further analysis revealed a significant group-by-occupation interaction; differences were largely confined to the enlisted groundcrew category. Both the Ranch Hand and Comparison groups noticeably improved their perceptions of health from the 1982 Baseline examination.

Only 10 individuals were reported as appearing acutely ill or distressed at the followup examination, 4 were Ranch Hands and 6 were Comparisons. This difference was not statistically significant and the data were insufficient for adjusted analyses.

TABLE 9-21.

Overall Summary Results of Unadjusted and Adjusted Analyses of General Health Variables

	Unadjusted		Adjusted	
Variable	Categorical	Mean	Categorical	Mean
Self-Perception of Health	NS	--	****	--
Appearance of Illness/Disstress	NS	--	--[a]	--
Appearance of Relative Age	NS	--	****	--
Sedimentation Rate	0.013	NS	0.011	NS
Percent Body Fat	NS	0.037	NS	0.035

--Analysis not performed.

****Group-by-covariate interaction.

[a]Analysis not possible due to sparse data.

Appearance of relative age, as determined by the examining physician, showed 1.6 percent of the Ranch Hands appearing younger than their stated age, 94.3 percent appearing the same, and 4.1 percent appearing older (as contrasted to 0.7%, 95.4%, and 3.9%, respectively, in the Comparison group). There was a significant group-by-occupation interaction, but none of the estimated relative risks for the occupational categories was significant. This observation at the followup examination contrasted with the significant tendency at the Baseline for a higher percentage of Ranch Hands than Comparisons to appear younger than their stated ages.

The geometric mean sedimentation rates (5.05 mm/hr Ranch Hand versus 4.93 mm/hr Comparison) did not differ significantly by group, either unadjusted or after adjustment for age, race, occupation, personality score, and an age-by-personality score interaction. However, in the dichotomous form, 5.8 percent of the Ranch Hands had sedimentation rate abnormalities as contrasted to 3.6 percent in the Comparison group. This difference was significant by both unadjusted and adjusted tests. Also, this finding was opposite to that of the Baseline examination, where it was noted that younger Comparisons had significantly elevated sedimentation rates.

The mean percent body fat of the Ranch Hands was significantly lower than the Comparisons (21.10%±0.15, 21.54%±0.14, respectively, p=0.037), and was of nearly the same magnitude after adjustment for age, race, and occupation. However, both unadjusted and adjusted categorical tests did not reveal significant group differences, although the percent obese was lower in the Ranch Hands than in the Comparisons. No group differences in percent body fat were noted at the Baseline examination.

Detailed exposure analyses were done on four general health variables (appearance of acute distress was too sparse for testing). Only one analysis demonstrated statistical significance, i.e., a positive association of sedimentation rate abnormalities with increasing exposure in the enlisted flyer cohort. Overall, no consistent pattern of exposure effects was discernible, and the exposure findings at the third-year followup were similar to the findings at Baseline.

Longitudinal differences between the 1982 Baseline and the 1985 followup examination were assessed by analyses of two discrete variables, self-perception of health and sedimentation rate. Perceived health showed no significant group differences over time, but both the Ranch Hand and Comparison groups paradoxically reported symmetrical improvements in their perceptions over the 3-year period. The sedimentation rate analysis revealed a highly significant group difference (p=0.002), due to a reversal of findings between examinations, i.e., a significant detriment in the younger Comparisons at the Baseline versus a significant detriment in the Ranch Hands at the followup. The cause(s) and biological relevance of this observation are unclear.

In conclusion, a nonspecific assessment of general physical health has shown relatively close similarity between the Ranch Hand and Comparison groups, with the Ranch Hands continuing to perceive their health more negatively than the Comparisons, having a slightly more favorable percent body-fat proportion, but a higher proportion of abnormal sedimentation rates that reflects a marked change since the Baseline examination. These findings must be placed in context with the organ and system-specific evaluations found in the succeeding chapters.

CHAPTER 9

REFERENCES

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CHAPTER 10

MALIGNANCY

INTRODUCTION

Cancer is a major suspect disease following exposure to chlorophenols, phenoxy herbicides, and dioxin. Both systemic cancer and skin cancer are key focal points of this study.

The issue of military service related cancer in Vietnam veterans first arose in 1978-1979. Media presentations emphasized several early cancer deaths in several Army veterans, which were allegedly caused by exposure to Agent Orange. The media reinforced the causal allegations by citing animal studies, which demonstrated a carcinogenic effect, and a few human studies, which showed excessive cancer in specific occupational groups. So effective and sustained were the media presentations that today the public equates dioxin and Agent Orange exposure to cancer.

In the larger context of environmental controversies, Young aptly described the Agent Orange issue as being at the crossroads of science and social concern.[1] The scientific community has responded to the dioxin question by a massive research effort, which in concert with class action lawsuits, is expected to cost more than a billion dollars in the near future.[2] The core of the overall research effort is basic and applied cancer research.[3]

Traditional animal-to-man extrapolation difficulties and interspecies variability have limited the direct applicability of much of the experimental work to the controversy. Major epidemiologic challenges have included: the ability to control/characterize bias; selection of suitable controls or reference groups; quality/quantity of exposure; misclassification of exposure; confounding exposure to known injurious chemicals; sample size and statistical power; number and selection of relevant risk factors; lack of antecedent disease or syndromes (other than chloracne); time to event (latency); rarity of the endpoint; and tumor type (carcinoma, sarcoma) differences found in many studies.

For these reasons, there is no scientific consensus on the dioxin-cancer question. There is, however, a common thread, raising concern over soft tissue sarcomas (STS) and non-Hodgkin's lymphoma (NHL). Pertinent animal and human studies underscore the concern over cancer.

Numerous animal studies have been conducted to delineate the role of TCDD on tumor initiation, tumor promotion, mutagenesis, cocarcinogenesis, and DNA reactivity. The consensus of most research is that TCDD is only weakly mutagenic, does not covalently bind to DNA or cause it to initiate repair synthesis, and behaves as a strong tumor promoter in already initiated cells.[4]

The oncogenic response to TCDD in animals has been repeatedly shown to depend upon animal species and strain, dose, age, sex, and route of administration. Conventional skin bioassays in mice produced mixed results in some studies[5,6] but caused significant dermal fibrosarcomas in other studies using different strains of animals.[7] In the presence of a strong carcinogen, TCDD induced skin papillomas in homozygous hairless mice (but not in the heterozygous strain), clearly supporting the promoter role of TCDD, a non-genetic mechanism judged to be related to receptor binding.[8]

Ingestion studies in several rat strains at doses of 0.07-0.1 µg/kg/day produced hepatocellular carcinomas, squamous cell carcinomas of the oropharynx and lung, and follicular cell thyroid adenomas.[9,10] In two mouse strains, gavage doses of 0.07-0.3 µg/kg/day produced hepatocellular carcinomas and thyroid tumors.[10] In the presence of partial hepatectomy and diethylnitrosamine, subcutaneous TCDD administration to rats resulted in hepatocellular carcinomas, demonstrating the promoter mechanism of TCDD.[11]

Based upon these and other studies, the International Agency for Research on Cancer (IARC) designated TCDD as carcinogenic in 1982. There are insufficient data to implicate 2,4-D and 2,4,5-T as carcinogens. The majority of animal studies have shown carcinomas rather than sarcomas, the tumor cited in some human studies. If TCDD oncogenicity in humans is to be supported, the differences in tumor types between animals and man requires explanation.

In a series of publications beginning in 1974, commonly known as the "Swedish studies," extensive inquiry was made into occupational cancer following exposure to a variety of herbicides. Four related efforts[12-15] using Swedish railroad workers found an increased cancer incidence mostly associated with non-TCDD herbicides. However, a case-control analysis of these data by other investigators suggested cancer promotion following phenoxy acid exposure.[16]

Prompted by a slight increase in STS in the railroad workers and clinical experience with a case series of STS, Hardell and coworkers launched an extensive second round of studies.[17-25] These efforts showed statistically significant increased risks for STS, Hodgkin's Disease (HD), and NHL. For exposure to phenoxy acids alone, the risk ratio ranged from 5.3 to 6.8 for STS in northern and southern Sweden, respectively, while a range of 3.3 to 6.6 was noted for exposure to chlorophenol alone. For malignant lymphoma (HD plus NHL), risk ratios of 8.4 and 4.8 were respectively demonstrated for chlorophenol and phenoxy acid exposures. An association of nasal and nasopharyngeal cancer to chlorophenol exposure (risk ratio, 6.7) was also detected,[23] but other specifically focused studies of primary liver cancer and colon cancer were negative with respect to phenoxy acid or chlorophenol exposure.[22,24] The colon cancer study was conducted specifically to demonstrate a lack of respondent bias to "validate" previous questionnaire and interview methods used in the STS studies.

From the outset, the Swedish studies have been criticized on methodologic issues,[26-28] prompting the primary authors, Axelson and Hardell, to respond with clarifications, new calculations, amplifying studies on additional cohorts, and studies on other cancers.[22,25,29-31] The chief criticisms centered upon possible respondent and observational biases,

selection of controls, confounding exposures, and degree of true exposure to phenoxy acids and chlorophenols. The authors answered these criticisms within the inherent constraints of the case-control methodology. Their efforts have been characterized as careful, clever, and properly stated, and have received favorable reviews.[32,33]

Four small industrial mortality studies were conducted in the late 1970's and early 1980's.[34-37] NIOSH investigators pooled the data from these studies and noted that three of the 105 deaths (2.9%) in these studies were due to STS as contrasted to an expected 0.07 percent in the U.S. general population.[38] This study has been criticized for the hasty addition of possibly noncomparable industrial cohorts, and the lack of histologic confirmation of the STS cases. A subsequent case report added another STS case to the industrial studies,[39] and two other reports revealed three unrelated STS cases also arising from the industrial sector.[40,41] However, upon closer inspection, only two of the first four cases were confirmed as STS by an independent histologic review.[42] Other review findings of the seven total cases were noteworthy: there was poor agreement on the histologic subtype of the soft tissue tumors, and because of a quirk in the International Classification of Diseases (ICD) System, wherein organ-specific sarcomas are coded separately from soft and connective tissue tumors (ICD 171), death-certificate based studies will underascertain STS by approximately 40 percent.[42,43] This latter problem did not affect the Swedish studies.

Other cancer studies throughout the world showed mixed support for the Swedish findings. An Italian case-control effort[44] showed a weak association between ovarian mesothelial tumors and herbicide exposure, whereas a Finnish study of a small number of pesticide sprayers understandably did not detect any cases of STS or malignant lymphomas (ML).[45] A study of more than 4,000 Danish phenoxy herbicide workers noted five STS cases (versus 1.8 expected) and seven ML cases (versus 5.4 expected).[46] The author concluded that the STS observation supported the Swedish work and that the ML rate did not. One New Zealand case-control study showed a nonsignificant relative risk of 1.3 for STS among occupations consistent with phenoxy herbicide exposure,[47] although a risk of 7.2 was noted for STS and potential chlorophenol exposure in tanneries.

A related second cancer registry-based case-control study revealed significant excesses of agricultural and forestry occupations from ML cases and multiple myeloma cases (odds ratio 1.25).[48] In a similar but larger cancer registry study in Sweden, there was no increased risk of STS (relative risk 0.9) in agricultural or forestry workers as contrasted to other industrial workers.[49] Further, the STS risk was constant over time in spite of increased usage of phenoxy acid herbicides from 1947 to 1970. This Swedish study did not confirm or show a trend consistent with the earlier Hardell Swedish studies.

A recent U.S. case-control study from the Kansas cancer registry has provided partial support for Hardell's observations.[50] The Kansas study was very similar in methodology to the early Swedish studies and tried to avoid bias and misclassification. An overall risk of 1.6 was found for NHL in men exposed to herbicides, particularly 2,4-D. As the frequency of herbicide exposure increased to more than 20 days per year, the risk of NHL increased to sixfold vis-a-vis nonfarmers. For herbicide applicators, the risk for NHL

was 8.0. A simultaneously published review of the Kansas work noted that this should shift scientific concern from STS to NHL.[51] A population-based case-control study of STS and NHL in western Washington found no overall increased risk of these diseases associated with an occupational history of exposure to chlorophenols or phenoxy herbicides.[52] However, risks of NHL were significantly elevated in the specific occupational categories of farmers, forestry herbicide applicators, and those individuals potentially exposed to phenoxy herbicides in any occupation for 15 years or more. An increased risk of NHL was also noted among those with occupational exposure to insecticides, organic solvents, lead, and welding fumes.

A number of Vietnam veteran studies has attempted to determine whether veterans have experienced excessive mortality, particularly from cancer.[53-60] Most of the studies used proportionate mortality ratio (PMR) methodology and equated Vietnam service with potential exposure to Agent Orange, a procedure of considerable imprecision (misclassification). These exposure allocation difficulties, coupled with the inherent methodological weaknesses of the PMR technique, have minimized the contribution of these studies to the overall cancer issue.

As might be predicted by these problems, almost all of the veteran studies were negative for generic cancer associations, as well as for STS, HD, and NHL associations. As an example of the veteran studies, the Australian retrospective cohort mortality effort revealed an overall relative mortality ratio of 0.99, an overall cancer mortality ratio of 0.95, and nonsignificant statistical differences for STS, NHL, and HD.[56] In a recent Vietnam experience study of STS using the case-control method, no significant association was found between military service in Vietnam and the subsequent occurrence of STS.[61]

No consistent pattern for other cancer types has emerged from the entire body of herbicide literature. None of the leukemias has been associated with exposure to Herbicide Orange nor any of its constituents. Two studies noted slight increases in gastric cancer[13,62] and two others cited modest risks for lung cancer.[63,64] A recent Swedish study reported slight excesses of rectal cancer in male workers and increased cervical cancer from the exposed female cohort.[46] Overall, these and other observations have not been consistent with the expectation that dioxin, as a cancer promoter, should increase the occurrence of common "background" cancers.

From another perspective, if clear-cut exposure to 2,4-D or dioxin is shown to cause an immunological deficiency (see Chapter 19), an expectation would be an excessive representation of B-cell tumors from the population of NHL cases.[65-67] An excess of B-cell neoplasms has, in fact, not been described in NHL cases from industrial or veteran cohorts to date.

It is unlikely that the cancer question will be clearly resolved in the near future. Dioxin exposure in industry and agriculture has fallen precipitously since the 1970's, while exposures to 2,4-D and non-TCDD containing herbicides have continued. Veteran studies characterized by low or undocumented exposure to Agent Orange, and/or of small cohort size are unlikely to contribute substantive data for the evaluation of type-specific cancers although they may contribute to the resolution of the generic cancer issue.

In summary, Swedish studies first noted an approximate sixfold risk of soft tissue sarcoma and malignant lymphoma in forestry workers exposed to both phenoxy acid herbicides (not containing the dioxin contaminant) and chlorophenols (containing dioxin). A large number of international studies were predominantly nonsupportive of the Swedish observations. Recent U.S. research on agricultural workers, however, provided some support for a non-Hodgkin's lymphoma-phenoxy acid exposure association. The future scientific focus is expected to shift from dioxin herbicides to nondioxin herbicides and from soft tissue sarcomas to malignant lymphomas. Studies of other veteran populations will not likely contribute to the new emphasis, largely because of exposure uncertainties.

Baseline Summary Results

Cancer received major emphasis during the 1982 AFHS. The assessment of malignancy used data from both the in-home questionnaire and the review-of-systems questionnaire obtained during the physical examination as well as data from the examination itself. All subjective data were verified by medical record reviews. In addition, tabulation of mortality count data from the Baseline Mortality Report[68] was used in conjunction with cancer morbidity information. The overall results showed an equivalence of systemic cancer ($p=0.46$) in the two groups but significantly more nonmelanotic skin cancer ($p=0.03$) in the Ranch Hands.

Of 50 reported systemic cancers from the Ranch Hand and Comparison groups, 28 (14 in each group) were verified by medical records and pathology reports. A visual inspection of anatomic sites showed a slight excess of genitourinary cancer and oropharyngeal cancer but a relative deficit of digestive system neoplasms in the Ranch Hands. A combined morbidity-mortality analysis derived from the initial 1:1 match (Ranch Hand to the C-1 Comparison member) disclosed similar distributions. One case of soft tissue sarcoma and one case of Hodgkin's Disease were confirmed, both in the Comparison group. Exposure analyses for industrial chemicals and x rays were negative as were most of the herbicide exposure analyses in the Ranch Hand group. All of the exposure analyses were based upon very small numbers, and interactions were noted in several strata.

Questionnaire data verified by medical record reviews revealed significantly more skin cancer in the Ranch Hands (relative odds 2.35). Basal cell carcinoma accounted for 83.9 percent of the reported skin cancers in both groups and was concentrated anatomically on the face, head, and neck. The few melanoma and squamous cell cancers were evenly distributed between the Ranch Hand and Comparison groups. All skin cancers occurred in nonblacks. Adjustments for occupational exposures (e.g., asbestos, degreasing chemicals) did not alter the increased rate of skin cancer in the Ranch Hand group.

Skin cancer in both groups was associated with exposure to industrial chemicals ($p=0.03$). Herbicide exposure analyses in the Ranch Hand group were essentially negative, although confounding was noted in many of the analyses. Outdoor occupations subsequent to military service as a covariate did not account for the significant skin cancer association.

Parameters of the 1985 Malignancy Assessment

The emphasis on cancer was increased during the first followup study in 1985. With the Baseline finding of excessive skin cancer in the Ranch Hands, and the lack of covariate data to refine that association, considerable attention was devoted to skin cancer. The questionnaire was altered to collect information on each geographic location in which a participant lived for more than 12 months in order to calculate a cumulative "lifetime" sun exposure index based on geographic latitude, since ultraviolet light exposure has been acknowledged as the primary cause of basal cell carcinoma. Detailed data on skin tannability, eye, skin, and hair color, and parental ethnicity were also obtained. In addition, emphasis at the dermatologic examination was shifted from acne/chloracne to skin cancer, and punch biopsies were sought for all suspected malignant lesions.

The participants were asked to bring copies of their medical records to facilitate the verification of reported malignancies. Highly structured smoking data were collected for more detailed covariate adjustments, and Baseline questions on exposure to other carcinogens were repeated to gather interval data. No invasive procedures were used at the followup physical examination to detect evidence of systemic cancer.

Thus, the dependent variables of the analyses below are similar to the Baseline analyses, but covariate analyses have been expanded for both skin and systemic cancers. The lifetime occurrence of cancer, as well as the interval occurrence of skin and systemic cancers between the Baseline and followup examinations, is analyzed.

Minor numeric differences in various tables that follow reflect missing data from the covariates. The statistical methods used throughout this chapter are Fisher's exact test, chi-square tests of association, and logistic regression models (BMDP®-LR) for adjusted group contrasts of neoplasm incidence rates.

RESULTS AND DISCUSSION

General

Malignant and benign neoplasms, carcinomas in situ, and neoplasms of uncertain behavior or unspecified nature are studied in this chapter. The term "systemic" is used throughout to denote a nonskin neoplasm. The term "unspecified" is used to denote a neoplasm of uncertain behavior or unspecified nature. Neoplasm refers to any new and abnormal growth which may or may not be malignant. Malignant neoplasms (malignancies, cancer) are those neoplasms that are capable of invasion and metastasis.

Questionnaire Data

At the followup examination, participants provided information on cancer during the interval between examinations and participants who were new to the study gave their lifetime history. All reported neoplasms entered the medical records review process for verification. Only 11 Ranch Hands (1.1%) and 12 Comparisons (0.9%) reported neoplastic conditions which could not be

substantiated (all of the skin); the group difference was nonsignificant ($p=0.833$).

Physical Examination Data

Some possible neoplastic conditions were discovered by the physicians at the physical examination. Many suspicious skin lesions were biopsied and the pathology determined. However, for some suspected skin neoplasms and all suspected systemic neoplasms, verification was not complete at the time of writing this report, and thus both verified and suspected neoplasms are described and analyzed. The term suspected is used throughout to denote those possible neoplastic conditions noted by the physicians at the followup examination for which the results of verification are not yet available. Consideration of suspected neoplasms was justifiable in particular for skin neoplasms, for which the biopsy confirmation rate is high.

Statistical Analysis

The statistical analysis is described in three sections. The first section presents unadjusted and adjusted analyses of skin and systemic neoplasm incidence in the Baseline-followup interval, and is referred to as interval analysis. In the second section, unadjusted and adjusted analyses of lifetime skin and systemic neoplasm incidence are analyzed for the followup participants, incorporating Baseline information. Since there were very few neoplasm occurrences before the SEA tours, this combined interval and Baseline analysis is referred to throughout as lifetime analysis. Lastly, the neoplasm history and mortality of the fully compliant Baseline participants subsequent to Baseline are described. All analyses are of the numbers of participants with (one or more) neoplasms, and not of the total number of neoplasms.

The purpose of these three analyses is to present a comprehensive picture of the neoplasia history of the followup participants, and to provide some additional information on the neoplasia status of the Baseline participants subsequent to Baseline. There was a slight difference between the Baseline and followup cohorts. The interval and lifetime analyses pertain to neoplasm incidence among followup participants only. The third section pertains to Baseline participants only, describing their history of neoplasm incidence and mortality since Baseline. A fully combined morbidity-mortality analysis was not feasible for this report.

Assuming a (two-sided) α-level of 0.05 and power 0.8, the sample sizes were sufficient to detect a relative risk of 2.56 when the Comparison neoplasm incidence rate is 1 percent, and a relative risk of 1.63 when the Comparison neoplasm incidence rate is 5 percent. For nonblacks only, the corresponding detectable relative risks are 2.63 and 1.65, respectively.

All analyses of data from Ranch Hands and the Original Comparisons only are given in Appendix H. This appendix also contains other tabulations, such as covariate and interaction tables.

Baseline-Followup Interval

Table 10-1 shows the Baseline-followup interval neoplasm history for the followup participants. The interval began in January 1982 for participants new to the study, i.e., the 45 new Ranch Hands, the 71 new replacement Comparisons, and 83 newly compliant Original Comparisons.

The total numbers of participants with verified neoplasms were 161/1,016 (15.8%) Ranch Hands and 170/1,293 (13.1%) Comparisons; the group difference was marginally significant (p=0.073). The relative frequencies of participants with verified plus suspected neoplasms, 17.4 percent of Ranch Hands and 16.2 percent of Comparisons, did not differ significantly between groups (p=0.466).

Appendix Table H-1 gives the numbers of participants with verified or suspected neoplasms and unadjusted analyses for the Ranch Hands and Original Comparisons in the Baseline-followup interval.

Interval Skin Neoplasms

Of Ranch Hands with verified neoplasms of all types (malignant, benign, and uncertain) 70.8 percent (114/161) had skin neoplasms; the corresponding percentage for the Comparisons was 68.2 percent (116/170). The difference in these proportions was not significant (p=0.634). When suspected neoplasms were included, the contrast was 70.1 percent (124/177) versus 67.6 percent (142/210), again not significant (p=0.660).

No Blacks were found to have skin cancer, as anticipated since Blacks have a lower susceptibility to sun-induced skin cancer. Therefore, analysis of skin cancer was limited to nonblacks.

Of Ranch Hands with skin neoplasms, 32.5 percent (37/114) had malignant neoplasms, as contrasted to 34.5 percent (40/116) of the Comparisons (p=0.781). When suspected malignant skin neoplasms were included, the contrast was 37.9 percent (47/124) versus 42.3 percent (60/142), and was not significant (p=0.531).

For the remainder of this section, only malignant skin neoplasms are analyzed. The dependent variables examined were basal cell carcinomas, melanomas, squamous cell carcinomas, all skin cancers combined, and a group of skin cancers called sun exposure-related skin malignancies. The sun exposure-related skin malignancies were defined as basal cell carcinomas, melanomas, and malignant epithelial neoplasms not otherwise specified (NOS). The latter were included because they are frequently misdiagnosed basal cell carcinomas; three Ranch Hands had this diagnosis.

Interval Malignant Skin Neoplasms

Table 10-2 presents the numbers of participants with verified and suspected malignant skin neoplasms by cell type: basal cell carcinomas, squamous cell carcinomas, melanomas, all skin malignancies combined, and the sun exposure-related skin malignancies, together with the results of unadjusted group contrasts. For the sake of completeness, the total numbers of malignancies of each type are also given. The majority of the

TABLE 10-1.

Unadjusted Analyses of Followup Participants with Verified and Suspected Neoplasms in the Baseline-Followup Interval by Group (Nonblacks and Blacks)

Site	Neoplasm Behavior and Status	Group* Ranch Hand Number**	Ranch Hand Percent	Comparison Number**	Comparison Percent	Total**	p-Value***
Skin	Malignant						
	Verified	37	3.6	40	3.1	77	0.485
	Verified and Suspected	47	4.6	60	4.6	107	0.999
	Benign						
	Verified	76	7.5	77	6.0	153	0.152
	Verified and Suspected	78	7.7	83	6.4	161	0.250
	Uncertain Behavior and Unspecified Nature:						
	Verified	1	0.1	1	0.1	2	0.999
	Verified and Suspected	1	0.1	1	0.1	2	0.999
	Any Skin Neoplasm[a]						
	Verified	114	11.2	116	9.0	230	0.080
	Verified and Suspected	124	12.2	142	11.0	266	0.393
Systemic	Malignant						
	Verified	8	0.8	7	0.5	15	0.603
	Verified and Suspected	12	1.2	12	0.9	24	0.680
	Benign						
	Verified	42	4.1	50	3.9	92	0.749
	Verified and Suspected	48	4.7	61	4.7	109	0.999
	Uncertain Behavior and Unspecified Nature:						
	Verified	6	0.6	7	0.5	13	0.999
	Verified and Suspected	6	0.6	11	0.9	17	0.625
	Any Systemic Neoplasm[b]						
	Verified	55	5.4	61	4.7	116	0.445
	Verified and Suspected	65	6.4	80	6.2	145	0.863
All	Malignant, Benign, Uncertain Behavior, Unspecified Nature[c]						
	Verified	161	15.8	170	13.1	331	0.073
	Verified and Suspected	177	17.4	210	16.2	387	0.466

*Sample sizes: 1,016 Ranch Hands and 1,293 Comparisons.
**Number of participants.
***Fisher's exact test.
[a]Participant has one or more malignant, benign, or unspecified skin neoplasms.
[b]Participant has one or more malignant, benign, or unspecified systemic neoplasms.
[c]Participant has one or more malignant or benign skin or systemic neoplasms.

TABLE 10-2.

Unadjusted Analyses of Nonblack Followup Participants with Verified and Suspected Malignant Skin Neoplasms in the Baseline-Followup Interval by Cell Type and Group

Cell Type	Status	Statistic**	Group* Ranch Hand		Group* Comparison		Est. Relative Risk (95% C.I.)	p-Value
Basal Cell Carcinoma	Verified	Number/%	29	3.0%	30	2.5%	1.23 (0.73,2.07)	0.429
		Total Neoplasms	42		40			
	Verified & Suspected	Number/%	36	3.8%	48	4.0%	0.95 (0.61,1.47)	0.824
		Total Neoplasms	53		63			
Squamous Cell Carcinoma	Verified	Number/%	4	0.4%	4	0.3%	1.27 (0.32,5.08)	0.738
		Total Neoplasms	6		4			
	Verified & Suspected	Number/%	4	0.4%	5	0.4%	1.01 (0.27,3.78)	0.999
		Total Neoplasms	6		5			
Melanoma	Verified	Number/%	1	0.1%	3	0.3%	0.42 (0.04,4.06)	0.635
		Total Neoplasms	2		3			
	Verified & Suspected	Number/%	1	0.1%	6	0.5%	0.21 (0.03,1.75)	0.142
		Total Neoplasms	2		7			
All Malignant Skin Neoplasms	Verified	Number/%	37	3.9%	40	3.3%	1.18 (0.75,1.86)	0.486
		Total Neoplasms	56		52			
	Verified & Suspected	Number/%	47	4.9%	60	5.0%	0.99 (0.67,1.47)	0.999
		Total Neoplasms	70		81			
Sun-Exposure Related Malignant Neoplasms[a]	Verified	Number/%	32	3.4%	33	2.7%	1.24 (0.75,2.02)	0.447
		Total Neoplasms	47		43			
	Verified & Suspected	Number/%	39	4.1%	53	4.4%	0.93 (0.61,1.42)	0.749
		Total Neoplasms	58		71			

*Number of participants--956 Ranch Hands and 1,210 Comparisons.
**Number and percent of participants; total number of malignant neoplasms of specified cell type.
[a]Basal cell carcinoma, melanoma, and malignant epithelial neoplasms NOS.

participants with verified skin malignancies had basal cell carcinomas: 78.4 percent (29/37) Ranch Hands versus 75.0 percent (30/40) Comparisons; the difference between the groups was not significant (p=0.792).

Unadjusted Analyses

Table 10-2 shows that no significant group differences were found in the incidence rates of either verified or verified plus suspected malignant skin neoplasms. For verified basal cell carcinomas, the estimated relative risk of Ranch Hands versus Comparisons was 1.23 (95% C.I.: [0.73,2.07]) and was not significant (p=0.429). The estimated relative risk for verified squamous cell carcinoma, 1.27 (95% C.I.: [0.32,5.08]), was also not significant (p=0.738). The estimated relative risk for verified melanoma, 0.42 (95% C.I.: [0.04,4.06]), was also not significant (p=0.635). There were very few occurrences of melanoma (one Ranch Hand and three Comparisons) since this is a much rarer condition than other kinds of skin cancer. There were no significant differences between the groups for all verified malignant skin cancers combined (Est. RR: 1.18, 95% C.I.: [0.75,1.86], p=0.486) or for the category of sun exposure-related skin malignancies (Est. RR: 1.24, 95% C.I.: [0.75,2.02], p=0.447). When both verified and suspected malignant skin neoplasms were analyzed, the conclusions were similar, namely, there were no significant differences between the groups, and moreover, the estimated relative risks were closer to 1. No group differences were found in the parallel contrasts of Ranch Hands versus Original Comparisons (see Table H-2 of Appendix H).

As shown in Table 10-3, additional analyses contrasted group differences in the anatomic location of basal cell carcinomas, melanomas, and sun exposure-related skin malignancies. Most occurrences of basal cell carcinoma and sun exposure-related skin malignancies were on the face, head, or neck, or the upper extremities. The relative frequency of occurrences of verified basal cell carcinomas at these combined sites was 89.7 percent for Ranch Hands and 80.0 percent for Comparisons of the total number of occurrences in each group, respectively. The group contrast (26/29 versus 24/30) was not significant (p=0.472). These combined sites accounted for 90.6 percent (29/32) of the sun exposure-related malignancies for Ranch Hands versus 72.7 percent (24/33) for Comparisons; this contrast was also not significant (p=0.108). The corresponding contrasts, when suspected malignant neoplasms were included with the verified malignant neoplasms, were also not significant. One Ranch Hand had verified melanoma of the face, and three Comparisons had verified melanoma on the trunk. Two other Comparisons had suspected melanoma, also on the trunk. The group contrast for melanomas on the trunk was not significant for verified conditions (p=0.260), but was marginally significant for verified plus suspected conditions (p=0.071), the detriment being in the Comparison group.

Table 10-4 gives the frequencies of participants with face, head, and neck skin malignancies by group and occupation. Specifically, nonmelanoma malignant skin neoplasms and the sun exposure-related malignant skin neoplasms are listed by occupational category. For officers and enlisted groundcrew, the frequencies of participants with face, head, and neck malignant skin neoplasms (both malignant nonmelanoma and the malignant sun exposure-related skin neoplasms) did not differ significantly by group. However, the Ranch Hand enlisted flyers had a significantly higher frequency

TABLE 10-3.

Unadjusted Analyses of Nonblack Followup Participants with Verified and Suspected Malignant Skin Neoplasms in the Baseline-Followup Interval by Anatomic Site and Group

Site	Status**	Basal Cell Carcinoma				Sun-Exposure Related Malignancies				Melanoma			
		Group*				Group*				Group*			
		Ranch Hand		Comparison	p-Value	Ranch Hand		Comparison	p-Value	Ranch Hand		Comparison	p-Value
Face, Head, Neck	Number/%												
	Verified	24	2.5%	23 1.9%	0.374	27	2.8%	23 1.9%	0.194	1	0.1%	0 0.0%	0.441
	Verified & Suspected	29	3.0%	35 2.9%	0.899	32	3.4%	36 3.0%	0.622	1	0.1%	1 0.1%	0.999
Upper extremities	Number/%												
	Verified	5	0.5%	3 0.3%	0.313	5	0.5%	3 0.3%	0.313	0	0.0%	0 0.0%	—[a]
	Verified & Suspected	5	0.5%	4 0.3%	0.520	5	0.5%	5 0.4%	0.757	0	0.0%	0 0.0%	—[a]
Trunk	Number/%												
	Verified	2	0.2%	6 0.5%	0.479	2	0.2%	9 0.7%	0.126	0	0.0%	3 0.3%	0.260
	Verified & Suspected	4	0.4%	11 0.9%	0.200	4	0.4%	14 1.2%	0.093	0	0.0%	5 0.4%	0.071
Lower Extremities	Number/%												
	Verified	0	0.0%	0 0.0%	—[a]	0	0.0%	0 0.0%	—[a]	0	0.0%	0 0.0%	—[a]
	Verified & Suspected	0	0.0%	0 0.0%	—[a]	0	0.0%	0 0.0%	—[a]	0	0.0%	0 0.0%	—[a]
Other Sites and Sites NOS	Number/%												
	Verified	1	0.1%	2 0.2%	0.999	1	0.1%	2 0.2%	0.999	0	0.0%	0 0.0%	—[a]
	Verified & Suspected	1	0.1%	2 0.2%	0.999	1	0.1%	2 0.2%	0.999	0	0.0%	0 0.0%	—[a]
All Locations	Number/%												
	Verified	29	3.0%	30 2.5%	0.429	32	3.4%	33 2.7%	0.447	1	0.1%	3 0.3%	0.635
	Verified & Suspected	36	3.8%	48 4.0%	0.824	39	4.1%	53 4.4%	0.749	1	0.1%	6 0.5%	0.142

*Number of participants — 956 Ranch Hands, 1,210 Comparisons.

**Number and percent of participants.

[a]No occurrences in either group.

TABLE 10-4.

Unadjusted Analyses of Nonblack Followup Participants with Nonmelanoma Malignant Skin Neoplasms and Sun-Exposure Related Skin Malignancies in the Baseline-Followup Interval Occurring on the Face, Head, or Neck by Occupation

Occupation	Status	Statistic	Nonmelanoma Malignant Skin Neoplasms					Sun-Exposure Related Skin Malignancies				
			Group*					Group*				
			Ranch Hand		Comparison		p-Value	Ranch Hand		Comparison		p-Value
			Number	Percent	Number	Percent		Number	Percent	Number	Percent	
Officer	Verified	n	373		477			373		477		
		Face, Head, Neck	14	3.8	17	3.6	0.999[a]	12	3.2	13	2.7	0.688[a]
		Other Site	5	1.3	4	0.8	0.516[b]	3	0.8	5	1.1	0.999[b]
		No Cancer	354	94.9	456	95.6		358	96.0	459	96.2	
	Verified & Suspected	Face, Head, Neck	20	5.4	23	4.8	0.754[a]	17	4.6	20	4.2	0.866[a]
		Other Site	7	1.9	8	1.7	0.999[b]	4	1.1	9	1.9	0.408[b]
		No Cancer	346	92.8	446	93.5		352	94.4	448	93.9	
Enlisted Flyer	Verified	n	167		193			167		193		
		Face, Head, Neck	8	4.8	3	1.6	0.121[a]	8	4.8	2	1.0	0.049[a]
		Other Site	1	0.6	0	0.0	0.456[b]	1	0.6	1	0.5	0.999[b]
		No Cancer	158	94.6	190	98.5		158	94.6	190	98.5	
	Verified & Suspected	Face, Head, Neck	8	4.8	5	2.6	0.396[a]	8	4.8	4	2.1	0.238[a]
		Other Site	1	0.6	1	0.6	0.999[b]	1	0.6	2	1.0	0.999[b]
		No Cancer	158	94.6	187	96.9		158	94.6	187	96.9	
Enlisted Groundcrew	Verified	n	416		540			416		540		
		Face, Head, Neck	7	1.7	9	1.7	0.999[a]	7	1.7	8	1.5	0.800[a]
		Other Site	1	0.2	4	0.7	0.395[b]	1	0.2	4	0.7	0.395[b]
		No Cancer	408	98.1	527	97.6		408	98.1	528	97.8	
	Verified & Suspected	Face, Head, Neck	7	1.7	13	2.4	0.500[a]	7	1.7	12	2.2	0.644[a]
		Other Site	3	0.7	6	1.1	0.739[b]	2	0.5	6	1.1	0.477[b]
		No Cancer	406	97.6	521	96.5		407	97.8	522	96.7	

*Number and percent of participants.
[a]Fisher's exact test for face, head, or neck versus no malignancy.
[b]Fisher's exact test for other site versus no malignancy.

of malignant sun exposure-related skin neoplasms than the corresponding Comparisons, 4.8 percent versus 1.0 percent ($p=0.049$). For nonmelanoma malignant skin neoplasms, the contrast was 4.8 percent versus 1.6 percent, but the difference was not significant ($p=0.121$). Inclusion of suspected malignant neoplasms with the verified malignant neoplasms reduced the significance of the difference between the groups for both the sun exposure-related skin malignancies and the nonmelanoma malignant skin neoplasms.

Adjusted group contrasts of the incidence rate of basal cell carcinomas and malignant sun exposure-related skin neoplasms were done for verified and verified plus suspected conditions. Adjusted analyses were not carried out, however, for melanomas or squamous cell carcinomas because of the small frequencies.

Covariates

The covariates considered for the adjusted analyses of malignant skin neoplasm incidence, listed in Table 10-5, were the matching variables age and occupation; history of alcohol and cigarette use; host factors, comprising skin color, eye color, hair color, and ethnic background; reaction of skin to sun exposure; average lifetime residential latitude; and exposure to recognized carcinogens. Age was used as a continuous variable in the adjusted analyses, but was categorized for ease of presentation in the report.

Eye color, hair color, and skin color were coded by the dermatologist at the physical examination. Hair color was determined by comparing the hair at the back of the neck with 17 numbered standardized hair samples[69] and selecting the most closely matching hair sample. Similarly, skin color groupings from dark brown to pale peach were determined by comparing standardized flesh-colored squares[70] against the skin of the inside upper arm. For the analysis, hair and skin colors were grouped as shown in Table 10-5. Each participant was assigned to one of four ethnic groups according to his responses to questions on race, as given in Table 10-5. (Blacks were omitted from the table because the analysis of malignant skin neoplasia was restricted to nonblacks.) These ethnic categories are approximate groupings in terms of susceptibility to sun-induced skin damage. The ethnic categories also generally correlate to skin color, a commonly known important risk factor for skin cancer.

A lifetime residential history was obtained from all participants by a questionnaire. Residential history, relative to the equator, is a surrogate measure of sun exposure (but does not account for altitude or average sun-days at each location), an important risk factor for skin cancer. Each participant was asked to list all residences chronologically, citing both the city (or military installation) and the years of residence at each location since birth. Residences of less than 1 year were not sought because of the frequent short-term military travels of these cohorts.

By standardized geographic atlases, the latitude (in degrees and minutes) of each residence was recorded. The Air Force subsequently checked all of the latitude determinations for accuracy. The average lifetime residential latitude of each participant was calculated by dividing the total degree-years (i.e., sum of latitude [degrees] times number of years lived there) from all residences by the total number of residential years listed.

TABLE 10-5.

Covariates for Analyses of Malignant Skin Neoplasms

Covariate	Category
Age	Born ≥1942, 1923-1941, ≤1922[a]
Occupation	Officer, Enlisted Flyer, Enlisted Groundcrew
Lifetime Cigarette Smoking	Pack-years: 0, >0-20, >20-40, >40
Lifetime Alcohol Consumption	Drink-years: 0, >0-5, >5-30, >30-100, >100
Ethnic Background	A, B, C, D[b]
Skin Color	Dark, medium, pale, dark peach, pale peach
Hair Color	Black, dark brown, light brown, blond, red
Eye Color	Brown, hazel, green, gray, blue[c]
Reaction of Skin to Sun Exposure[d]:	
(A.1) After first 30 minutes of summer sun	Burns, usually burns, burns mildly, rarely burns
(A.2) After ≥2 hours, after first exposure	Burns painfully, burns, becomes red, no reaction
(A.3) After repeated sun exposures	Freckles with no tan, tans mildly, tans moderately, tans deep brown
Sun-Reaction Index (Composite)[d]	(1) Burns painfully (A.2) and/or freckles with no tan (A.3) (2) Burns (A.2) and/or tans mildly (A.3) (3) All other reactions
Residential History (Average Latitude)	Average latitude <37°, ≥37°
Exposure to Carcinogens/Groups of Carcinogens	
Set 1[d]	
Asbestos	Yes, No
Nonmedical X Rays	Yes, No
Industrial Chemicals	Yes, No
Herbicides	Yes, No
Insecticides	Yes, No
Degreasing Chemicals	Yes, No

TABLE 10-5. (continued)

Covariates for Analyses of Malignant Skin Neoplasms

Covariate	Category
Set 2[e]	
Anthracene	Yes, No
Arsenic	Yes, No
Benzene	Yes, No
Benzidene	Yes, No
Chromates	Yes, No
Coal Tar	Yes, No
Creosote	Yes, No
Aminodiphenyl	Yes, No
Chloromethyl Ether	Yes, No
Mustard Gas	Yes, No
Naphthylamine	Yes, No
Cutting Oils	Yes, No
Trichloroethylene	Yes, No
Ultraviolet Light (not sun)	Yes, No
Vinyl Chloride	Yes, No
Composite Carcinogen Exposure	Yes, if yes for exposure to any carcinogen in set 2, otherwise no.

[a]Used as a continuous variable in adjusted analysis.

[b]A - English, Welsh, Scottish, Irish.
B - Scandinavian, German, Polish, Russian, other Slavic, Jewish, French.
C - Spanish, Italian, Greek.
D - Mexican, American Indian, Asian.

[c]Participant with one green eye and one brown eye is coded as green.

[d]Questionnaire data (see Appendix B).

[e]AFHS Form 2 (see Appendix C).

Recognizing that both total degree-years and average lifetime latitude could be covariates for malignant sun exposure-related skin neoplasms, average latitude was selected because of the high correlation of degree-years with chronological age, a separate risk factor already used in the analyses. Further, average residential latitude was believed to be a more stable measure in the presence of some lack of precision in the source data. In all analyses, the average residential latitude was used as a dichotomous variable (less than 37° N latitude, greater than or equal to 37° N latitude). A line across the United States at 37° N approximates a line from San Francisco, California, to Richmond, Virginia.

Examination of the group distributions of the latitude variable suggest that it is a significant confounding variable. Specifically, 56.7 percent of the nonblack Ranch Hands had an average lifetime residential latitude greater than or equal to 37° N latitude versus 49.4 percent of the nonblack Comparisons ($p=0.001$). Although the average lifetime group residential latitudes appear similar (37.21° N latitude for the Ranch Hands, and 36.74° N latitude for the Comparisons), this difference is also highly significant ($p=0.003$), reflecting the substantial power of the analysis of continuous data.

Participants reported their susceptibility to the effects of sun-exposure damage by answering three questions about their skin reaction to sun: the reaction after the first 30 minutes of exposure to summer sun, the reaction after 2 or more hours of sun exposure after the first 30-minute exposure, and the reaction after repeated exposures (see questions 10-12 on page 71 of the questionnaire provided in Appendix B). Since these three responses are highly correlated, a composite sun-reaction variable for use in the adjusted analysis, called the sun-reaction index, was constructed from the last two questions (2-hour and repeated exposure reactions) after examination of the association between basal cell carcinoma incidence and the three skin reaction variables. The sun-reaction index had three categories. The first category corresponded to the most sensitive reaction on the last two questions, the second category corresponded to the next less sensitive reaction on these two questions, and the third category comprised the remaining responses.

Detailed questionnaire information on exposure to asbestos, nonmedical x rays, industrial chemicals, herbicides, insecticides, and degreasing chemicals was obtained from each participant. Self-reported information on exposure to 15 individual carcinogens was obtained at the physical examination. A composite carcinogen exposure variable was constructed from these responses on individual carcinogens: A participant had a positive score for this variable if he reported exposure to one or more of the 15 carcinogens, otherwise he had a negative score. Self-reported information on asbestos and radiation exposure was not used because this information was obtained in more detail from the questionnaire.

The nonblack Ranch Hands differed significantly from the nonblack Comparisons in their exposure (yes/no) to nonmedical x rays (19.3% versus 25.6%, $p<0.001$). They also differed significantly from the Comparisons in their exposure to herbicides (94.1% versus 29.8%, $p<0.001$) and insecticides (70.2% versus 53.1%, $p<0.001$), possibly reflecting Vietnam experience. These variables were not used in the adjusted analysis. Further, there were significant or marginally significant group differences in the self-reported exposures to several individual carcinogens, in each instance relatively more (nonblack) Ranch Hands than Comparisons reported exposure: arsenic (2.7%

versus 1.2%, p=0.016), naphthylamine (3.3% versus 1.7%, p=0.024), cutting oils (12.7% versus 8.7%, p=0.003), benzene (4.3% versus 2.7%, p=0.056), and benzidine (0.8% versus 0.3%, p=0.070). Results were similar when Blacks were included in the analysis.

Covariate Associations

Table 10-6 gives a summary of the chi-square tests of association between all covariates and the incidence of basal cell carcinomas and sun exposure-related malignancies. Details of these tests of association are provided in Appendix H, Table H-3.

There was a significant increase in the incidence rate of verified basal cell carcinomas with increasing age (p=0.001). There was a significant difference in the incidence rate of basal cell carcinomas among occupation groups, with enlisted groundcrew having a lower incidence rate (1.8%) than officers (3.7%) and enlisted flyers (3.1%) (p=0.047). Since officers are, on the average, 5 years older than enlisted participants, this occupation effect may be due to some confounding with age. There was a higher incidence rate for average lifetime residential latitude less than 37° N versus greater than or equal to 37° N latitude (p=0.008). Furthermore, there was a strong difference for different levels of the sun-reaction index ($p<0.001$), and the three skin-reaction-to-sun variables ($p \leq 0.001$ for all). Participants who tended to burn most had a lower rate (1.4%) than those with a milder reaction (6.0%), and a similar rate to those who tended to tan (1.9%) (an unexpected finding). There was a significant relationship between the incidence rate of basal cell carcinoma and total pack-years of lifetime smoking (p=0.023 for verifieds). This effect may also be due to confounding with age rather than to a primary smoking effect (see Table H-5 of Appendix H). No significant association was found between the incidence rate of verified basal cell carcinoma and lifetime drink-years.

No significant associations were found with ethnic group, skin color, eye color, and hair color. However, when the ethnic group categories were dichotomized as Celtic or English versus other ethnic groups, the association was marginally significant (p=0.093). Skin color was dichotomized as dark peach or light peach versus other colors, and the association was significant (Est. RR: 3.00, 95% C.I.: [1.08,8.33], p=0.024). Hair color was dichotomized as blond or red versus other colors. The association of hair color with basal cell carcinoma incidence was not significant (p=0.384). Furthermore, no significant relationship was found between basal cell carcinoma incidence and the composite carcinogen-exposure variable (p=0.523) or the grouped or individual carcinogens.

The associations between the covariates and the incidence of verified plus suspected basal cell carcinomas paralleled those for the verified basal cell carcinomas only, except that the difference in rates among ethnic groups was significant (p=0.046), hair color was significant (p=0.040), and a marginally significant positive relationship was found with nonmedical x-ray exposure (p=0.084) and herbicide exposure (p=0.072). The difference among occupation groups, however, was more significant (p=0.003).

TABLE 10-6.

Summary of Associations Between Incidence Rates of Basal Cell Carcinoma and Sun Exposure-Related Skin Malignancies and the Covariates, in the Baseline-Followup Interval for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Basal Cell Carcinoma		Sun Exposure-Related Skin Malignancies	
	Verified p-Value	Verified & Suspected p-Value	Verified p-Value	Verified & Suspected p-Value
Age	0.001	<0.001	0.004	<0.001
Occupation	0.047	0.003	NS*	0.006
Lifetime Cigarette Smoking	0.023	0.005	0.012	0.007
Lifetime Alcohol Consumption	NS	NS	NS	NS
Ethnic Background	NS	0.046	NS	0.036
Skin Color	NS**	NS	NS	NS**
Hair Color	NS	0.040	NS	NS*
Eye Color	NS	NS	NS	NS
Reaction of Skin to Sun Exposure:				
(Q.1) After first 30 minutes of summer sun	0.001	<0.001	<0.001	<0.001
(Q.2) After ≥2 hours, after first exposure	<0.001	0.027	0.001	0.016
(Q.3) After repeated sun exposures	<0.001	0.001	<0.001	<0.001
Sun-Reaction Index (Composite)	<0.001	<0.001	<0.001	<0.001
Residential History (Average Latitude)	0.008	0.004	0.011	0.003
Exposure to Carcinogens/Groups of Carcinogens				
Set 1[a]				
Asbestos	NS	NS	NS	NS
Non-medical X Rays	NS	NS*	NS	NS
Industrial Chemicals	NS	NS	NS	NS
Herbicides	NS	NS*	NS	NS
Insecticides	NS	NS	NS	NS
Degreasing Chemicals	NS	NS	NS	NS

TABLE 10-6. (continued)

Summary of Associations Between Incidence Rates of Basal Cell Carcinoma and Sun Exposure-Related Skin Malignancies and the Covariates, in the Baseline-Followup Interval for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Basal Cell Carcinoma		Sun Exposure-Related Skin Malignancies	
	Verified p-Value	Verified & Suspected p-Value	Verified p-Value	Verified & Suspected p-Value
Set 2[b]				
Anthracene	NS	NS	NS	NS
Arsenic	NS	NS	NS	NS
Benzene	NS	NS	NS	NS
Benzidene	NS	NS	NS	NS
Chromates	NS	NS	NS	NS
Coal Tar	NS	NS	NS	NS
Creosote	NS	NS	NS	NS
Aminodiphenyl	NS	NS	NS	NS
Chloromethyl Ether	NS	NS	NS	NS
Mustard Gas	NS	NS	NS	NS
Naphthylamine	NS	NS	NS	NS
Cutting Oils	NS	NS	NS	NS
Trichloroethylene	NS	NS	NS	NS
Ultraviolet Light (not sun)	NS	NS	NS	NS
Vinyl Chloride	NS	NS	NS	NS
Composite Carcinogen Exposure	NS	NS	NS	NS

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

NS*: Borderline significant ($0.05<p\leq 0.010$).

**Not significant when five categories of skin color examined; however, when dichotomized, $p=0.024$ for verified basal cell carcinoma and $p=0.036$ for verified and suspected sun exposure-related skin malignancies.

[a]Questionnaire data.

[b]AFHS Form 2.

As expected, the relationships between the incidence of verified sun exposure-related skin malignancies and the covariates were similar to those just described for basal cell carcinomas (Table 10-6 and Table H-4 of Appendix H). For verified conditions, there was a strong increase in incidence rate with age ($p=0.004$), total lifetime smoking ($p=0.012$), average lifetime residential latitude ($p=0.011$), the reaction-to-sun exposure variables ($p \leq 0.001$ for all), and the sun-reaction index ($p<0.001$), with similar strong associations for the verified plus suspected conditions. The difference among occupation groups was marginally significant ($p=0.077$) for verified conditions; this difference was significant ($p=0.006$) for verified plus suspected sun exposure-related skin malignancies (officers 5.9%, enlisted flyers 4.2%, enlisted groundcrew 2.8%). There was no association with the composite carcinogen-exposure variable, either for verified ($p=0.879$) or for verified plus suspected conditions ($p=0.608$).

Table 10-6 shows no significant association between the incidence rate of verified sun exposure-related skin malignancies and ethnic group, hair color, skin color, or eye color. When suspected conditions were included, the ethnic group association was significant ($p=0.036$), and the association with hair color became borderline significant ($p=0.051$). There were higher incidence rates among those of Celtic or English background as opposed to other ethnic backgrounds, and among participants with blond or red hair as opposed to other colors (see Table H-4 of Appendix H). As in the analysis of basal cell carcinomas, the ethnic group, hair color, and skin color categories were collapsed, resulting in (for verified conditions): $p=0.054$ for those of Celtic or English backgrounds versus other ethnic backgrounds (Est. RR: 2.04, 95% C.I.: [1.00,4.17]) and $p=0.031$ for skin color peach versus not-peach (Est. RR: 2.61, 95% C.I.: [1.04,6.58]), but no significant association with hair color grouped as blond or red versus other ($p=0.268$) was found.

Adjusted Analyses

Because of the obvious interrelatedness among the host factors of hair color, skin color, eye color, ethnic background, and reaction of skin to sun, and because a smaller set of covariates was required for the adjusted analyses, a "main-effects" statistical model of basal cell carcinoma with the following covariates was used: age, occupation, total pack-years, lifetime drinking, ethnic background (dichotomized), hair color (blond or red versus other), eye color, skin color (peach tones versus other), the three skin-reaction-to-sun variables, average lifetime residential latitude (less than 37° N versus greater than or equal to 37° N), and the composite carcinogen exposure variable. The results of this analysis are given in Appendix H, Table H-5. The results showed that ethnic background, hair color, and the 30-minute skin-reaction-to-sun variable, while individually associated with basal cell carcinoma incidence, are relatively less important than the other host factors, namely skin color, and the 2-hour and repeated-exposure skin-reaction-to-sun variables, and were thus not included in the adjusted analyses. Total drink-years and the composite carcinogen exposure variable were not significant and thus were not used in the adjusted analyses. A parallel analysis was conducted in which the composite sun-reaction index replaced all three skin-reaction-to-sun variables, and it was found that this substitution could be made without altering the relative contributions of the other covariates. For further reduction of the number of covariates, pack-years of smoking, although of interest ($p=0.096$), was

also omitted. Thus, a reduced set of covariates for further analysis of the group contrasts was identified as age, occupation, skin color, average lifetime residential latitude, and the sun-reaction index.

The results of adjusted analyses of group contrasts in the incidence rate of basal cell carcinoma and sun exposure-related skin malignancies are presented in Table 10-7. Parallel results for Ranch Hands contrasted with the Original Comparisons are given in Appendix H, Table H-6. A significant group-by-occupation interaction was found for verified interval basal cell carcinoma ($p=0.044$). Significant covariates were age ($p=0.003$), average residential latitude ($p=0.003$) and the sun-reaction index ($p<0.001$). The interaction was due to a significant difference in rates for enlisted flyers but not for officers or enlisted groundcrew: Ranch Hand enlisted flyers had a significantly ($p=0.019$) greater incidence rate of basal cell carcinomas than the corresponding Comparisons, 5.4 percent versus 1.0 percent (Adj. RR: 6.50, 95% C.I.: [1.36,31.01]) (see Appendix H, Table H-7).

There was a significant group-by-sun-reaction index interaction in the analysis of verified plus suspected basal cell carcinomas ($p=0.024$); this was in part attributable to the absence of Ranch Hands who reported burning easily. The group frequencies for the three levels of this variable (burn easily, intermediate reaction, tan easily) were: Ranch Hands 0 (0%), 17 (8.9%), and 19 (2.7%), respectively, and Comparisons 4 (5.2%), 15 (5.7%), and 28 (3.2%), respectively. The incidence rate for Ranch Hands who had a moderate reaction to sun was (nonsignificantly) greater than that of the Comparisons. The details of this interaction are given in Appendix H, Table H-7. A skin color-by-age interaction ($p=0.044$) and average latitude ($p=0.003$) made significant contributions to the model.

Results of the analyses for Original Comparisons were nonsignificant for verified conditions, although a marginally significant group-by-sun reaction interaction was found ($p=0.051$). The results for verified plus suspected conditions revealed a significant group-by-sun reaction index interaction ($p=0.007$) (see Table H-6 of Appendix H). Ranch Hands who had a moderate skin reaction to sun revealed a significantly greater incidence rate of verified basal cell neoplasms than corresponding Original Comparisons (Adj. RR: 2.81, 95% C.I.: [1.05,7.55], $p=0.040$) (Table H-8). This finding was marginally significant with the inclusion of suspected carcinomas (Adj. RR: 2.38, 95% C.I.: [0.98,5.76], $p=0.055$).

The adjusted relative risk for the incidence rate of verified sun exposure-related skin malignancies was 1.37 (95% C.I.: [0.83,2.28]) and was not significant ($p=0.221$) (Table 10-7). Age ($p<0.001$), the sun-reaction index ($p<0.001$), and average lifetime residential latitude ($p=0.008$) contributed to the adjustment. No group difference was apparent when suspected malignancies were included. The adjusted relative risk was 1.05 (95% C.I.: [0.68,1.62], $p=0.825$), and the significant covariates were a skin color-by-sun-reaction index interaction ($p=0.028$), a skin color-by-age interaction ($p=0.028$), and a skin color-by-residential latitude interaction ($p=0.041$).

TABLE 10-7.

Adjusted Analyses of Nonblack Followup Participants for Malignant Skin Neoplasm Incidence During the Baseline-Followup Interval

Variable	Status	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Basal Cell Carcinoma	Verified	****	****	AGE (p=0.003) LAT (p=0.003) SUNREAC (p<0.001) GRP*OCC (p=0.044)
	Verified & Suspected	****	****	LAT (p=0.003) GRP*SUNREAC (p=0.024) SKIN*AGE (p=0.044)
Sun-Exposure Malignant Skin Neoplasms	Verified	1.37 (0.83,2.28)	0.221	AGE (p<0.001) SUNREAC (p<0.001) LAT (p=0.008)
	Verified & Suspected	1.05 (0.68,1.62)	0.825	SKIN*SUNREAC (p=0.028) SKIN*AGE (p=0.028) SKIN*LAT (p=0.041)

*Abbreviations:

LAT: average lifetime residential latitude
SUNREAC: sun reaction index
GRP: group
OCC: occupation
SKIN: skin color

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

Analysis of the Ranch Hands versus Original Comparisons contrasts found a significant group-by-skin color interaction for verified sun exposure-related malignancies (p=0.036), and a significant group-by-sun reaction index interaction (p=0.030), similar to that found for basal cell carcinoma, for the verified plus suspected malignant neoplasms (see Appendix H, Tables H-6 and H-8, for details). The group-by-skin color interaction was due to a lower incidence rate for nonpeach Ranch Hands than Original Comparisons (Adj. RR: 0.20, 95% C.I.: [0.02,1.80], p=0.150), but a higher incidence rate for peach toned Ranch Hands than Original Comparisons (Adj. RR: 1.70, 95% C.I.: [0.95,3.04], p=0.073). The group-by-sun reaction index interaction (verified and suspected) was again due to Ranch Hands who react moderately to the sun having a higher incidence rate than similar Original Comparisons (Adj. RR: 2.74, 95% C.I.: [1.14,6.63], p=0.025).

Interval Systemic Neoplasms

As shown in Table 10-1, eight Ranch Hands (0.8%) and seven Comparisons (0.5%) had verified malignant systemic neoplasms in the interval between the Baseline and followup examinations. When suspected malignant systemic neoplasms were included, the numbers were 12 Ranch Hands (1.2%) and 12 Comparisons (0.9%). The proportions of malignancies among the systemic neoplasms of all types (malignant, benign, uncertain) were similar in the two groups: 14.5 percent (8/55) for Ranch Hands and 11.5 percent (7/61) for Comparisons (p=0.783). Inclusion of suspected conditions did not change the conclusion from this contrast: 18.5 percent (12/65) Ranch Hands versus 15.0 percent (12/80) Comparisons (p=0.656).

For the remainder of this section, only malignant (verified and suspected) systemic neoplasms occurring in the Baseline to followup interval are analyzed. These occurrences were distinct from those reported at Baseline. No new metastatic systemic neoplasms were reported in the interval.

Interval Malignant Systemic Neoplasms

Table 10-8 shows the sites of the new malignant neoplasms reported by the eight Ranch Hands and seven Comparisons. Classification of malignancies was based on ICD-9 with special coding for tumor type as well as site, thus avoiding problems of underreporting of STS. Six Ranch Hands and five Comparisons had suspected systemic neoplasms in this interval (Table 10-9), making a total of 12 in each group, since 2 Ranch Hands with verified systemic neoplasms also had suspected systemic neoplasms. The frequencies were too small for indepth analysis of individual sites. Table 10-8 shows that two Ranch Hands had malignant neoplasms of the oral cavity and pharynx versus no Comparisons, and three Comparisons but no Ranch Hands had malignant neoplasms of the colon. For all digestive system malignancies (esophagus plus colon), there were four occurrences among Comparisons but none among Ranch Hands. The analyses that follow are based on the combination of all interval malignant systemic neoplasms regardless of specific site, both verified and verified plus suspected.

Table H-9 of Appendix H lists the malignancy sites for the eight Ranch Hands and the six Original Comparisons in the Baseline-followup interval.

TABLE 10-8.

Summary of Followup Participants with Verified Malignant Systemic Neoplasms in Baseline-Followup Interval by Group

Site	Group		Total
	Ranch Hand	Comparison	
Oral Cavity and Pharynx	2[a,b]	0	2
Thyroid Gland	0	1	1
Esophagus	0	1[c]	1
Bronchus and Lung	1	0	1
Colon	0	3[d,*]	3
Kidney and Bladder	2	1	3
Prostate	1	1	2
Testicles	1	0	1
Connective and Other Soft Tissue	1	0	1
Total	8	7	15

[a]Includes one Ranch Hand with separate malignancies of tongue and epiglottis and also malignant neoplasm of bone.

[b]Includes one Ranch Hand with separate malignant neoplasms of tongue and oropharynx and secondary malignant neoplasm of other site.

[c]Also has malignant neoplasm of bone.

[d]Includes one Comparison with secondary malignant neoplasms of liver and bone and bone marrow.

[*]Includes one Comparison with secondary malignant neoplasm of liver.

TABLE 10-9.

Summary of Followup Participants with Suspected Malignant Systemic Neoplasms at Physical Examination by Group

Site	Group		Total
	Ranch Hand	Comparison	
Bronchus and Lung	4[a,b]	2	6
Rectum	0	1	1
Liver	1[c]	0	1
Prostate	0	1	1
Lymphatic and Hematopoietic Tissue	1[d]	0	1
Unspecified Site	0	1	1
Total	6	5	11

[a]Includes one Ranch Hand with a suspected maglignant neoplasm of either lung, mediastinum, esophagus, or ill-defined site within digestive organs and peritoneum.

[b]Includes one Ranch Hand with a suspected secondary malignant neoplasm of lung.

[c]Not specified as primary or secondary.

[d]Suspected as either Hodgkins disease, leukemia, or lymphoma.

There is no parallel table for suspected malignant systemic neoplasms since the five Comparisons with suspected conditions in Table 10-9 are Original Comparisons.

Unadjusted Analyses

As shown in Table 10-10, the unadjusted group contrast for all verified malignant systemic neoplasms was not significant (p=0.603), with an estimated relative risk of 1.46 (95% C.I.: [0.53,4.03]). When suspected malignant neoplasms were included with the verified malignancies, the estimated relative risk was 1.28 (95% C.I.: [0.57,2.85]), and was also not significant (p=0.680). A parallel unadjusted analysis for Ranch Hands versus Original Comparisons gave similar nonsignificant results (Appendix Table H-10).

Covariates

The covariates considered for the adjusted analysis of all interval malignant systemic neoplasms combined were age, race, occupation, smoking and drinking history, exposure to the groups of carcinogens, exposure to the individual carcinogens, and the composite carcinogen exposure variable as listed in Table 10-5. The categories used for age, pack-years, and drink-years were the same. Age was used as a continuous variable in the adjusted analyses but was categorized for ease of presentation in the report. No Blacks had verified systemic neoplasms, but in contrast to the skin cancer analysis, Blacks were retained in the analysis.

Covariate Associations

Table 10-11 summarizes the results of chi-square tests of association between the incidence rate of all malignant systemic neoplasms combined and the covariates considered for use in the adjusted analyses. Details of the covariate relationships are given in Appendix H, Table H-11.

There was a significant increase in the incidence rate of all verified interval malignant systemic neoplasms with increasing age ($p<0.001$) and a marginally significant difference among occupations (p=0.056). The incidence rates for officers, enlisted flyers, and enlisted groundcrew were 1.2 percent, 0.5 percent, and 0.3 percent, respectively. There was a marginally significant association with total lifetime alcohol consumption (p=0.082). The test for differences in incidence rates among pack-year levels of smoking was not significant (p=0.220), although an increasing trend was apparent. Some of the occupation effect may be attributable to confounding with age.

There was a significant negative association with insecticide exposure for verified malignant systemic neoplasms (p=0.014). Table H-11 of Appendix H shows that there were a few significant or marginally significant positive associations with individual carcinogens: e.g., with naphthylamine (p=0.050), benzidine (p=0.088), and coal tar (p=0.079). However, in many instances the self-reported exposure frequencies were very small.

TABLE 10-10.

Unadjusted Analyses of Followup Participants with Verified and Suspected Malignant Systemic Neoplasms in the Baseline-Followup Interval by Group

Status	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Verified	Number of Participants/%	8	0.8%	7	0.5%	1.46 (0.53,4.03)	0.603
	Total Neoplasms	12		10			
Verified & Suspected	Number of Participants/%	12	1.2%	12	0.9%	1.28 (0.57,2.85)	0.680
	Total Neoplasms	23		16			

TABLE 10-11.

Summary of Associations Between Incidence Rates of All Malignant Systemic Neoplasms Combined and the Covariates in the Baseline-Followup Interval for Combined Followup Ranch Hand and Comparison Groups

Covariate	Verified p-Value	Verified & Suspected p-Value
Age	<0.001	0.001
Race	NS	NS
Occupation	NS*	NS
Lifetime Cigarette Smoking	NS	NS
Lifetime Alcohol Consumption	NS*	NS
Exposure to Carcinogens/Groups of Carcinogens:		
Set 1[a]		
Asbestos	NS	NS
Non-medical X Rays	NS	0.049
Industrial Chemicals	NS	NS
Herbicides	NS	NS
Insecticides	0.014	NS*
Degreasing Chemicals	NS	NS
Set 2[b]		
Anthracene	NS	NS
Arsenic	NS	NS*
Benzene	NS	NS
Benzidene	NS*	NS
Chromates	NS	NS
Coal Tar	NS*	NS
Creosote	NS	NS
Aminodiphenyl	NS	NS*
Chloromethyl Ether	NS	0.023
Mustard Gas	NS	NS*
Naphthylamine	0.050	0.019
Cutting Oils	NS	NS
Trichloroethylene	NS	NS
Ultraviolet Light (not sun)	NS	NS
Vinyl Chloride	NS	NS
Composite Carcinogen Exposure	NS	NS

NS*: Borderline significant ($0.05<p\leq0.10$).

NS: Not significant ($p>0.10$)

[a]Questionnaire data.

[b]AFHS Form 2.

The covariate associations for verified plus suspected malignant systemic neoplasms were similar to those for verified only. The association with occupation was no longer significant (p=0.193), and there was a significant positive association with nonmedical x-ray exposure (p=0.049). There were some significant and marginally significant positive associations with individual carcinogens: with naphthylamine (p=0.019), chloromethyl ether (p=0.023), arsenic (p=0.069), mustard gas (p=0.090), and aminodiphenyl (p=0.061) (see Appendix H, Table H-11).

The covariates used for the adjusted group contrast of the incidence rate of all malignant systemic neoplasms were race, age (continuous), occupation, and pack-years.

Adjusted Analyses

The adjusted relative risks for all verified and verified plus suspected malignant systemic neoplasms are presented in Table 10-12. For verified malignant systemic neoplasms, there was no significant difference between groups (Adj. RR: 1.51, 95% C.I.: [0.54,4.22], p=0.434). Age made a significant contribution to the adjustment (p<0.001). Parallel results for Ranch Hands contrasted with Original Comparisons are given in Table H-12 of Appendix H.

A significant group-by-occupation interaction was found in the adjusted analysis of verified plus suspected malignant systemic neoplasms (p=0.027). This was due to significantly more cases of malignant systemic neoplasms among Ranch Hand enlisted flyers than among corresponding Comparisons (4/175 [2 verified, 2 suspected] versus 0/209, Fisher's exact test=0.042), whereas the incidence rate for officers was lower (but not significantly) for Ranch Hands than for the corresponding Comparisons, and equivalent for the enlisted groundcrew (see Table H-13 of Appendix H). Age (p<0.001) and a race-by-pack-year interaction (p=0.035) made significant contributions to the adjustment. Comparable results were found for the contrast of Ranch Hands with the Original Comparisons (see Tables H-12 and H-14 of Appendix H).

Lifetime (Baseline and Interval)

Data from the Baseline and followup examinations were merged to obtain records of the lifetime history of neoplasm incidence for those followup participants who participated at Baseline. New participants provided lifetime information at the followup examination. Neoplasms prior to service in Southeast Asia were excluded from all analyses. All data from the Baseline study have been verified, but as described in the previous section, the status of some suspected interval neoplasms remains unclear, and thus both verified and verified plus suspected neoplasms are described and analyzed in this section.

Table 10-13 shows that 21.3 percent (216/1,016) of Ranch Hands and 16.2 percent (209/1,293) of Comparisons had skin or systemic neoplasms of some type (malignant, benign, and uncertain). The group difference in incidence rates was significant (p=0.002), with an estimated relative risk of 1.40 (95% C.I.: [1.13,1.73]). When suspected neoplasms were included, the contrast was less marked (22.7% [231] of Ranch Hands versus 19.3% [249] of Comparisons) but still statistically significant (p=0.044), with an estimated relative risk of 1.23 (95% C.I.: [1.01,1.51]).

TABLE 10-12.

Adjusted Analyses of Followup Participants for the Incidence of All Malignant Systemic Neoplasms During the Baseline-Followup Interval

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Malignant Systemic Neoplasms (Verified)	1.51 (0.54,4.22)	0.434	AGE (p<0.001)
Malignant Systemic Neoplasms (Verified & Suspected)	****	****	GRP*OCC (p=0.027) AGE (p<0.001) RACE*PACKYR (p=0.035)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

TABLE 10-13.

Unadjusted Analyses of Followup Participants with Lifetime Occurrence of Verified and Suspected Neoplasms by Group (Nonblacks and Blacks)

Site	Neoplasm Behavior and Status	Group* Ranch Hand Number**	Ranch Hand Percent	Comparison Number**	Comparison Percent	Total**	p-Value***
Skin	Malignant						
	Verified	66	6.5	66	5.1	132	0.175
	Verified and Suspected	75	7.4	85	6.6	160	0.458
	Benign						
	Verified	84	8.3	79	6.1	163	0.049
	Verified and Suspected	86	8.5	85	6.6	171	0.093
	Uncertain Behavior and Unspecified Nature:						
	Verified	1	0.1	1	0.1	2	0.999
	Verified and Suspected	1	0.1	1	0.1	2	0.999
	Any Skin Neoplasm[a]						
	Verified	150	14.8	140	10.8	290	0.005
	Verified and Suspected	159	15.7	165	12.8	324	0.053
Systemic	Malignant						
	Verified	17	1.7	17	1.3	34	0.491
	Verified and Suspected	21	2.1	22	1.7	43	0.538
	Benign						
	Verified	51	5.0	64	5.0	115	0.999
	Verified and Suspected	57	5.6	75	5.8	132	0.857
	Uncertain Behavior and Unspecified Nature:						
	Verified	15	1.5	14	1.1	29	0.453
	Verified and Suspected	15	1.5	18	1.4	33	0.862
	Any Systemic Neoplasm[b]						
	Verified	81	8.0	87	6.7	168	0.259
	Verified and Suspected	91	9.0	106	8.2	197	0.548
All	Malignant, Benign, Uncertain Behavior, Unspecified Nature[c]						
	Verified	216	21.3	209	16.2	425	0.002
	Verified and Suspected	231	22.7	249	19.3	480	0.044

*Sample sizes: 1,016 Ranch Hands, 1,293 Comparisons.
**Number of participants.
***Fisher's exact test.
[a]Participant has one or more malignant, benign, or unspecified skin neoplasm.
[b]Participant has one or more malignant, benign, or unspecified systemic neoplasm.
[c]Participant has one or more malignant or benign skin or systemic neoplasm.

Table H-15 of Appendix H is parallel to Table 10-13 for Ranch Hands and Original Comparisons only.

Lifetime Skin Neoplasms

As seen in Table 10-13, 69.4 percent (150/216) of Ranch Hands with neoplasms had skin cancer; the corresponding percentage for Comparisons was 67.0 percent (140/209). The group difference in these proportions was not significant (p=0.604). This contrast, when suspected neoplasms were included, was 68.8 percent (159/231) versus 66.3 percent (165/249), which again was not significant (p=0.560).

The overall percentage of Black and nonblack Ranch Hands with verified lifetime skin neoplasms of any type was 14.8 percent (150/1,016), versus 10.8 percent (140/1,293) for Comparisons. No Black followup participants had ever had skin neoplasms, nor did any Baseline Black participants. The overall percentage of nonblack Ranch Hands with skin neoplasms of any type was 15.7 percent (150/956) and was significantly (p=0.006) greater than that of the Comparisons with 11.6 percent (140/1,210). The estimated relative risk was 1.42 95% C.I.: [1.11,1.82]). When both verified and suspected neoplasms were in the analysis, the contrast was marginally significant (p=0.060): Ranch Hands 16.6 percent (159/956) versus Comparisons with 13.6 percent (165/1,210) (Estimated RR: 1.26, 95% C.I.: [1.00,1.60]).

For the remainder of this subsection, only malignant skin neoplasms are examined. Furthermore, the analysis was restricted to nonblacks.

The dependent variables examined were the same as those of the previous section (basal cell carcinoma, melanoma, squamous cell carcinoma, all malignant skin neoplasms combined and sun exposure-related skin malignancies).

Lifetime Malignant Skin Neoplasms

Table 10-14 presents the unadjusted analyses of the frequencies of nonblack participants in each group with lifetime occurrences of basal cell carcinoma, squamous cell carcinoma, melanoma, all malignant skin neoplasms, and the sun exposure-related skin malignancies. For completeness, the total number of malignancies of each type is also given. Table H-16 of Appendix H presents parallel analyses for Ranch Hands and Original Comparisons.

Unadjusted Analyses

There was a higher relative frequency (5.5%) of Ranch Hands who had basal cell carcinomas than of Comparisons (4.1%), but the difference was not significant (p=0.128). The estimated relative risk was 1.36 (95% C.I.: [0.92,2.02]). With the inclusion of suspected basal cell carcinoma, the estimated relative risk was also not significant (p=0.579).

Of the 53 Ranch Hands with verified basal cell carcinomas, 17 (32.1%) had 2 or more occurrences. The corresponding number for the Comparisons was 14/50 (28.0%). The group contrast of the percentages with multiple basal cell carcinomas versus no basal cell carcinomas was not significant (17/920 versus 14/1,174, p=0.274), nor was the corresponding contrast when suspected basal cell carcinomas were included (19/916 versus 16/1,159, p=0.234).

TABLE 10-14.

Unadjusted Analyses of Nonblack Followup Participants with Lifetime Occurrence of Verified and Suspected Malignant Skin Neoplasms by Cell Type and Group

Cell Type	Status	Statistic**	Group* Ranch Hand		Group* Comparison		Est. Relative Risk (95% C.I.)	p-Value
Basal Cell Carcinoma	Verified	Number/%	53	5.5%	50	4.1%	1.36 (0.92,2.02)	0.128
		Total Neoplasms	77		76			
	Verified & Suspected	Number/%	59	6.2%	67	5.5%	1.12 (0.78,1.61)	0.579
		Total Neoplasms	88		99			
Squamous Cell Carcinoma	Verified	Number/%	4	0.4%	6	0.5%	0.84 (0.24,3.00)	0.999
		Total Neoplasms	6		7			
	Verified & Suspected	Number/%	4	0.4%	7	0.6%	0.72 (0.21,2.47)	0.764
		Total Neoplasms	6		8			
Melanoma	Verified	Number/%	5	0.5%	5	0.4%	1.27 (0.37,4.39)	0.757
		Total Neoplasms	6		6			
	Verified & Suspected	Number/%	5	0.5%	8	0.7%	0.79 (0.26,2.42)	0.784
		Total Neoplasms	6		10			
All Malignant Skin Neoplasms	Verified	Number/%	66	6.9%	66	5.5%	1.29 (0.90,1.83)	0.175
		Total Neoplasms	100		100			
	Verified & Suspected	Number/%	75	7.9%	85	7.0%	1.13 (0.82,1.56)	0.508
		Total Neoplasms	114		129			
Sun-Exposure Related Malignant Neoplasms[a]	Verified	Number/%	59	6.2%	55	4.6%	1.38 (0.95,2.02)	0.100
		Total Neoplasms	87		83			
	Verified & Suspected	Number/%	65	6.8%	74	6.1%	1.12 (0.79,1.58)	0.537
		Total Neoplasms	98		111			

*Number of participants--956 Ranch Hands and 1,210 Comparisons.
**Number and percent of participants; total number of malignant neoplasms of specified cell type.
[a]Basal cell carcinoma, melanoma, and malignant epithelial neoplasms NOS.

The frequencies of participants who had squamous cell carcinoma were very small: 4 Ranch Hands (0.4%) and 6 Comparisons (0.5%). The estimated relative risk was 0.84 (95% C.I.: [0.24,3.00]), and the contrast was far from significant (p=0.999). Inclusion of suspected squamous cell carcinoma did not change this finding.

The frequency of Ranch Hands who had melanoma, 5 (0.5%), was slightly greater than that of the Comparisons, 5 (0.4%), but the contrast was not significant (p=0.757); the estimated relative risk was 1.27 (95% C.I.: [0.37,4.39]). Inclusion of suspected melanoma inverted the relative risk to 0.79, which was again not significant. This analysis had little power due to small frequencies.

For sun exposure-related skin malignancies, there was a higher percentage of Ranch Hands than Comparisons (6.2% versus 4.6%), but the contrast was only of borderline significance (p=0.100); the estimated relative risk was 1.38 (95% C.I.: [0.95,2.02]). When suspected sun exposure-related skin malignancies were included, the group difference was not significant (p=0.537), with estimated relative risk 1.12 (95% C.I.: [0.79,1.58]).

As in the previous section, adjusted analyses were only carried out for basal cell carcinoma and the sun exposure-related skin malignancies.

Covariates

The same covariates as for the interval analysis (Table 10-5) were considered for the adjusted analysis of the lifetime incidence rates of basal cell carcinoma and sun exposure-related skin malignancies: age, occupation, history of cigarette smoking and alcohol consumption, the same host factors and average latitude, and exposure to the same recognized carcinogens. The covariates used for the adjusted analyses were the same as in the interval analysis, namely age, occupation, sun reaction index, average lifetime residential latitude, and skin color.

Covariate Associations

Table 10-15 presents details of the associations between the incidence rate of basal cell carcinoma and the following covariates: age; occupation; pack-years of smoking, lifetime drink-years; ethnic background, hair color, skin color, eye color; skin-reaction-to-sun variables, sun-reaction index; average residential latitude, and exposure to individual carcinogens and groups of carcinogens.

For the incidence of verified basal cell carcinoma, the same associations were found as in the interval analysis, namely, an increasing incidence rate with increasing age (p<0.001), a significant difference among occupations (p=0.017; officers 6.4%, enlisted flyers 4.2%, enlisted groundcrew 3.6%), and significant associations with average lifetime residential latitude (p=0.026), all the skin-reaction-to-sun variables (p<0.001 for all), the sun-reaction index (p<0.001), and increasing total pack-years (p=0.024). There was evidence of a higher incidence rate of basal cell carcinomas among the heavy drinkers, although the test for the difference among drinking categories was not significant.

TABLE 10-15.

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Age	Born ≥1942	882	21	2.4	<0.001	24	2.7	<0.001
	Born 1923-41	1,197	75	6.3		91	7.6	
	Born ≤1922	87	7	8.1		11	12.6	
Occupation	Officer	850	54	6.4	0.017	68	8.0	0.002
	Enlisted Flyer	360	15	4.2		18	5.0	
	Enlisted Groundcrew	956	34	3.6		40	4.2	
Total Lifetime Smoking (Pack-Years)	0	616	32	5.2	0.024	37	6.0	0.010
	>0-20	998	36	3.6		43	4.3	
	>20-40	391	21	5.4		31	7.9	
	>40	157	14	8.9		15	9.6	
Total Lifetime Alcohol Consumption (Drink-Years)	0	141	7	5.0	0.548	8	5.7	0.855
	>0-5	717	37	5.2		43	6.0	
	>5-30	655	29	4.4		34	5.2	
	>30-100	479	19	4.0		30	6.3	
	>100	104	8	7.7		8	7.7	
Ethnic Background[a]	A	1,582	85	5.4	0.132	107	6.8	0.016
	B	424	16	3.8		16	3.8	
	C	63	1	1.6		1	1.6	
	D	42	0	0.0		0	0.0	
Skin Color	Dark	1	0	0.0	0.339	0	0.0	0.263
	Medium	73	2	2.7		2	2.7	
	Pale	308	9	2.9		11	3.6	
	Dark Peach	1,262	69	5.5		82	6.5	
	Pale Peach	520	23	4.4		31	6.0	

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Eye Color	Brown	645	30	4.7	0.338	35	5.4	0.853
	Hazel	455	29	6.4		30	6.6	
	Green	119	3	2.5		6	5.0	
	Grey	93	5	5.4		7	7.5	
	Blue	850	36	4.2		48	5.7	
Hair Color	Black	439	20	4.6	0.278	24	5.5	0.120
	Dark Brown	1,038	42	4.1		53	5.1	
	Light Brown	563	32	5.7		38	6.8	
	Red	16	2	12.5		3	18.8	
	Blond	108	7	6.5		8	7.4	
Residential History (Average Latitude)	≥37°	1,136	43	3.8	0.026	51	4.5	0.006
	<37°	1,022	60	5.9		75	7.3	
Skin Reaction to First 30 Min. of Sun Exposure	Burns	247	21	8.5	<0.001	25	10.1	<0.001
	Usually Burns	429	36	8.4		44	10.3	
	Burns Mildly	805	29	3.6		32	4.0	
	Rarely Burns	681	16	2.4		24	3.5	
Skin Reaction to >2 Hrs of Sun After First Exposure	Burns Painfully	120	9	7.5	<0.001	11	9.2	0.001
	Burns	338	31	9.2		33	9.8	
	Becomes Red	1,043	42	4.0		54	5.2	
	No Reaction	663	21	3.2		28	4.2	
Skin Reaction After Repeated Exposure to Sun	Freckles, No Tan	45	4	8.9	<0.001	5	11.1	<0.001
	Tans Mildly	314	31	9.9		36	11.5	
	Tans Moderately	1,019	37	3.6		47	4.6	
	Tans Deep Brown	783	30	3.8		37	4.7	

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category		Total Participants	Verified			Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Sun Reaction Index	Tends to Burn		145	10	6.9	<0.001	12	8.3	<0.001
	Mild Reaction		454	41	9.0		46	10.1	
	Tends to Tan		1,562	51	3.3		67	4.3	
Exposures to Carcinogens	Asbestos	Yes	458	18	3.9	0.389	25	5.5	0.822
		No	1,708	85	5.0		101	5.9	
	Nonmedical X Rays	Yes	494	29	5.9	0.187	37	7.5	0.080
		No	1,672	74	4.4		89	5.3	
	Industrial Chemicals	Yes	1,126	49	4.4	0.365	60	5.3	0.314
		No	1,040	54	5.2		66	6.4	
	Herbicides	Yes	1,261	65	5.2	0.357	81	6.4	0.164
		No	905	38	4.2		45	5.0	
	Insecticides	Yes	1,313	69	5.3	0.181	82	6.3	0.303
		No	853	34	4.0		44	5.2	
	Degreasing Chemicals	Yes	1,261	60	4.8	0.999	72	5.7	0.852
		No	905	43	4.8		54	6.0	
Composite Carcinogen Exposure		Yes	489	21	4.3	0.716	24	4.9	0.379
		No	1,653	80	4.8		100	6.1	

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens	Anthracene	Yes 2	0	0.0	0.999	0	0.0	0.999
		No 2,161	103	4.8		126	5.8	
	Arsenic	Yes 41	4	9.8	0.124	5	12.2	0.084
		No 2,124	98	4.6		120	5.7	
	Benzene	Yes 74	6	8.1	0.162	7	9.5	0.198
		No 2,091	97	4.6		119	5.7	
	Benzidine	Yes 11	1	9.1	0.416	1	9.1	0.484
		No 2,154	102	4.7		125	5.8	
	Chromates	Yes 84	4	4.8	0.999	5	6.0	0.812
		No 2,079	97	4.7		119	5.7	
	Coal Tar	Yes 68	2	2.9	0.770	3	4.4	0.795
		No 2,097	101	4.8		123	5.9	
	Creosote	Yes 159	9	5.7	0.560	10	6.3	0.726
		No 2,007	94	4.7		116	5.8	
	Aminodiphenyl	Yes 6	0	0.0	0.999	0	0.0	0.999
		No 2,157	102	4.7		125	5.8	
	Chloromethyl Ether	Yes 21	2	9.5	0.264	2	9.5	0.348
		No 2,142	101	4.7		124	5.8	
	Mustard Gas	Yes 6	0	0.0	0.999	0	0.0	0.999
		No 2,159	103	4.8		126	5.8	

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category		Total Participants	Verified			Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens (continued)	Naphthylamine	Yes	52	3	5.8	0.734	4	7.7	0.540
		No	2,112	99	4.7		121	5.7	
	Cutting Oils	Yes	226	12	5.3	0.622	15	6.6	0.549
		No	1,939	91	4.7		111	5.7	
	Trichloroethylene	Yes	184	5	2.7	0.207	7	3.8	0.253
		No	1,979	98	5.0		119	6.0	
	Ultraviolet Light	Yes	44	5	11.4	0.055	5	11.4	0.179
		No	2,120	98	4.6		121	5.7	
	Vinyl Chloride	Yes	31	0	0.0	0.399	1	3.2	0.999
		No	2,133	103	4.8		125	5.9	

*Number of participants with basal cell carcinomas.

[a]Ethnic Background:

A - English, Welsh, Scottish, Irish
B - Scandinavian, German, Polish, Russian, Other Slavic, Jewish, French
C - Spanish, Italian, Greek.
D - Mexican, American Indian, Asian.

There was a significant ($p<0.001$) association with the sun-reaction index. Participants with the most sensitive skin had a somewhat lower rate (6.9%) of verified basal cell carcinoma lifetime than the participants in the next most sensitive category (9.0%), although the difference was not as marked as in the Baseline-followup interval. However, the rate for those who tanned easily was much lower (3.3%) than for those who did not. A marginally significant positive association was found with self-reported exposure to non-sun ultraviolet light ($p=0.055$).

The results were similar for the verified plus suspected basal cell carcinomas. There was a significant ($p=0.016$) difference among ethnic backgrounds, with participants with Celtic or English backgrounds having higher incidence rates than those with other backgrounds. Further, there were marginally significant positive associations in incidence rates with non-medical x-ray exposure ($p=0.080$) and arsenic ($p=0.084$), a recognized skin carcinogen, but the association with ultraviolet light was not significant.

The details of associations between the incidence rates of verified and suspected sun exposure-related skin malignancies and the covariates are given in Appendix H, Table H-17. The significant covariates for verified conditions were age ($p<0.001$), occupation ($p=0.009$), total pack-years ($p=0.021$), average latitude ($p=0.026$), and sun-reaction index ($p<0.001$). The same pattern held for verified plus suspected sun exposure-related skin malignancies. There was a marginally significant positive association with ultraviolet light exposure ($p=0.078$) for the verified conditions only, and with herbicide exposure ($p=0.076$) for the verified plus suspected conditions.

The covariates chosen for the adjusted analysis were age, occupation, skin color, average lifetime residential latitude and the sun-reaction index.

Adjusted Analysis

The results of adjusted analyses of group contrasts for lifetime skin malignancies are given in Table 10-16. There was significant evidence of a higher incidence rate of verified basal cell carcinoma in the Ranch Hand group as contrasted with the Comparisons ($p=0.035$). The adjusted relative risk was 1.56 (95% C.I.: [1.03,2.37]). A sun-reaction index-by-average latitude interaction ($p=0.026$), a skin color-by-sun-reaction index interaction ($p<0.001$), and an occupation-by-age interaction ($p=0.047$) made significant contributions to the model. The adjustment by average residential latitude, which is greater for Ranch Hands than Comparisons, contributed to a higher relative risk resulting from the adjusted analysis than from the unadjusted (see Table 10-14). When suspected basal cell carcinomas were included in the analysis, a significant group-by-sun-reaction index interaction ($p=0.040$) was found. Age ($p<0.001$), a skin color-by-average residential latitude ($p=0.024$), and a skin color-by-sun-reaction index interaction ($p<0.001$) made significant contributions to the adjustment. This was due to a significant increase in basal cell carcinoma incidence for Ranch Hands with an intermediate skin reaction to sun over similar Comparisons (Adj. RR: 1.97, 95% C.I.: [1.04,3.73], $p=0.038$) (Appendix H, Table H-18).

Similar results were found in the contrast of Ranch Hand versus Original Comparisons (Table H-19). Namely, for verified basal cell carcinoma, and for verified plus suspected basal cell carcinomas, significant group-by-sun-reaction index interactions were found ($p=0.010$ and $p=0.003$, respectively [see Table H-20 for additional details on the interactions]).

TABLE 10-16.

Adjusted Analyses of Nonblack Followup Participants for Lifetime Malignant Skin Neoplasm Incidence

Variable	Status	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Basal Cell Carcinoma	Verified	1.56 (1.03,2.37)	0.035	SKIN*SUNREAC (p<0.001) OCC*AGE (p=0.047) SUNREAC*LAT (p=0.026)
	Verified & Suspected	****	****	AGE (p<0.001) GRP*SUNREAC (p=0.040) SKIN*LAT (p=0.024) SKIN*SUNREAC (P<0.001)
Malignant Sun-Exposure Skin Neoplasms	Verified	1.54 (1.04,2.29)	0.030	AGE (p<0.001) SKIN*LAT (p=0.016) SKIN*SUNREAC (p<0.001)
	Verified & Suspected	1.23 (0.86,1.77)	0.252	AGE (p<0.001) SKIN*LAT (p=0.013) SKIN*SUNREAC (p<0.001)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

As shown in Table 10-16, there was a significantly higher incidence rate of sun exposure-related skin malignancies among Ranch Hands as contrasted with Comparisons (Adj. RR: 1.54, 95% C.I.: [1.04,2.29], p=0.030). Significant contributions were noted for age (p<0.001), a skin color-by-sun-reaction index interaction (p<0.001), and an average latitude-by-skin color interaction (p=0.016). When suspected sun exposure-related skin malignancies were included in the analysis, the adjusted relative risk became 1.23 (95% C.I.: [0.86,1.77]) and was no longer significant (p=0.252). Age (p<0.001), a skin color-by-sun-reaction index interaction (p<0.001), and average latitude-by-skin color interaction (p=0.013) contributed significantly to the adjustment. When Ranch Hands were contrasted to Original Comparisons, significant group-by-sun reaction index interactions were found for verified, and verified plus suspected, sun-exposure related skin neoplasms (p=0.045,p=0.016, respectively). These interactions were due to significant relative risks for those participants with intermediate reactions of skin to sun, as was also found for basal cell carcinomas only (see Appendix Tables H-19 and H-20 for details).

Lifetime Systemic Neoplasms

Table 10-13 shows that 81 (8.0%) Ranch Hands and 87 (6.7%) Comparisons had a verified history of systemic neoplasms of any type (malignant, benign, or uncertain). The estimated relative risk was 1.20 (95% C.I.: [0.88,1.65]), and was not significant (p=0.259). With the inclusion of suspected systemic neoplasms, the frequencies were 9.0 percent (91/1,016) for Ranch Hands and 8.2 percent (106/1,293) for Comparisons, with an estimated relative risk of 1.10 (95% C.I.: [0.82,1.48]), and the contrast was also not significant (p=0.548).

For Ranch Hands with systemic neoplasms of any type, the percentage with malignant neoplasms was 21.0 percent (17/81) and the corresponding rate for Comparisons was 19.5 percent (17/87), a nonsignificant group difference (p=0.849). Including suspected systemic malignancies, these frequencies were 23.1 percent (21/91) for Ranch Hands and 20.8 percent (22/106) for Comparisons. Again, the group difference was not significant (p=0.731).

For the remainder of this section, only malignant systemic neoplasms are discussed.

Lifetime Malignant Systemic Neoplasms

Table 10-17 presents the frequencies of verified lifetime malignant systemic neoplasms by site. Three Ranch Hands versus no Comparisons had malignant neoplasms of the oral cavity and pharynx; these occurred at ages 45, 52, and 57. The group difference in incidence rate was marginally significant (p=0.085). No Ranch Hands but 5 Comparisons had malignant neoplasms of the colon; the group difference in incidence rate was also marginally significant (p=0.072). Three Ranch Hands but no Comparisons had testicular malignancies, but the group difference in incidence rates was only marginally significant (p=0.085). These occurred at ages 35, 38, and 54. The suspected malignant neoplasms are listed in Table 10-9. Table H-21 of Appendix H gives a list of verified lifetime malignant systemic neoplasms for Ranch Hands and Original Comparisons.

TABLE 10-17.

Summary of Followup Participants With Lifetime Incidence of Verified Malignant Systemic Neoplasms by Group

Site	Group		Total
	Ranch Hand	Comparison	
Eye	1	0	1
Oral Cavity and Pharynx	3[a,b]	0	3
Larynx	0	1	1
Thyroid Gland	0	2	2
Esophagus	0	1[c]	1
Bronchus and Lung	2	0	1
Colon	0	5[d,•]	5
Kidney and Bladder	4	3	7
Prostate	2	2	4
Testicles	3	0	3
Connective and Other Soft Tissue	1	1	2
Hodgkin's Disease	0	1	1
Ill-Defined Sites	1[f]	1[g]	2
Total	17	17	34

[a]Includes one Ranch Hand with separate malignancies of tongue and epiglottis and also malignant neoplasm of bone.

[b]Includes one Ranch Hand with separate malignant neoplasms of tongue and oropharynx and secondary malignant neoplasm of other site.

[c]Also has malignant neoplasm of bone.

[d]Incudes one Comparison with secondary malignant neoplasms of liver and bone and bone marrow.

[•]Includes one Comparison with secondary malignant neoplasm of liver.

[f]Malignant neoplasm of thorax.

[g]Malignant neoplasm of face, head, or neck.

One Ranch Hand and one Comparison had neoplasms of connective and other soft tissue. The Comparison had a fibrosarcoma at age 28 (reported at Baseline) and the Ranch Hand participant had malignant fibrous histiocytoma at age 63 (reported at followup). Both of these conditions are classified as soft tissue sarcoma.

Since soft tissue sarcoma and malignant neoplasms of the lymphatic system are of concern in this study, the occurrences of these malignancies are shown by group in Table 10-18. The occurrences of these four malignancies are too small to support further statistical analysis.

TABLE 10-18.

Summary of Followup Participants with Lifetime Soft Tissue Sarcoma, Leukemia or Lymphoma by Group

Site	Group	
	Ranch Hand	Comparison
Verified Soft Tissue Sarcoma	1	1
Verified Hodgkin's Disease	0	1
Suspected Leukemia, Hodgkin's Disease, or non-Hodgkin's Lymphoma	1	0

Unadjusted Analysis

Table 10-19 shows the results of unadjusted analyses of the frequencies of participants in each group with verified or verified plus suspected malignant systemic neoplasms combined. The estimated relative risk for all malignant systemic neoplasms was 1.28 (95% C.I.: 0.65,2.51) and was not significant (p=0.491). With the inclusion of suspected malignant neoplasms, the estimated relative risk was 1.22 (95% C.I.: 0.67,2.23) and was also not significant (p=0.538). Similar nonsignificant results were found for Ranch Hands contrasted with Original Comparisons (see Table H-22 of Appendix H).

Covariates

The same covariates used for the interval history of malignant systemic neoplasms were used for the adjusted analysis of lifetime malignant systemic neoplasms, namely, age, race, occupation, history of cigarette smoking and alcohol consumption, and exposure to carcinogens. Total smoking and alcohol consumption were estimated up to the followup examination, and may be different if estimated only up to the year of diagnosis of a neoplasm (if any). Further, age at followup rather than age at diagnosis was used in the analysis.

TABLE 10-19.

Unadjusted Analyses of Lifetime Incidence Rates
of All Malignant Systemic Neoplasms Combined, by Group

Status	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Verified	Number of Participants/%	17 1.7%	17 1.3%	1.28 (0.65, 2.51)	0.491
	Total Neoplasms	25	22		
Verified & Suspected	Number of Participants/%	21 2.1%	22 1.7%	1.22 (0.67,2.23)	0.538
	Total Neoplasms	36	27		

Covariate Associations

Associations between the incidence rate of all malignant systemic neoplasms combined and the covariates are presented in Table 10-20. For verified malignant systemic neoplasms, strong associations were found with increasing age ($p<0.001$) and occupation (officers 2.3%, enlisted flyers 1.3%, and enlisted groundcrew 0.9%, $p=0.028$). These same associations were also found for verified plus suspected systemic malignancies. The association with smoking history was not significant, either for verified or for verified plus suspected malignancies. The incidence rate of all malignant systemic neoplasms increased marginally significantly ($p=0.073$) with increasing levels of total lifetime alcohol consumption. For verified plus suspected malignancies, the difference among drink-year categories was also marginally significant ($p=0.080$). No significant association was found with the composite carcinogen exposure variable. A significant association was found between the incidence of verified malignant systemic neoplasms and naphthylamine ($p=0.048$). There was a significant positive association between the verified plus suspected conditions and naphthylamine ($p=0.019$), and a marginally significant association with chloromethyl ether ($p=0.067$).

The covariates used for the adjusted analysis of the incidence of malignant systemic neoplasms were race, age (continuous), occupation, pack-years, drink-years, and the composite carcinogen-exposure variable.

Adjusted Analysis

Table 10-21 shows that, in the adjusted analysis of the group contrast in incidence of all systemic malignancies combined, there was a significant group-by-occupation interaction ($p=0.023$). This was due to a difference in rates for the enlisted flyers, 5 Ranch Hands versus 0 Comparisons (unadjusted p-value=0.019), whereas the incidence rates for officers and enlisted groundcrew did not differ significantly between groups ($p=0.698$ and 0.922, respectively) (Table H-23). Age made a significant contribution to the adjustment. When suspected systemic malignancies were combined with the verified systemic malignancies, a group-by-occupation interaction ($p=0.002$)

TABLE 10-20.

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Age	Born ≥1942	961	4	0.4	<0.001	7	0.7	<0.001
	Born 1923-41	1,261	24	1.9		30	2.4	
	Born ≤1922	87	6	6.9		6	6.9	
Race	Nonblack	2,166	34	1.6	0.267	42	1.9	0.517
	Black	143	0	0.0		1	0.7	
Occupation	Officer	864	20	2.3	0.028	23	2.7	0.069
	Enlisted Flyer	387	5	1.3		7	1.8	
	Enlisted Groundcrew	1,058	9	0.9		13	1.2	
Total Lifetime Smoking (Pack-Years)	0	658	6	0.9	0.237	8	1.2	0.324
	>0-20	1,081	15	1.4		20	1.9	
	>20-40	406	9	2.2		11	2.7	
	>40	158	4	2.5		4	2.5	
Total Lifetime Alcohol Consumption (Drink-Years)	0	151	1	0.7	0.073	2	1.3	0.080
	>0-5	760	7	0.9		10	1.3	
	>5-30	703	8	1.1		10	1.4	
	>30-100	508	11	2.2		13	2.6	
	>100	108	4	3.7		5	4.6	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified			Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Exposures to Carcinogens	Asbestos	499	Yes	5	1.0	0.405	7	1.4	0.459
		1,810	No	29	1.6		36	2.0	
	Nonmedical X Rays	541	Yes	9	1.7	0.684	14	2.6	0.150
		1,768	No	25	1.4		29	1.6	
	Industrial Chemicals	1,199	Yes	14	1.2	0.229	20	1.7	0.539
		1,110	No	20	1.8		23	2.1	
	Herbicides	1,339	Yes	18	1.3	0.601	23	1.7	0.538
		970	No	16	1.7		20	2.1	
	Insecticides	1,389	Yes	17	1.2	0.223	23	1.7	0.432
		920	No	17	1.9		20	2.2	
	Degreasing Chemicals	1,343	Yes	18	1.3	0.600	26	1.9	0.876
		966	No	16	1.7		17	1.8	
Composite Carcinogen Exposure		519	Yes	7	1.4	0.999	8	1.5	0.711
		1,762	No	27	1.5		34	1.9	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified				Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens	Anthracene	2	Yes	0	0.0	0.999	0	0.0	0.999
		2,303	No	34	1.5		43	1.9	
	Arsenic	42	Yes	0	0.0	0.999	2	4.8	0.183
		2,266	No	34	1.5		41	1.8	
	Benzene	83	Yes	2	2.4	0.348	2	2.4	0.666
		2,225	No	32	1.4		41	1.8	
	Benzidine	14	Yes	1	7.1	0.188	1	7.1	0.227
		2,293	No	33	1.4		41	1.8	
	Chromates	88	Yes	2	2.3	0.375	2	2.3	0.679
		2,218	No	32	1.4		41	1.9	
	Coal Tar	73	Yes	2	2.7	0.292	2	2.7	0.397
		2,235	No	32	1.4		41	1.8	
	Creosote	164	Yes	2	1.2	0.999	4	2.4	0.543
		2,145	No	32	1.5		39	1.8	
	Aminodiphenyl	6	Yes	0	0.0	0.999	1	16.7	0.107
		2,300	No	34	1.5		42	1.8	
	Chloromethyl Ether	23	Yes	1	4.4	0.291	2	8.7	0.067
		2,282	No	33	1.5		41	1.8	
	Mustard Gas	9	Yes	0	0.0	0.999	1	11.1	0.156
		2,299	No	34	1.5		42	1.8	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified				Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens (continued)	Naphthylamine	56	Yes	3	5.4	0.048	4	7.1	0.019
		2,251	No	31	1.4		39	1.7	
	Cutting Oils	243	Yes	5	2.1	0.396	7	2.9	0.209
		2,065	No	29	1.4		36	1.7	
	Trichloroethylene	200	Yes	5	2.5	0.211	6	3.0	0.264
		2,106	No	29	1.4		37	1.8	
	Ultraviolet Light	51	Yes	1	2.0	0.535	1	2.0	0.621
		2,256	No	33	1.5		42	1.9	
	Vinyl Chloride	33	Yes	0	0.0	0.999	1	3.0	0.465
		2,273	No	34	1.5		42	1.9	

*Number of participants with malignant systemic neoplasms.

TABLE 10-21.

Adjusted Analyses for Lifetime Incidence of All Malignant Systemic Neoplasms Combined

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Systemic Malignancies (Verified)	****	****	GRP*OCC (p=0.023) AGE (p<0.001)
Systemic Malignancies (Verified & Suspected)	****	****	GRP*OCC (p=0.002) AGE (p<0.001) RACE*PACKYR (p=0.032)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

was also found; this was also due to the high rates for the Ranch Hand enlisted flyers.

Comparison of Baseline, Interval, and Lifetime Results

Table 10-22 compares the unadjusted and adjusted contrasts from the Baseline report with those from the Baseline-followup interval and the whole post-SEA period, for the incidence of all verified malignant skin neoplasms combined, verified basal cell carcinomas, and all verified malignant systemic neoplasms combined. There were, of course, differences in the Baseline and followup cohorts, but there was a sufficiently large overlap to make such a comparative tabulation useful.

Malignant Skin Neoplasms

The significant relative risks for all malignant skin neoplasms seen at Baseline were not evident for the Baseline-followup interval. However, for lifetime basal cell carcinoma, a significant adjusted group contrast was found (p=0.035). The difference in the incidence rates of all skin neoplasms and in basal cell carcinomas only between the Ranch Hands and the Comparisons appears to have decreased over time, as evidenced by the fact that the interval estimated and adjusted relative risks were closer to 1 than those for the lifetime, i.e., interval plus Baseline period.

Malignant Systemic Neoplasms

The unadjusted group contrasts in incidence rates of all malignant systemic neoplasms combined were not significant for Baseline, for the Baseline-followup interval, or for lifetime (Baseline plus interval), nor was the adjusted group contrast for the Baseline-followup interval. The

TABLE 10-22.

Unadjusted and Adjusted Analyses of the Incidence of All Verified Malignant Skin and Systemic Neoplasms and Basal Cell Carcinoma: Baseline, Baseline-Followup Interval, and Lifetime Occurrence

Site	Statistic	Baseline[a]		Baseline-Followup Interval[b]		Lifetime Occurrence[b]	
All Malignant Skin Neoplasms	Number of Participants with Neoplasms/Percent:[c]						
	Ranch Hand	35	3.3%	37	3.9%	66	6.9%
	Comparison	25	2.0%	40	3.3%	66	5.4%
	Est. RR/p-Value	1.62	(0.07)[d]	1.18	(0.486)[e]	1.29	(0.175)[e]
	Adj. RR/p-Value	—*	—*	—*	—*	—*	—*
Basal Cell Carcinoma	Number of Participants with Neoplasms/Percent:[c]						
	Ranch Hand	31	3.0%	29	3.0%	53	5.5%
	Comparison	21	1.7%	30	2.5%	50	4.1%
	Est. RR/p-Value	1.71	(0.047)[d]	1.23	(0.429)[e]	1.36	(0.128)[e]
	Adj. RR/p-Value	—*	—*	****	****	1.56	(0.035)
All Malignant Systemic Neoplasms	Number of Participants with Neoplasms/Percent:[f]						
	Ranch Hand	13	1.2%	8	0.8%	17	1.7%
	Comparison	11	0.9%	7	0.5%	17	1.3%
	Est. RR/p-Value	1.35	(0.46)[d]	1.46	(0.603)[e]	1.28	(0.491)[e]
	Adj. RR/p-Value	—*	—*	1.51	(0.434)	****	****

—*Analysis not done

[a]Baseline participants: 1,045 Ranch Hands, 1,224 Comparisons.

[b]Followup participants: 1,016 Ranch Hands, 1,293 Comparisons.

[c]Nonblacks only for followup participants (956 Ranch Hands, 1,210 Comparisons), both nonblacks and Blacks for Baseline participants.

[d]Chi-square test.

[e]Fisher's exact test.

[f]All participants.

****Group-by-covariate interaction.

estimated lifetime relative risk appears closer to 1 than for the two intervals separately, but the small number of occurrences and intervening mortality preclude more definitive statements.

Baseline Participants

This brief section summarizes the mortality and malignant neoplasm history of the fully compliant Baseline participants in the interval up to the followup examination. Mortality information up through the end of 1985 was considered. This discussion is directed to the question of whether competing mortality affected the preceding analysis of incident cancers among living participants.

Of the 1,045 Ranch Hands and 1,224 Comparisons who were fully compliant at Baseline, 971 Ranch Hands and 1,139 Comparisons returned to the followup examination. Table 10-23 presents the numbers of Baseline participants according to whether they completed the followup examination and whether they were alive at the end of 1985.

TABLE 10-23.

Fully Compliant Baseline Participants by Status at Followup Examination and Group

Participated in Followup Examination	Status	Group		
		Ranch Hand	Comparison	Total
Yes	Dead[a]	3	2	5
	Alive	968	1,137	2,105
No	Dead	9	15	24
	Alive	65	70	135
Total		1,045	1,224	2,269

[a]Died in 1985, but subsequent to participation in the examination.

For the participants who did not return for the followup examination, Table 10-24 shows that 2 of the 9 deaths among Ranch Hands were due to malignant neoplasms, compared with 5 of the 15 deaths among the Comparisons. One Ranch Hand who died had a malignant skin neoplasm, but this was not the primary cause of death. Among the 65 Ranch Hands who did not return for the followup examination, 5 had verified malignant neoplasms at Baseline, including 1 systemic neoplasm (of the kidney), as contrasted with 2 among 70 Comparisons who had verified malignant (skin) neoplasms. Thus, among the 74 Ranch Hands not returning for followup, there were 8 with incident or fatal neoplasms, as compared to 7 of 85 Comparisons; the group difference was not significant ($p=0.788$).

TABLE 10-24.

Fully Compliant Baseline Participants Who Did Not Participate in Followup Examination by Status and Group

Status	Group		Total
	Ranch Hand	Comparison	
Dead--Primary Cause of Death:			
Malignant Neoplasm	2[a]	5[b]	7
Other Causes	7[c]	10	17
Lost to Followup:			
Verified Malignant Neoplasm at Baseline	5[d]	2[e]	7
No Malignant Neoplasm at Baseline	60	68	128

[a]Both with lung cancer.

[b]Three with lung cancer, one with malignant neoplasm of intestine (location unspecified), one with malignant neoplasm of an ill-defined site (face, head, or neck).

[c]Includes one Ranch Hand with malignant skin neoplasm.

[d]Four with malignant skin neoplasms, one with malignant systemic neoplasm (kidney).

[e]Two with malignant skin neoplasms.

For the participants who did return for the followup examination, Table 10-25 gives the frequencies and percentages of the respective group totals according to neoplasm status at Baseline and at followup. Analysis showed that there was no significant group difference ($p=0.115$) in the pattern of neoplasm incidence at Baseline and/or at followup.

The results of this section show approximate equivalence between the groups for the disease of cancer (fatal or nonfatal) since Baseline, and in the proportions of participants with malignancies at Baseline, followup, or both.

EXPOSURE INDEX ANALYSES

Unadjusted and adjusted exposure index analyses were conducted within each occupational cohort of the Ranch Hand group (see Chapter 8 for details on the exposure index). Interval and lifetime occurrences of basal cell carcinomas, sun-exposure related malignant skin neoplasms, and malignant systemic neoplasms were examined. As was done in the core analyses, verified conditions and verified plus suspected malignancies were each investigated. Blacks were excluded from all malignant skin neoplasm analyses. Group contrasts in incidence rates of malignant skin neoplasms were adjusted for the covariates of age, sun reaction index, and average residential latitude. Adjusted analyses for malignant systemic neoplasms accounted for the effects of age and race.

For each dependent variable, exposure level frequencies and percentages are presented in Appendix Tables H-26 and H-27, for interval and lifetime, respectively, along with the results of the unadjusted analyses. Pearson's chi-square test was used to reflect overall exposure index differences, and Fisher's exact test was used to investigate medium versus low and high versus low exposure level contrasts. Results of the adjusted analyses are presented in Tables 10-26 and 10-27, for interval and lifetime, respectively. These results are presented in the context of a main effects model containing exposure index and all adjusting covariates.

Several significant or marginally significant overall results were found. None was suggestive of a strictly increasing dose response effect; in fact, most showed decreasing incidence rates with increasing exposure.

Among officers, in the unadjusted interval analysis, significant or marginally significant results were found among nonblacks for verified and suspected basal cell carcinomas (overall $p=0.042$), sun-exposure related malignant skin neoplasms (verified: overall $p=0.096$, verified plus suspected: overall $p=0.021$), and among Blacks and nonblacks for verified plus suspected malignant systemic neoplasms (overall $p=0.081$). These findings were primarily due to higher percentages of malignancies in the medium exposure level than in the high or low categories for each variable (see Appendix Table H-26 for frequencies). The corresponding adjusted analyses were nonsignificant for basal cell carcinoma (overall $p=0.156$), verified sun-exposure malignancies (overall $p=0.272$), and systemic malignant neoplasms (overall $p=0.109$). The adjusted results were marginally significant for verified plus suspected sun-exposure malignancies (overall $p=0.095$).

TABLE 10-25.

Fully Compliant Baseline Participants Also in Followup Examination by Malignant Neoplasm Status

Malignant Neoplasm at Baseline	Malignant Neoplasm at Followup	Group				Total
		Ranch Hand		Comparison		
		Number	Percent	Number	Percent	
Yes	Yes	10	1.0	15	1.3	25
	No	37	3.8	28	2.5	65
No	Yes	36	3.7	31	2.7	67
	No	888[a]	91.5	1,065[a]	93.5	1,953
Total		971		1,139		2,110

[a]Includes three Ranch Hands and two Comparisons who died after followup.

TABLE 10-26.

Adjusted Exposure Index Analysis for Followup Participants for occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index Low Total*	Medium Total*	High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	124	127	121	Overall		0.415
					M vs. L	2.02 (0.50,8.10)	0.320
					H vs. L	0.91 (0.18,4.68)	0.908
Basal Cell[a] Carcinoma (Verified Only)	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.346
					M vs. L	0.51 (0.07,3.53)	0.496
					H vs. L	0.19 (0.02,2.14)	0.179
	Officer	124	127	121	Overall		0.156
					M vs. L	2.40 (0.73,7.88)	0.149
					H vs. L	0.91 (0.22,3.76)	0.892
Basal Cell[a] Carcinoma (Verified and Suspected)	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.165
					M vs. L	0.36 (0.06,2.25)	0.274
					H vs. L	0.14 (0.01,1.44)	0.098

TABLE 10-26. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Sun-Exposure[a] Related Malignancies (Verified Only)	Officer	124	127	121	Overall		0.272
					M vs. L	2.38 (0.61,9.30)	0.214
					H vs. L	0.95 (0.18,4.88)	0.949
	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.767
					M vs. L	0.83 (0.15,4.55)	0.826
					H vs. L	0.50 (0.07,3.39)	0.481
Sun-Exposure[a] Related Malignancies (Verified and Suspected)	Officer	124	127	121	Overall		0.095
					M vs. L	2.68 (0.83,8.67)	0.100
					H vs. L	0.93 (0.22,3.86)	0.921
	Enlisted Flyer	54	60	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.514
					M vs. L	0.59 (0.12,2.94)	0.519
					H vs. L	0.36 (0.06,2.20)	0.268

TABLE 10-26. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	127	130	123	Overall		0.365
					M vs. L	1.60 (0.15,17.22)	0.696
					H vs. L	--	--
Systemic[b] Malignancies (Verified Only)	Enlisted Flyer	55	65	57	Overall		--
					M vs. L	--	--
					H vs. L	--	--
	Enlisted Groundcrew	154	163	142	Overall		--
					M vs. L	--	--
					H vs. L	--	--
	Officer	127	130	123	Overall		0.109
					M vs. L	2.95 (0.31,27.73)	0.344
					H vs. L	--	--
Systemic[b] Malignancies (Verified and Suspected)	Enlisted Flyer	55	65	57	Overall		0.557
					M vs. L	0.25 (0.02,3.90)	0.326
					H vs. L	0.38 (0.03,4.90)	0.458
	Enlisted Groundcrew	154	163	142	Overall		--
					M vs. L	--	--
					H vs. L	--	--

*Total number of participants.
[a]Nonblacks only.
[b]Blacks and nonblacks.
--Analyses not done due to sparse cells.

TABLE 10-27.

Adjusted Exposure Index Analysis for Followup Participants for Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index Low Total*	Medium Total*	High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	124	127	121	Overall		0.841
					M vs. L	1.33 (0.48,3.66)	0.580
					H vs. L	1.27 (0.45,3.60)	0.647
Basal Cell Carcinoma (Verified Only)[a]	Enlisted Flyer	54	61	51	Overall		0.024
					M vs. L	0.23 (0.03,1.61)	0.141
					H vs. L	0.08 (0.01,0.78)	0.030
	Enlisted Groundcrew	138	149	129	Overall		0.937
					M vs. L	1.10 (0.31,3.86)	0.881
					H vs. L	0.87 (0.24,3.20)	0.832
	Officer	124	127	121	Overall		0.699
					M vs. L	1.49 (0.59,3.78)	0.404
					H vs. L	1.22 (0.46,3.24)	0.694
Basal Cell Carcinoma (Verified and Suspected)[a]	Enlisted Flyer	54	60	51	Overall		0.024
					M vs. L	0.23 (0.03,1.61)	0.141
					H vs. L	0.08 (0.01,0.78)	0.030
	Enlisted Groundcrew	138	149	129	Overall		0.860
					M vs. L	0.89 (0.27,2.97)	0.849
					H vs. L	0.71 (0.20,2.48)	0.589

TABLE 10-27. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index Low Total*	Medium Total*	High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Sun-Exposure Related Malignancies (Verified Only)[a]	Officer	124	127	121	Overall		0.906
					M vs. L	1.19 (0.47,3.00)	0.717
					H vs. L	0.99 (0.37,2.64)	0.980
	Enlisted Flyer	54	61	51	Overall		0.045
					M vs. L	0.42 (0.08,2.19)	0.300
					H vs. L	0.09 (0.01,0.89)	0.039
	Enlisted Groundcrew	138	149	129	Overall		0.785
					M vs. L	1.35 (0.40,4.58)	0.627
					H vs. L	0.88 (0.24,3.25)	0.850
Sun-Exposure Related Malignancies (Verified and Suspected)[a]	Officer	124	127	121	Overall		0.722
					M vs. L	1.33 (0.56,3.16)	0.518
					H vs. L	0.97 (0.38,2.47)	0.952
	Enlisted Flyer	54	60	51	Overall		0.045
					M vs. L	0.42 (0.08,2.19)	0.300
					H vs. L	0.09 (0.01,0.89)	0.039
	Enlisted Groundcrew	138	149	129	Overall		0.785
					M vs. L	1.10 (0.34,3.52)	0.879
					H vs. L	0.72 (0.20,2.52)	0.603

TABLE 10-27. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	127	130	123	Overall		0.902
					M vs. L	1.11 (0.18,7.01)	0.911
					H vs. L	1.49 (0.24,9.16)	0.669
Systemic Malignancies (Verified Only)[b]	Enlisted Flyer	55	65	57	Overall		0.806
					M vs. L	0.86 (0.11,7.08)	0.892
					H vs. L	0.46 (0.04,5.46)	0.540
	Enlisted Groundcrew	154	163	142	Overall		0.073
					M vs. L	--	--
					H vs. L	--	--
	Officer	127	130	123	Overall		0.829
					M vs. L	1.69 (0.30,9.65)	0.554
					H vs. L	1.47 (0.24,8.95)	0.679
Systemic Malignancies (Verified and Suspected)[b]	Enlisted Flyer	55	65	57	Overall		0.741
					M vs. L	0.51 (0.08,3.47)	0.494
					H vs. L	0.54 (0.08,3.57)	0.527
	Enlisted Groundcrew	154	163	142	Overall		0.087
					M vs. L	--	--
					H vs. L	--	--

*Total number of participants.
[a]Nonblacks only.
[b]Blacks and nonblacks.
--Analyses not done due to sparse cells.

For the interval analysis, enlisted flyers exhibited a marginally significant decreasing dose-response effect for verified basal cell carcinomas in both the unadjusted (p=0.073) and adjusted analyses (p=0.080). (All Ranch Hand enlisted flyer interval malignant skin neoplasms were verified basal cell carcinomas; thus, interval results for verified and verified plus suspected basal cell carcinoma and the corresponding sun-exposure related neoplasms were identical. Similarly, for lifetime analyses, verified and verified plus suspected analyses were the same). The percentages of participants with interval basal cell neoplasms were 11.1 percent, 3.3 percent, and 1.9 percent for the low, medium, and high exposure categories, respectively. The enlisted groundcrew exhibited a nonsignificant decreasing dose-response effect for basal cell carcinomas and sun-exposure related malignant neoplasms.

In the adjusted lifetime analysis for enlisted flyers (Table 10-27), there were significant findings, similar to the interval analysis, namely a decreasing dose-response effect for basal cell carcinomas (overall p=0.024; Adj. RR [medium versus low]: 0.23, 95% C.I.: [0.03, 1.61], Adj. RR [high versus low]: 0.08, 95% C.I.: [0.01, 0.78]), and for sun-exposure related skin malignancies (overall p=0.045; Adj. RR [medium versus low]: 0.42, 95% C.I.: [0.08, 2.19], Adj. RR [high versus low]: 0.09, 95% C.I.: [0.01, 0.89]). The percentages of participants with lifetime basal cell carcinomas were 13.0 percent, 3.3 percent, and 1.9 percent for the low, medium, and high exposure categories, respectively. The corresponding percentages for lifetime sun-exposure related skin malignancies were 13.0 percent, 4.9 percent, and 1.9 percent. For the enlisted groundcrew cohort, a marginally significant result was found for all systemic malignancies combined in the adjusted analyses (verified only: overall p=0.073; verified plus suspected: overall p=0.087). Of the four verified systemic malignancies, three were in the medium exposure category and one was from the high category. There was one additional suspected malignant neoplasm in the high exposure category. No significant results were found for officers in the lifetime analysis.

DISCUSSION

The statistical analyses of cancer endpoints in this chapter have carefully followed the prescribed boundaries of the SAIC analytic plan approved by the Air Force. Specific latency analyses of certain cancers associated with environmental exposures were not performed, nor were contrasts of cancer-specific incidence rates to SEER data judged appropriate. Further, embedded case control studies on selected cancers were not performed due to concern for bias.

The statistical analyses focused on neoplasms occurring during the time interval between 1982 and 1985 (Baseline to followup). However, because these relatively young and healthy cohorts yielded small numbers of cancers in this short interval, and because of the intense scientific interest in malignant disease, the analysis went beyond the assessment of the incidence of malignant neoplasms in this interval. Lifetime (Baseline and followup data combined) analyses of malignant incident neoplasms were conducted. Cancers occurring prior to military duty in SEA were excluded. A full cancer mortality-morbidity analysis was not attempted but simple tabulations of cancer incidence and mortality of Baseline participants were made. Interval and lifetime analyses were expanded to include suspected cancers noted at followup. Further, grouped cancers that were not likely related were

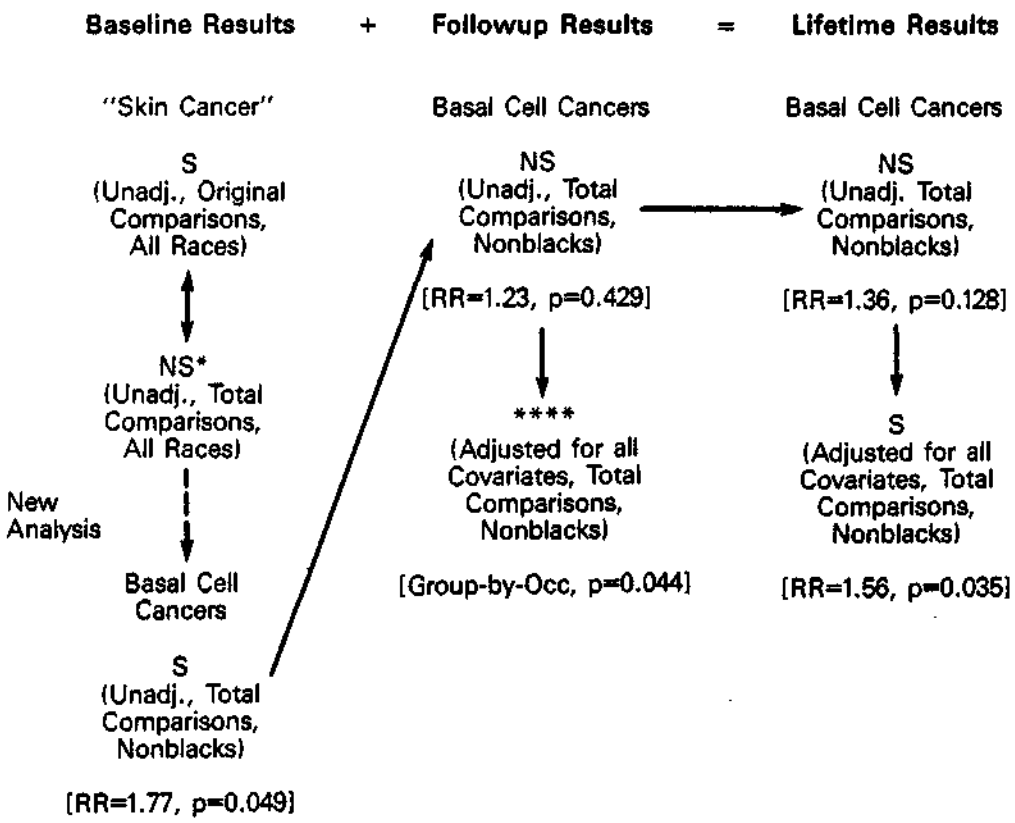
analyzed (all systemic cancers and malignant sun exposure-related skin neoplasms). These efforts, however, have introduced several subtle interpretive issues that should be noted, e.g., skin cancer rates are for nonblacks only, whereas systemic cancer rates are for all races; lifetime group rates are on only those attending the followup examination; and verified and suspected cancer categories included more cases but the data are less reliable. Further, contrasts of cancer rates, particularly skin cancer, between the Baseline results and followup results, or lifetime results, must account for the slight differences in the Baseline and followup cohorts, racial adjustment (Blacks were not omitted from skin cancer analyses at Baseline), skin cancer classification, the change in focus from the Original Comparisons to the total Comparison group, and whether the data were adjusted for covariates.

Skin Cancer

The emphasis on skin cancer at the followup examination was predicated upon the finding of a significant excess of such cancers at the Baseline examination, and the lack of risk factor data to conduct appropriate adjusted analyses. Because of shifting factors (cited above) between the examinations, a "direct look" at the skin cancer association is not straightforward. Figure 10-1 is presented as an aid to clarify the skin cancer observations over the two examinations.

This diagram compares the Baseline and followup analyses. So that the unadjusted Baseline results could be contrasted to the followup results, the estimated relative risk of basal cell carcinoma among nonblack Ranch Hands versus all nonblack Comparisons (not just Originals) was calculated, using data in the Baseline Report. This unadjusted analysis gave a significant relative risk of 1.77 (p=0.049). These results could then be directly contrasted to the unadjusted followup results, which showed a narrowing of group differences over the 3-year interval (Est. RR: 1.23, p=0.429). (It is noted that this contrast compares skin cancer rates of approximately 23 years to 3 years at different levels of age risk.) The adjusted analysis revealed a significant group-by-occupation interaction, due to a significantly higher rate of basal cell carcinomas among Ranch Hand enlisted flyers than the corresponding Comparisons (Adj. RR: 6.50, p=0.019), but very similar rates in the two groups for officers and enlisted groundcrew were seen.

The Baseline data were carefully merged (to avoid duplicate counts) with the followup data to assess the total lifetime incidence of basal cell carcinomas between groups. The addition of the nonsignificant followup results to the significant Baseline results produced a nonsignificant lifetime assessment (Est. RR: 1.36, p=0.128), as expected. However, when the lifetime data were adjusted for covariate effects, a significant result emerged (Adj. RR: 1.56, p=0.035), with Ranch Hands having a significant excess of lifetime basal cell carcinoma. A careful examination of the covariates showed that the variable of average residential lifetime latitude was most likely responsible for the significant adjusted results. The latitude variable was a significant confounding variable since it was associated with basal cell carcinomas and with average lifetime latitude which varied significantly by group.



S: Significant ($p \leq 0.05$).
NS: Not significant ($p > 0.10$).
NS*: Borderline significant ($0.05 < p \leq 0.10$).
****: Group-by-covariate interaction.

Figure 10-1.
Schematic Diagram of Unadjusted and Adjusted Skin Cancer Results, by Significance and Relative Risk, and by Examination Period (Time).

Because of the significant confounding effect of the latitude variable, it was examined closely for misclassification or bias. An initial review of the residential history forms showed occasional discrepancies between total residential years and chronologic age. This was generally due to sporadic underreporting, and to the data collection instructions which required the citation only of residences of one year or longer. However, analyses showed fairly good concordance between reported residential years and chronologic age. No significant group difference was found for the inaccuracy of residential reporting ($p=0.684$), validating the use of all residential histories even though some were slightly imprecise.

In the course of reviewing the covariate effects on basal cell carcinoma, the data suggested some unexpected associations. To sharpen these contrasts, adjusted risks were estimated at set levels of skin reaction to sun, skin color, average lifetime residential latitude, and age, relative to the lowest risk observed, i.e., Comparisons 40 years old (at Baseline) who have lived on average in northern latitudes and tan easily were arbitrarily assigned a risk of 1.00. These computed risks are given in Table 10-28.

These results show uniform increased risks in the Ranch Hands over both the base level of one and the Comparisons in the same covariate strata. Further, in all strata, age, latitude, and skin color behave as expected. However, the sun-reaction index does not behave as expected since those who burn easily have lower relative risks than those who have an intermediate reaction to sun, although they do have higher relative risks than those who tan easily. This may represent avoidance of sun exposure or the use of sunblock by those individuals.

Skin cancer, and particularly basal cell carcinoma, has been emphasized in this report because of the significant group differences detected at Baseline (and the theoretical link to TCDD causation), and the borderline significant adjusted results found for the lifetime rates. The results of the third-year followup analysis suggest that if group differences continue to narrow (where $p \geq 0.15$) at the fifth-year followup examination, the lifetime results would likely not be significant even with full adjustment.

Systemic Cancer

The analyses of systemic cancer for both the interval and lifetime periods have necessarily been limited by scant data. Cancer specific analyses, in particular, have not provided meaningful results because of low counts. However, some variation in tumor type was noted in the two groups: colon cancer (5 Comparisons, 0 Ranch Hands), testicular cancer (3 Ranch Hands, 0 Comparisons), and smoking related tumors of the oral cavity, pharynx, bronchus, and lung (5 Ranch Hands, 0 Comparisons). Testicular and smoking related tumors have not been associated with exposure to herbicides or TCDD. Table 10-18 cited counts of malignancies that have been associated to herbicides and dioxin exposure. Because of the relative rareness of the diseases soft tissue sarcoma (STS), Hodgkin's disease, and non-Hodgkin's lymphoma, lifetime rates were expected to be exceptionally low.

Most of the covariate associations with systemic cancer were anticipated, but the change in significance for smoking (significant at Baseline, borderline significant for lifetime cancers) was not expected, particularly as the cancer cases increased during the interval.

TABLE 10-28.

Computed Risks of Basal Cell Carcinoma
by Group at Varying Levels of Four
Risk Factors, Relative to Comparisons at Low Risk*

Covariate Categories			Skin Color: Not Peach		Skin Color: Peach	
Skin Reaction to Sun	Average Lifetime Residential Latitude	Age at Baseline	Comparison	Ranch Hand	Comparison	Ranch Hand
Tans Easily	≥37°N	40	1.00**	1.48	1.55	2.30
		60	2.99	4.43	4.62	6.85
	<37°N	40	1.63	2.42	2.52	3.74
		60	4.87	7.23	7.53	11.18
Intermediate Reaction	≥37°N	40	3.04	4.52	4.71	6.99
		60	9.09	13.50	14.06	20.87
	<37°N	40	4.97	7.37	7.68	11.40
		60	14.83	22.02	22.93	34.04
Burns Easily	≥37°N	40	2.02	3.00	3.13	4.64
		60	6.04	8.96	9.33	13.86
	<37°N	40	3.30	4.90	5.10	7.57
		60	9.85	14.62	15.22	22.60

*Computed from main effects model with latitude, skin reaction to sun, and skin color as covariates.

**Base Category (Lowest Risk).

All Cancers

As previously noted, the interrelatedness of many of the analyzed cancer variables has created a compounding of statistical significance, and care should be taken in making inferences and final conclusions. An almost uniform dilutional effect was created by adding "suspected" cancers to the analyses, as there were more of this category in the Comparisons than in the Ranch Hands. The use of suspected neoplasms was deemed necessary in order to best describe the complete cancer findings, recognizing that confirmation of all suspected cases was difficult.

Two patterns emerged from the analyses. All relative risks exceeded the value of one, except that of lifetime verified melanoma and verified or verified plus suspected squamous cell carcinoma. Some of the elevated risks were due to the relatedness of the variables as stated, but the relative risks for the unrelated variables skin cancer and systemic cancer both exceeded one. The joint consideration of both yielded a significant relative risk. The second pattern was of the group-by-covariate interactions observed for seven of the analyses; 3 of them involved the covariate of occupation and 4 involved skin reaction to sun. The three group-by-occupation interactions all showed a significant detriment to the Ranch Hand enlisted flying cohort. Further analyses of air crewmembers versus noncrewmembers revealed a significant risk of basal cell carcinoma for the Ranch Hand air crewmembers (RR: 1.94, $p=0.049$). Since enlisted Ranch Hand flyers in the interval exhibited more basal cell carcinomas (RR: 6.5, $p=0.019$) and more verified and suspected systemic cancers (4/175 RH with systemic neoplasms versus 0/209 Comparisons, $p=0.042$), there may be more reason to assume a biologic foundation than chance, although the reason is obscure. The four group-by-sun reaction index interactions all revealed a significant or marginally significant detriment to Ranch Hands who reacted mildly to the sun.

In full context, the cancer observations cannot be viewed as disturbing at this time. The skin cancer group differences have narrowed over a 3-year period. An additional analytic observation on skin cancer is that inclusion or exclusion of only one or two cases was shown to alter the choice of the best statistical model, affecting the presence or absence of both covariates and group-by-covariate interactions, and also change the p-value of the adjusted group difference above or below the alpha level of 0.05. For systemic cancer, both groups are at the lower end of the expected ascending cancer curves, where numeric and tumor type fluctuations are expected. A recognized bench-mark for the latency of many cancers is 20 years, and this will not be achieved by most participants until the 5-year followup examination, 2 years from now. Cancer findings at that time will be the basis upon which firm conclusions can be made.

SUMMARY AND CONCLUSIONS

The cancer analysis focused on cancer occurrences in the Baseline-followup interval, and also included analyses of the Baseline plus interval cancer history. A summary of the cancer findings is given in Table 10-29.

No significant unadjusted differences were found between nonblack Ranch Hands and Comparisons in the Interval (Baseline-Followup) incidence rates of basal cell carcinoma, melanoma, squamous cell carcinoma, all malignant skin cancers, sun-exposure related malignant neoplasms (comprising basal cell

TABLE 10-29.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval and Lifetime Skin and Systemic Cancer Incidence

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Malignant Skin Cancer (Nonblacks only)				
Verified Basal Cell Carcinoma	NS	****	NS	S
Verified plus Suspected Basal Cell Carcinoma	NS	****	NS	****
Verified Melanoma	NS	--[a]	NS	--[a]
Verified plus Suspected Melanoma	NS	--[a]	NS	--[a]
Verified Squamous Cell Carcinoma	NS	--[a]	NS	--[a]
Verified plus Suspected Squamous Cell Carcinoma	NS	--[a]	NS	--[a]
Verified Sun Exposure Skin Cancers	NS	NS	NS*	S
Verified plus Suspected Sun Exposure Skin Cancers	NS	NS	NS	NS
All Verified Malignant Skin Cancers	NS	--[a]	NS	--[a]
Verified plus Suspected Malignant Skin Cancers	NS	--[a]	NS	--[a]
Verified Skin Cancers of Any Type	NS*	--	S	--
Verified plus Suspected Skin Cancers of Any Type	NS	--	NS*	--

TABLE 10-29.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval and Lifetime Skin and Systemic Cancer Incidence (continued)

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Malignant Systemic Cancer (Blacks and Nonblacks)				
Verified Systemic Cancer	NS	NS	NS	****
Verified plus Suspected Systemic Cancer	NS	****	NS	****
All Neoplasms (Blacks and Nonblacks)				
Any Type, Any Location[b] Verified	NS*	--[a]	S	--[a]

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

****Group-by-covariate Interaction.

--[a]Analysis not done.

NS*: Borderline significant ($0.05<p\leq0.10$).

[b]Comprises malignant, benign, uncertain behavior.

S: Significant ($p\leq0.05$).

carcinoma, melanoma, and epithelial neoplasms NOS) or all malignant skin cancers as a group. The unadjusted group contrast of all skin neoplasms (comprising malignant and benign neoplasms, and neoplasms of uncertain behavior or unspecified nature) was marginally significant, with a higher rate among Ranch Hands. When suspected malignant skin cancers (noted at Followup but not verified at the time of writing) were included in the analyses with the verified conditions, all the unadjusted group contrasts were nonsignificant.

The covariates used for the adjusted analyses of basal cell carcinoma and the sun exposure related skin malignancies were age, occupation, skin color, reaction of skin to sun, and average latitude, all of which were highly associated with skin cancer incidence. Other host factors were related to skin cancer incidence, but not as strongly as those included in the analysis. A borderline association with smoking history was noted, and was determined to be partly an age effect.

Analysis of the incidence of interval basal cell carcinoma revealed a significant group-by-occupation interaction, due to a significant group difference for enlisted flyers, but not for officers or enlisted groundcrew. Inclusion of suspected basal cell carcinoma resulted in a group-by-sun reaction index interaction. This was due to Ranch Hands with an intermediate reaction to sun having a higher relative risk than the corresponding Comparisons. The adjusted group contrast of the incidence rates of verified sun-exposure related skin cancers was not significant; inclusion of suspected conditions did not alter this lack of significance.

There was no significant group difference for Blacks and nonblacks in the unadjusted incidence rates of all interval verified malignant systemic neoplasms combined, nor was there a significant difference in the adjusted group rates. Analysis of the verified plus suspected interval systemic cancers showed a nonsignificant unadjusted group difference, but a group by occupation interaction was found in the adjusted analysis. This was due to a significant group difference of verified plus suspected systemic malignancies among the enlisted flyers with five occurrences among the Ranch Hands, but none among the Comparisons. Age and a race-by-packyear interaction were important adjusting factors.

The Baseline and Followup data were combined for the assessment of lifetime incidence of cancer; occurrences of cancer prior to Vietnam were excluded.

There were no significant unadjusted group differences in lifetime incidence rates among nonblacks for basal cell carcinoma, melanoma, squamous cell carcinoma, the sun exposure related skin cancers, or all malignant skin cancers combined. The unadjusted group contrast of all lifetime skin malignancies was significant, with a higher rate among Ranch Hands. Inclusion of suspected cancers with the verified cancers reduced the difference between the groups for all these malignant skin contrasts, except for the sun exposure related skin cancers, for which a marginally significant group difference was found. However, the contrast of all skin malignancies remained close to significance.

Adjusted analysis of the incidence rates of lifetime basal cell carcinoma revealed a significantly higher incidence rate among Ranch Hands

(Adj. RR: 1.56, p=0.035). Significant effects of an occupation-by-age interaction, a skin color-by-sun reaction index interaction, and a sun reaction index-by-average residential latitude interaction were seen. The adjustment resulted in a significant relative risk that, moreover, was higher than the unadjusted relative risk. Average residential latitude, associated with both group and skin cancer, and skin color, which was associated with the disease and marginally associated with group, played a major part in the change from the unadjusted analysis due to confounding. Inclusion of suspected basal cell carcinoma in the adjusted analysis resulted in a group by sun reaction index interaction, as was noted for the interval analysis.

The adjusted group contrast in incidence rates of the sun-exposure related skin cancers was also significant (Adj. RR: 1.54, p=0.030), which is not surprising since the majority are basal cell carcinoma. Inclusion of the suspected conditions resulted in a non-significant group contrast.

The unadjusted group contrasts of the incidence rates of all systemic cancers combined were not significant, both for verified and verified plus supected conditions.

There was one new occurrence of a soft tissue sarcoma (Ranch Hand) and one suspected cancer of the lymphatic system (Ranch Hand), in addition to the one previously reported soft tissue sarcoma and one Hodgkin's disease in the Comparison group.

Adjusted analysis of all lifetime malignant systemic neoplasms as a group, however, revealed a group by occupation interaction, due to a significantly higher rate for Ranch Hand enlisted flyers as contrasted to Comparisons. The same result was found for verified plus suspected systemic cancers.

In conclusion, there were no adjusted or unadjusted differences between groups in basal cell carcinoma incidence in the Baseline-followup interval. At Baseline, a significantly higher rate of basal cell carcinoma was found for Ranch Hands when contrasted with Original Comparisons. When the Baseline data were combined with the interval data, adjusted analysis, but not the unadjusted analysis, revealed a significantly higher rate of basal cell carcinoma among the Ranch Hands than among all Comparisons. The relative risk of basal cell carcinoma appears to be declining over time.

Relative risks of basal cell carcinoma and systemic cancer were found to be consistently larger than 1. Most of the skin cancers were basal cell carcinomas, upon which most of the skin cancer analysis focused, thus relative risks for sun-exposure related skin neoplasms and all malignant skin cancers as a group were very similar to those for basal cell carcinoma. The number of occurrences of systemic cancer was small, in part because the cohort is relatively young, and although the relative risks (lifetime and interval) are greater than 1, the difference between groups is not significant. Sufficient time may not have elapsed since Vietnam to enable a group difference in systemic neoplasms, if one exists, to be apparent.

CHAPTER 10

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CHAPTER 11

NEUROLOGICAL ASSESSMENT

INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and TCDD. Thus, the neurological system comprises a major examination focal point in all dioxin morbidity studies. This report carefully separates central and peripheral neurological status from "neurobehavioral" parameters, which are discussed in Chapter 12, Psychological Assessment.

Based on animal experiments, neurotoxicity can be attributed to the compounds 2,4-D and TCDD. For low to moderate doses, both central and peripheral acute effects occur but appear to be reversible.[1-3] The effects of 2,4-D are presumably due to disruption in the neuromuscular transport system of organic acid anions.[4] A variety of 2,4-D experiments in several animal species generally shows a wide range of neural pathology including electroencephalographic (EEG) desynchronization, demyelination, myotonia, loss of coordination, and uncontrolled motor activity. No substantive data support the isolated neurotoxicity of 2,4,5-T.

Numerous case reports following accidental human exposures or suicide attempts with 2,4-D have shown a remarkable neurologic parallel to the animal studies.[5-10] In particular, 2,4-D and TCDD have been implicated in a wide array of central neurological signs and symptoms, including headache, vomiting, dizziness, disorientation, sleep disturbance, stupor, memory loss, loss of coordination, and EEG abnormalities or alterations from a baseline tracing.[5-7,9,11-13] Peripheral abnormalities have included demyelination, acute degeneration of ganglion cells, temporary paralysis, anesthesia, hyperesthesia, paresthesia, neuralgic pain, numbness, tingling, muscle pain, muscle fasciculations, depressed or absent deep tendon reflexes, weakness, decreased nerve conduction velocities, "polyneuritis," and limb fatigue.[5-16] These peripheral signs and symptoms in industrial workers have received the generic diagnostic label "neurasthenia." Both the number and severity of symptoms tended to aggregate in individuals with chloracne as contrasted to those without chloracne.[11,16,17]

In general, there is consistency between the various case reports of neurasthenia and results from uncontrolled clinical studies. Of particular relevance is the consistency in findings from studies of both industrial manufacturing and industrial accidents. This literature provides the clear-cut conclusion that neurological impairment is caused directly by exposure to 2,4-D and TCDD. Not answered satisfactorily in the literature, however, are the issues of complete reversibilty of observed signs and symptoms and the long-term impact on health and quality of life.

Because of the conclusive evidence that two of three Agent Orange ingredients cause neurological "disease," it follows that significant exposure to Agent Orange could manifest neurologic signs, symptoms, or sequelae. In fact, over 10 percent of Vietnam veterans who enlisted in the VA Agent Orange Registry cited one or more symptoms of the neurasthenic complex.[18]

The VA Registry is a comprehensive listing, predominantly of veterans alleging health impairments due to Agent Orange exposure. The Registry does not purport to be a scientific effort upon which cause-and-effect relationships can be established. Nonetheless, some individuals believe that the symptom array in the VA Registry is so compatible with case reports and numerator-oriented clinical studies that the veterans must, in fact, have suffered adverse health effects from their Vietnam service and presumed exposure to Agent Orange. Others point to the intense media attention to "Agent Orange symptoms" during the formation of the Registry, and presume that the veterans' complaints are largely due to an "over-reporting" or compensation bias.

Clearly, only well-controlled, well-conducted epidemiologic studies of veterans known to have been exposed to Agent Orange can answer the question of cause and effect for illnesses, including the specific question of whether single or multiple neurologic signs and symptoms are also attributable to these exposures.

Baseline Summary Results

The 1982 AFHS neurological assessment consisted of questionnaire, physical examination, and electromyographic data obtained by examiners and technicians who were blinded to the group identity of each participant. The physical examination required an average of 30 minutes to complete. Those few individuals with positive RPR tests, a screening serological test for syphilis, and those with peripheral edema were deleted from the statistical analyses. Covariates of reported alcohol usage, exposure to insecticides and industrial chemicals, and glucose intolerance (diabetes) were analyzed. Results of the questionnaire disclosed no significant group differences in reported neurological diseases.

The physical examination did not reveal any statistically significant group differences in the function of all 12 cranial nerves, nor any effects due to the covariates of alcohol or diabetes. Peripheral nerve function was assessed by the quality of four reflexes (patellar, Achilles, biceps, and Babinski), muscle strength/bulk, and reaction to the stimuli of pin prick, light touch, and vibration. Other than a statistically significant increase ($p=0.03$) in Ranch Hand Babinski reflexes, significant group differences were not detected. The alcohol covariate demonstrated a marginal effect ($p=0.07$) on pin-prick reaction, while glucose intolerance showed a profound effect on the patellar and Achilles reflexes and reactions to light touch and vibration.

Nerve conduction velocities were obtained on the ulnar nerve, above and below the elbow, and the peroneal nerve by highly standardized methods. The results for each segmental measurement were nearly identical in the Ranch Hand and Comparison groups. Conduction velocity showed highly significant inverse relationships to both alcohol (measured in drink-years) and glucose intolerance in almost all of the anatomic measurements. No group associations or interactions were detected with the covariates of industrial and degreasing chemicals and insecticides.

No significant group differences were detected in four measures of central neurological function (tremor, finger-nose coordination, modified positive Romberg's sign, or abnormal gait). Alcohol usage was significantly associated with the presence of tremor, and glucose intolerance was highly correlated to abnormal balance and the presence of tremor.

Of a total of 84 exposure index analyses on all of the dependent variables, 3 were statistically significant but were either nonlinear or biologically implausible. In summary, the detailed neurological examination and assessment did not reveal statistically significant increases in abnormalities in the Ranch Hands, nor were consistent dose-response relationships noted for herbicide exposure. The classical neurological effects of alcohol ingestion and diabetes were repeatedly observed in the neurological evaluations.

Parameters of the 1985 Neurological Assessment

The 1985 AFHS neurological examination deleted the measurements of nerve conduction velocities but otherwise repeated the format of the Baseline examination. The questionnaire maintained a historical focus of neurasthenia via five questions for the 1982-1985 interval.

With this similarity in examination and questionnaire, the dependent variables of the analyses were almost identical to those of the Baseline study, however, the number of covariates was slightly increased. Diabetic status was trichotomized: Individuals reporting a history of diabetes (unverified) and individuals exhibiting glucose intolerance with postprandial glucose levels greater than or equal to 200 mg/dl were classified as diabetic, participants with glucose levels of at least 140 mg/dl but less than 200 mg/dl were classified as impaired, and participants with glucose levels less than 140 mg/dl were classified as normal. Race was included as a covariate, and lifetime alcohol use was updated on the basis of enhanced information from the 1985 questionnaire.

The analyses were based on 1,016 Ranch Hands and 1,293 Comparisons. Individuals confirmed to be positive for syphilis by fluorescent treponemal antibody (FTA) testing were excluded from all analyses. Individuals with peripheral pitting or nonpitting edema were excluded only for the analyses of pin prick, light touch, and vibration. Numeric differences in the following tables are due to missing dependent variables or covariate data. The exclusions and missing covariate data are summarized in Table 11-1. The unadjusted analyses used chi-square or Fisher's exact test for frequency table analyses. Adjusted analyses were not performed where only sparse numbers of abnormalities were found. Logistic regression models were used in all adjusted analyses. Parallel analyses using Original Comparisons can be found in Appendix I, Tables I-3 through I-13.

RESULTS AND DISCUSSION

General

Detailed neurological data were obtained on all participants by standard physical examination techniques. Four board-certified SCRF neurologists, all

TABLE 11-1.

Exclusions and Missing Data for Neurological Assessment by Group

Data Category	Group		Total
	Ranch Hand	Comparison	
Lifetime Alcohol History (Drink-Years); Missing Data	39	40	79
Peripheral Edema (Exclusion Category for Pin Prick, Light Touch, and Ankle Vibration)	13	16	29
Diabetic Class (Missing Data)	0	4	4
Positive Syphilis Serology (RPR and FTA) Exclusion Category	0	1	1

blinded to the exposure status of the participants, conducted the examinations. Data were collected to assess three specific clinical areas: cranial nerve function, peripheral nerve function, and central nervous system (CNS) function. The analyses in this chapter are presented in the order of these functional areas.

The unadjusted statistical analyses presented in this chapter are straightforward group contrasts of dichotomous (normal/abnormal) dependent variables using Fisher's exact test. Logistic regression models for adjusted analyses used the covariates of age (born in or after 1942, born between 1923 and 1941, born in or before 1922), race (Black, nonblack), occupation (OCC) (officer, enlisted flyer, enlisted groundcrew), diabetic class (DIAB) (normal, less than 140 mg/dl glucose; impaired, at least 140 mg/dl but less than 200 mg/dl glucose; diabetic, greater than or equal to 200 mg/dl glucose or past diabetic history), lifetime alcohol use (DRKYR) (total drink-years: 0, greater than 0 to 50, greater than 50), and unprotected exposure to insecticides (INS) (recorded as yes/no, excluding herbicide exposure). The models are "best-fit" following a step-down strategy beginning with all two-way interactions among the six covariates. Only variables with a substantial number of abnormalities were analyzed. Several summary indices were constructed for functionally related variables with low counts of abnormalities. A summary index was created for the cranial nerve function by combining the 15 cranial nerve parameters into a single index, which was classified as normal if all parameters were normal. Another cranial nerve function was created in a similar fashion, excluding neck range of motion due to the much higher percentage of abnormalities found for this variable relative to the other parameters. The four coordination parameters of the central nervous

system were similarly combined to form a summary index. These constructed indices are presented more for the purpose of inspection than for inference making. Since the corneal reflex (as one measure of the trigeminal nerve function) contained no abnormalities for either group, no table is presented with this variable.

The statistical power to detect a given relative risk in many of the subsequent analyses was somewhat limited. With the use of a two-sided α-level of 0.05 and power of 0.80, the sample sizes were sufficient to detect a 49 percent increase in the frequency of abnormal values for neck range of motion, a 69 percent increase for light touch but only a doubling for tremor, and an elevenfold increase for gag reflex. Power was generally poor in these analyses because of the extremely small number of abnormalities observed in both the Ranch Hand and Comparison groups.

Questionnaire Data

For the interval questionnaire, each participant was asked to update his health history for neurologic conditions occurring between 1982 and 1985. All affirmative histories were subjected to medical record verification, and appropriate ICD-9-CM coding. All verified neurological diseases were placed into six broad disease categories. These data are summarized in Table 11-2.

TABLE 11-2.

Unadjusted Analysis for Verified Neurological Disease by Group*--1982-1985

	Group Abnormalities					
	Ranch Hand		Comparison			
Disease Category	Number	Percent	Number	Percent	Total	p-Value**
Inflammatory Diseases	0	0.0	0	0.0	0	--
Hereditary and Degenerative Diseases	2	0.2	0	0.0	2	0.194
Peripheral Disorders	18	1.8	27	2.1	45	0.651
Disorders of the Eye	5	0.5	7	0.5	12	0.999
Disorders of the Ear	6	0.6	7	0.5	13	0.999
Other Disorders	8	0.8	3	0.2	11	0.069

*Based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may be classified in more than one category.

**Fisher's exact test.

All of these analyses were based on very small numbers of abnormalities, but none of the six general disease categories showed statistically significant differences between groups, although the marginal significance of the Other Disorders category is of interest.

To determine whether lifetime differences in neurologic disease exist between the Ranch Hand and Comparison groups, verified followup data were combined with verified Baseline historical data. This tabulation is presented in Table 11-3.

TABLE 11-3.

Unadjusted Analysis for Verified Neurological Disease by Group*--Baseline and First Followup Studies Combined

	Group Abnormalities					
	Ranch Hands		Comparisons			
Disease Category	Number	Percent	Number	Percent	Total	p-Value**
Inflammatory Diseases	3	0.3	2	0.2	5	0.660
Hereditary and Degenerative Diseases	2	0.2	3	0.2	5	0.999
Peripheral Disorders	23	2.3	38	2.9	61	0.361
Disorders of the Eye	16	1.6	23	1.8	39	0.747
Disorders of the Ear	24	2.4	29	2.2	53	0.889
Other Disorders	15	1.5	14	1.1	29	0.453

*Based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may be classified in more than one category.

**Fisher's exact test.

Like the followup data, the combined data revealed no statistically significant differences in any disease category. Also, there was no significant difference in patterns of disease for each group (p=0.721).

Physical Examination Data

Dependent Variable and Covariate Relationships: Cranial Nerve Function, Peripheral Nerve Status, and Central Nervous System Coordination

Responses from both groups were combined and analyzed with the six covariates. In addition, current drinking (yes/no) and lifetime history of

unprotected exposure to industrial and degreasing chemicals (yes/no) were also evaluated. Indices constructed from dependent variables from the cranial nerve function and central nervous system coordination processes were also included. A summary tabulation of covariate associations is shown in Table 11-4. The 10 variables in this table include variables from the peripheral nerve status and CNS process as well as the cranial nerve function and constitute the subset of variables for which adjusted analyses were performed.

These results generally showed the profound association of classical risk factors for neurological deficits. Increases in the percentages of abnormalities for Achilles reflex, muscle status, neck range of motion, and the cranial nerve function index (which included neck range of motion) were associated with increases in age. Increasing percentages of abnormalities for pin prick and light touch were noted for increasing age from the young category (3.4% and 2.7% for pin prick and light touch, respectively) to the middle-aged category (8.1% and 4.7%, respectively), but a declining proportion of abnormalities was observed from the middle- to older-age categories (7.3% and 1.2%, respectively). No age effect was noted for gait, the CNS index, the cranial nerve index (neck range of motion excluded), and, surprisingly, for tremor.

Race was not a significant covariate for any dependent variable. A significant occupational effect was observed for the CNS summary index ($p=0.021$, with both enlisted categories having a higher frequency of abnormalities [5.7% and 4.1% for enlisted flyers and enlisted groundcrew, respectively] than the officer category [2.6%]) and for the neck range of motion variable ($p=0.010$, with increasing proportions of abnormalities from the enlisted groundcrew [4.6%] to officers [7.5%] to enlisted flyers[8.0%]).

Abnormalities in the Achilles tendon reflex were related to a graduated increase in drink-years of alcohol. For the variables of pin prick, light touch, muscle status, neck range of motion, and cranial nerve index (with neck range of motion included), the 0 drink-year category was related to a higher frequency of abnormalities than the greater than 0 to 50 drink-year category, which in turn was associated with a lower frequency of abnormalities than the greater than 50 drink-year category. For the current drinker (which was not used for modeling), the percentage of abnormalities for Achilles reflex and gait was significantly greater ($p=0.007$ and $p=0.001$ for Achilles reflex and gait, respectively) for current nondrinkers than for current drinkers. This relationship was reversed for the CNS summary index.

For both the Achilles tendon reflex and the response to pin prick, the frequencies of abnormalities significantly increased from the diabetic classes of normal to impaired to diabetic ($p<0.001$ for both variables). For the variables of light touch, muscle status, gait, and CNS summary index, the associations with diabetic status were mixed: The normal diabetic class had a higher proportion of abnormalities than the impaired stratum which, in turn, had a lower proportion of abnormalities than the overtly diabetic class. Unexpectedly, the proportion of tremor abnormalities was highest for the normal diabetic class and became successively lower in the impaired and diabetic strata (2.48%, 0.45%, and 0%, respectively).

A higher proportion of pin prick abnormalities was associated with a history of unprotected exposure to insecticides ($p=0.040$; 6.94% for exposed versus 4.8% for unexposed). The other dependent variables were not

TABLE 11-4.

Association Between Seven Neurological Variables and
Three Summary Indices and the Covariates in the Combined Ranch Hand and Comparison Groups

Dependent Variable	Covariate						Exposure		
	Age	Race	Occupation	Total Drink-years	Current Drinking*	Diabetic Class	Insecticides	Industrial Chemicals*	Degreasing Chemicals*
Achilles Reflex	<0.001	NS	NS	0.022	0.007	<0.001	NS	0.050	NS
Pin Prick	<0.001	NS	NS	0.004	NS	<0.001	0.040	NS	NS
Light Touch	0.027	NS	NS	0.006	NS	0.026	NS**	NS	NS
Muscle Status	<0.001	NS	NS	0.001	NS**	<0.001	NS	0.025	NS**
Gait	NS	NS	NS	NS	0.001	0.033	NS	NS	NS
CNS Index	NS	NS	0.021	NS	0.012	0.016	NS	NS	NS
Tremor	NS	NS	NS	NS	NS	0.011	NS	NS	NS
Neck Range of Motion	<0.001	NS	0.010	0.014	NS	NS**	NS	0.039	NS
Cranial Nerve Function Index	<0.001	NS	NS**	0.032	NS	NS	NS	NS**	NS
Cranial Nerve Function Index (Neck Range of Motion Excluded)	NS	NS	NS	NS**	NS	NS	NS	NS	NS

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

* Variable not used in adjusted analyses.

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

significantly affected by the insecticide covariate. For most dependent variables, both Ranch Hands and Comparisons exposed to degreasing or industrial chemicals exhibited a smaller percentage of abnormalities than participants without exposure. Because the biologic basis of these findings is not readily apparent, these two variables were not used as adjusting covariates.

Cranial Nerve Function

All 12 cranial nerves were assessed as unilateral or bilateral; these unadjusted data are presented in Table 11-5. All bilateral assessments (e.g., right visual field, left visual field) were combined for the analyses; an abnormality consisted of a right and/or a left abnormality.

The analysis of the 12 variables and two cranial nerve function summary indices did not reveal statistically significant group differences. Since no abnormalities are present for the variables of speech and tongue position in the Comparison group, the estimated relative risk for these variables was approximated by adding 0.5 to each cell. The low frequency of abnormal counts in all variables, except neck range of motion, contrasts with the 1982 Baseline findings, which found substantially more abnormalities. For example, ocular movement was recorded as abnormal in more than 30 percent of the participants at Baseline while only 0.7 percent of participants were found to be abnormal at followup.

Because of the few abnormalities for all variables except neck range of motion, two summary indices of cranial nerve function were constructed. One indicated whether or not a participant is abnormal for any of the 15 variables, while the other was a composite for all except neck range of motion. The analyses of these indices are reflected in Table 11-5, and showed no statistically significant group differences, although the index excluding neck range of motion is of borderline significance. Speech and tongue position relative to midline were also of borderline significance, although the analysis was affected by sparse numbers of abnormalities. The constructed indices are presented more for the purpose of inspection than for inference making.

Because of sparse numbers of abnormalities, adjusted analyses were performed only on the variable neck range of motion and the cranial nerve function summary indices, with and without neck range of motion data. The results of these analyses are given in Table 11-6.

None of the results were statistically significant, although the cranial nerve function index, without neck range of motion, was marginally significant ($p=0.061$) when participants with missing drink-years were included. In the primary adjusted analysis for this variable, drink-years was included in a significant covariate interaction. However, an alternative model was also examined that included participants with missing drink-years due to the disparity in group response for these participants (4 out of 39 Ranch Hands abnormal, 0 out of 40 Comparisons abnormal). The results of these adjusted analyses are nearly identical to the unadjusted analyses (see Table 11-5). A borderline significant result of a group (GRP)-by-age interaction ($p=0.0501$) for neck range of motion existed, and an additional analysis stratifying by age is provided in Table 11-7. This table presents the results of interaction analyses from variables assessing the peripheral nerve status and central nervous system coordination process as well.

TABLE 11-5.

Unadjusted Analyses for Cranial Nerve Function by Group

Variable	Cranial Nerve	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Smell	I Olfactory	n	1,016		1,292			
		Abnormal	10	1.0	10	0.8	1.27 (0.53,3.07)	0.654
		Normal	1,006	99.0	1,282	99.2		
Visual Fields	II Optic	n	1,016		1,292			
		Abnormal	6	0.6	6	0.5	1.27 (0.41,3.96)	0.774
		Normal	1,010	99.4	1,286	99.5		
Light Reaction	III Oculomotor	n	1,015		1,289			
		Abnormal	8	0.8	9	0.7	1.13 (0.43,2.94)	0.811
		Normal	1,007	99.2	1,280	99.3		
Ocular Movements	III Oculomotor, IV Trochlear, VI Abducens	n	1,016		1,292			
		Abnormal	6	0.6	10	0.8	0.76 (0.28,2.10)	0.801
		Normal	1,010	99.4	1,282	99.2		
Facial Sensation	V Trigeminal	n	1,014		1,290			
		Abnormal	4	0.4	2	0.2	2.55 (0.47,13.95)	0.415
		Normal	1,010	99.6	1,288	99.8		
Jaw Clench	V Trigeminal	n	1,016		1,292			
		Abnormal	2	0.2	2	0.2	1.27 (0.18,9.05)	0.999
		Normal	1,014	99.8	1,290	99.8		
Smile	VII Facial	n	1,016		1,292			
		Abnormal	7	0.7	4	0.3	2.23 (0.67,7.41)	0.230
		Normal	1,009	99.3	1,288	99.7		
Palpebral Fissures	VII Facial	n	1,015		1,292			
		Abnormal	7	0.7	7	0.5	1.28 (0.45,3.65)	0.789
		Normal	1,008	99.3	1,285	99.5		
Balance	VIII Acoustic	n	1,015		1,292			
		Abnormal	2	0.2	1	0.1	2.55 (0.23,28.15)	0.586
		Normal	1,013	99.8	1,291	99.9		

TABLE 11-5. (continued)

Unadjusted Analyses for Cranial Nerve Function by Group

Variable	Cranial Nerve	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Gag Reflex	IX Glosso-pharyngeal	n	1,014		1,291			
		Abnormal	1	0.1	1	0.1	1.27 (0.08,20.38)	0.999
		Normal	1,013	99.9	1,290	99.9		
Speech	X Vagus	n	1,016		1,291			
		Abnormal	3	0.3	0	0.0	8.92 (0.46,172.89)[a]	0.085
		Normal	1,013	99.7	1,291	100.0		
Tongue Position Relative to Midline	X Vagus	n	1,015		1,292			
		Abnormal	3	0.3	0	0.0	8.94 (0.46,173.19)[a]	0.085
		Normal	1,012	99.7	1,292	100.0		
Palate and Uvula Movement	XI Spinal Accessory	n	1,014		1,291			
		Abnormal	2	0.2	1	0.1	2.55 (0.23,28.16)	0.586
		Normal	1,012	99.8	1,290	99.9		
Neck Range of Motion	XII Hypoglossal	n	1,016		1,292			
		Abnormal	61	6.0	84	6.5	0.92 (0.65,1.29)	0.666
		Normal	955	94.0	1,208	93.5		
Cranial Nerve Function Index		n	1,003		1,275			
		Abnormal	96	9.6	115	9.0	1.07 (0.80,1.42)	0.663
		Normal	907	90.4	1,160	91.0		
Cranial Nerve Function Index (Neck Range of Motion Excluded)		n	1,003		1,275			
		Abnormal	42	4.2	35	2.7	1.55 (0.98,2.44)	0.062
		Normal	961	95.8	1,240	97.3		

[a]Estimated relative risk and 95% confidence interval calculated after adding 0.5 to each cell.

TABLE 11-6.

Adjusted Analyses for Selected Variables of Cranial Nerve Function by Group

Variable	Statistic	Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk(95% C.I.)	p-Value	Covariate Remarks*
Neck Range of Motion	n	1,016		1,292		0.90 (0.63,1.27)	0.531	AGE(p<0.001)
	Abnormal	61	6.0	84	6.5			GRP*AGE
	Normal	955	94.0	1,208	93.5			(marginal:p=0.0501)
Cranial Nerve Function Index	n	1,003		1,275		1.07 (0.80,1.42)	0.666	AGE(p<0.001)
	Abnormal	96	9.6	115	9.0			
	Normal	907	90.4	1,160	91.0			
Cranial Nerve Function Index (Neck Range of Motion Excluded)	n	964		1,232		1.42 (0.88,2.30)	0.153	DIAB*INS(p=0.022)
	Abnormal	38	3.9	34	2.8			OCC*DRKYR(p=0.011)
	Normal	926	96.1	1,198	97.2			OCC*DIAB(p=0.015)
	Alternative Model—Includes Missing Drink-Year Participants[a,b]							
	n	1,003		1,271		1.56 (0.98,2.49)	0.061	DIAB*INS(p=0.017)
	Abnormal	42	4.2	34	2.7			OCC*DIAB(p=0.016)
	Normal	961	95.8	1,237	97.3			

*Abbreviations:

GRP: group
DIAB: diabetic class
INS: insecticide exposure
OCC: occupation
DRKYR: drink-years

[a]Lifetime alcohol consumption (total drink-years) not used as a covariate.

[b]79 missing drink-year participants: 4/39 Ranch Hands abnormal; 0/40 Comparisons abnormal.

TABLE 11-7.

Summary Table of Group-by-Covariate Interactions for Neurological Variables

Variable	Interaction	Stratification	Statistic	Group: Ranch Hands Number	Ranch Hands Percent	Group: Comparisons Number	Comparisons Percent	Adj. Relative Risk (95% C.I.)	p-Value
Neck Range of Motion	Group-by-Age	Born ≥ 1942	n	412		549		3.03 (1.02,9.00)	0.045
			Abnormal	10	2.4	5	0.9		
			Normal	402	97.6	544	99.1		
		Born 1923-1941	n	568		693		0.82 (0.55,1.21)	0.319
			Abnormal	47	8.3	70	10.1		
			Normal	521	91.7	623	89.9		
		Born ≤ 1922	n	36		50		(0.55 (0.16,1.97)	0.361
			Abnormal	4	11.1	9	18.0		
			Normal	32	88.9	41	82.0		
Pin Prick	Group-by-Diabetic Class	Abnormal	n	76		94		1.74 (0.71,4.24)	0.223
			Abnormal	13	17.1	10	10.6		
			Normal	63	82.9	84	89.4		
		Impaired	n	105		174		0.09 (0.01,0.69)	0.021
			Abnormal	1	1.0	16	9.2		
			Normal	104	99.0	158	90.8		
		Normal	n	822		1,005		1.02 (0.68,1.54)	0.920
			Abnormal	45	5.5	53	5.3		
			Normal	777	94.5	952	94.7		
Tremor	Group-by-Insecticides Exposure	Exposed to Insecticides	n	703		683		2.60 (1.15,5.90)	0.022
			Abnormal	22	3.1	8	1.2		
			Normal	681	96.9	675	98.8		
		Not Exposed to Insecticide	n	313		605		0.69 (0.22,2.19)	0.532
			Abnormal	4	1.3	11	1.8		
			Normal	309	98.7	594	98.2		

The stratified analysis for neck range of motion showed a higher proportion of younger Ranch Hands with neck range of motion abnormalities than younger Comparisons (p=0.045). Although not statistically significant, middle-aged and older Comparisons had higher proportions of abnormalities than did the Ranch Hands.

Peripheral Nerve Status

Peripheral nerve integrity was assessed by light pin prick, light touch (cotton sticks), visual inspection (and palpation, if indicated) of muscle mass, vibratory sensation as measured at the ankle with a tuning fork of 128 Hz, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. The unadjusted analyses are given in Table 11-8. As noted previously, the analyses of pin prick, light touch, and vibratory sensation excluded the 29 participants with peripheral edema. These results showed that peripheral nerve function did not vary significantly by group.

Adjusted analyses were performed by logistic regression on four peripheral nerve variables. The other variables had relatively sparse numbers of abnormalities. The covariates were age, race, occupation, drink-years of alcohol, diabetic class, and exposure to insecticides. These statistics are displayed in Table 11-9.

For the variables light touch, muscle status, and the Achilles reflex, group differences were nonsignificant; the results were nearly identical to the unadjusted analyses. For the variable pin prick, however, a significant group-by-diabetic class interaction (p=0.003) was observed. This interaction was explored and the results are depicted in Table 11-7. As shown, the interaction suggests a difference, due to a lower proportion of abnormal pin-prick results in Ranch Hand impaired diabetics than in Comparisons (Adj. RR: 0.09,95% C.I.: [0.01,0.69], p=0.021), whereas both the abnormal and normal diabetic classes showed no significant group differences.

Central Nervous System Coordination

CNS coordination was evaluated clinically with four variables: hand tremor, rapid finger-to-nose coordination, one-foot standing balance (modified Romberg sign), and observation of gait for at least 10 steps. In addition, a constructed variable, the CNS summary index, was derived by summarizing abnormalities from all four CNS variables. The unadjusted analyses of these five variables are shown in Table 11-10.

These results revealed no statistically significant group differences for the four primary CNS variables, although the borderline significance of tremor, with a higher proportion of abnormalities in the Ranch Hands, is interesting. The statistical power to detect a given relative risk was poor because of the small percentages of abnormalities. The CNS summary index was statistically significant, with Ranch Hands manifesting a higher proportion of abnormalities; this result should be interpreted with caution, however, since this index was constructed after the data were examined. Three of the five variables with sufficient proportions of abnormalities were adjusted by six covariates, and these results are summarized in Table 11-11.

TABLE 11-8.

Unadjusted Analyses for Peripheral Nerve Function by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Group: Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Pin Prick	n	1,003		1,276			
	Abnormal	59	5.9	80	6.3	0.93 (0.66,1.32)	0.725
	Normal	944	94.1	1,196	93.7		
Light Touch	n	1,003		1,276			
	Abnormal	38	3.8	47	3.7	1.03 (0.67,1.59)	0.912
	Normal	965	96.2	1,229	96.3		
Muscle Status	n	1,016		1,292			
	Abnormal	26	2.6	33	2.6	1.00 (0.60,1.69)	0.999
	Normal	990	97.4	1,259	97.4		
Vibratory Sensation	n	1,003		1,276			
	Abnormal	11	1.1	10	0.8	1.40 (0.59,3.32)	0.510
	Normal	992	98.9	1,266	99.2		
Patellar Reflex	n	1,016		1,290			
	Abnormal	11	1.1	16	1.2	0.87 (0.40,1.89)	0.846
	Normal	1,005	98.9	1,274	98.8		
Achilles Reflex	n	1,009		1,284			
	Abnormal	58	5.7	75	5.8	0.98 (0.69,1.40)	0.999
	Normal	951	94.3	1,209	94.2		
Biceps Reflex	n	1,016		1,292			
	Abnormal	9	0.9	10	0.8	1.15 (0.46,2.83)	0.819
	Normal	1,007	99.1	1,282	99.2		
Babinski Reflex	n	1,011		1,287			
	Abnormal	4	0.4	5	0.4	1.02 (0.27,3.80)	0.999
	Normal	1,007	99.6	1,282	99.6		

TABLE 11-9.

Adjusted Analyses for Selected Variables of Peripheral Nerve Function by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Group: Comparison Number	Comparison Percent	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Pin Prick	n	1,003		1,273		****	****	GRP*DIAB(p=0.003)
	Abnormal	59	5.9	79	6.2			AGE(p<0.001)
	Normal	944	94.1	1,194	93.8			
Light Touch	n	964		1,236		1.02 (0.65,1.60)	0.921	OCC*RACE(p=0.013)
	Abnormal	37	3.8	46	3.7			AGE(p=0.043)
	Normal	927	96.2	1,190	96.3			DRKYR(p=0.031)
Muscle Status	n	977		1,248		1.00 (0.57,1.75)	0.999	DRKYR*AGE(p=0.009)
	Abnormal	25	2.6	31	2.5			DIAB*INS(p=0.039)
	Normal	952	97.4	1,217	97.5			
Achilles Reflex	n	971		1,240		1.00 (0.69,1.45)	0.999	DRKYR*OCC(p=0.016)
	Abnormal	56	5.8	71	5.7			AGE(p<0.001)
	Normal	915	94.2	1,169	94.3			DIAB(p<0.001)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value are not presented.

TABLE 11-10.

Unadjusted Analyses for CNS Coordination Variables by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Group: Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Tremor	n	1,016		1,292			
	Abnormal	26	2.6	19	1.5	1.76 (0.97,3.20)	0.069
	Normal	990	97.4	1,273	98.5		
Coordination	n	1,015		1,292			
	Abnormal	9	0.9	7	0.5	1.64 (0.61,4.43)	0.327
	Normal	1,006	99.1	1,285	99.5		
Romberg Sign	n	1,015		1,292			
	Abnormal	2	0.2	1	0.1	2.55 (0.23,28.15)	0.586
	Normal	1,013	99.8	1,291	99.9		
Gait	n	1,016		1,290			
	Abnormal	20	2.0	16	1.2	1.60 (0.82,3.10)	0.178
	Normal	996	98.0	1,274	98.8		
CNS Summary Index	n	1,015		1,290			
	Abnormal	48	4.7	39	3.0	1.59 (1.04,2.45)	0.036
	Normal	967	95.3	1,251	97.0		

TABLE 11-11.

Adjusted Analyses for Selected Variables of CNS Coordination by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Tremor	n	1,016		1,288				GRP*INS
	Abnormal	26	2.6	19	1.5	1.70 (0.93,3.09)	0.080	(marginal:p=0.055)
	Normal	990	97.4	1,269	98.5			DIAB(p=0.001)
Gait	n	977		1,246				DIAB(p=0.030)
	Abnormal	20	2.0	15	1.2	1.74 (0.88,3.47)	0.110	DRKYR*INS(p=0.047)
	Normal	957	98.0	1,231	98.8			
CNS	n	1,015		1,286				DIAB(p=0.003)
Summary	Abnormal	48	4.7	38	3.0	1.57 (1.01,2.43)	0.042	OCC(p=0.018)
Index	Normal	967	95.3	1,248	97.0			

These statistics were quite similar to the unadjusted tests, and showed borderline significance for tremor, nonsignificance for gait, and significance for the CNS summary index. The unexpected inverse relationship of tremor abnormalities to diabetic classification is again noted. The borderline group-by-insecticide interaction was investigated, and the results are given in Table 11-7. As shown, the relative risk for Ranch Hands exposed to insecticides was statistically significant (RR: 2.60, 95% C.I.: [1.15,2.90], p=0.022), whereas the relative risk for unexposed Ranch Hands was nonsignificant. This finding may have both an operational and biologic foundation, because records indicate that some Ranch Hands were exposed to the insecticide Malathion®, a cholinesterase inhibitor, during insecticide missions for malaria prevention. Comparisons, by definition, did not fly these missions.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupation cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). All 27 variables and three summary indices were explored (unadjusted for any covariates) as with the unadjusted tests for group differences discussed previously in this chapter. These variables were investigated using Pearson's chi-square test and Fisher's exact

test. Adjusted analyses were performed by logistic regression for the 10 variables (7 neurological parameters and 3 summary indices) for which adjusted analyses of group differences were previously examined. These analyses were accomplished, adjusted for age, diabetic class, insecticide exposure, and drink-years (all discretized), and any significant pairwise interactions between the exposure index and these covariates. Race was not included in adjusted analyses because of the absence of any race effect in the previous group difference analyses. Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts in the proportion of abnormalities between the medium and low exposure levels, and between the high and low exposure levels. Exclusions were made as described previously.

Results of the adjusted analysis are presented in Table 11-12, and results for unadjusted analyses appear in Table I-1 of Appendix I. Results from further study of exposure index-by-covariate interactions are given in Table I-2 of Appendix I.

Unadjusted analyses revealed borderline significant differences among exposure index levels for pin prick in enlisted groundcrew ($p=0.052$) and Achilles reflex in enlisted flyers ($p=0.059$). The data did not support an increase in the proportion of abnormalities with increasing exposure levels, however.

Adjusted analyses yielded similar conclusions, in that significant or borderline significant results did not support an increase in the proportion of abnormalities with increasing exposure, and that very few significant results were observed. The pattern of abnormalities with the 10 variables was studied, and in no occupational strata was an increasing dose-response relationship evident. In fact, the high exposure level often had a smaller (although nonsignificant) proportion of abnormalities than the low and medium levels.

Interactions were present for 5 of the 10 variables, and occurred primarily in the enlisted groundcrew stratum. A summary of these interactions is presented in Table 11-13.

Meaningful interpretation of the interactions was difficult, due to the small numbers of abnormalities within a covariate strata. No significant adverse effects to participants with higher exposure levels were evident, however, in this analysis.

In summary, no evidence of an increasing dose-response relationship at the followup examination was observed. No increase in prevalence rates was seen as exposure levels increased. These results essentially were in agreement with the findings of the Baseline Study.

TABLE 11-12.

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	127	120	Overall		0.906
					M vs. L	0.82 (0.31,2.18)	0.686
					H vs. L	0.97 (0.37,2.56)	0.955
Neck Range of Motion	Enlisted Flyer	51	61	53	Overall		0.940
					M vs. L	0.79 (0.20,3.20)	0.744
					H vs. L	0.83 (0.21,3.31)	0.786
	Enlisted Groundcrew	148	160	132	Overall		0.299
					M vs. L	0.93 (0.27,3.21)	0.908
					H vs. L	0.36 (0.09,1.51)	0.163
	Officer	120	127	119	Overall		0.551
					M vs. L	0.63 (0.28,1.44)	0.277
					H vs. L	0.78 (0.35,1.78)	0.560
Cranial Nerve Function Index	Enlisted Flyer	51	60	53	Overall		0.808
					M vs. L	1.00 (0.29,3.43)	0.999
					H vs. L	0.68 (0.18,2.59)	0.569
	Enlisted Groundcrew	145	158	131	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Cranial Nerve Function (Neck Range of Motion Excluded)	Officer	120	127	119	Overall		0.148
					M vs. L	0.30 (0.08,1.22)	0.093
					H vs. L	0.36 (0.09,1.45)	0.150
	Enlisted Flyer	51	60	53	Overall		0.860
					M vs. L	1.04 (0.13,8.27)	0.969
					H vs. L	0.56 (0.05,6.58)	0.642
	Enlisted Groundcrew	145	158	131	Overall		0.894
					M vs. L	0.75 (0.23,2.45)	0.639
					H vs. L	0.84 (0.25,2.76)	0.773
Pin Prick	Officer	124	124	119	Overall		0.277
					M vs. L	0.43 (0.13,1.38)	0.156
					H vs. L	0.49 (0.17,1.43)	0.191
	Enlisted Flyer	51	60	53	Overall		0.399
					M vs. L	0.33 (0.05,2.35)	0.267
					H vs. L	1.02 (0.23,4.60)	0.979
	Enlisted Groundcrew	146	159	128	Overall		0.108
					M vs. L	0.86 (0.32,2.34)	0.765
					H vs. L	0.28 (0.07,1.07)	0.062

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index Low Total	Medium Total	High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	124	124	119	Overall		0.047
					M vs. L	0.39 (0.11,1.40)	0.148
					H vs. L	0.20 (0.05,0.83)	0.027
Light Touch	Enlisted Flyer	51	60	53	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)
	Enlisted Groundcrew	146	159	128	Overall		0.777
					M vs. L	1.27 (0.34,4.80)	0.725
					H vs. L	0.74 (0.16,3.35)	0.699
	Officer	125	127	120	Overall		0.105
					M vs. L	0.15 (0.02,1.01)	0.051
					H vs. L	0.57 (0.14,2.30)	0.433
Muscle Status	Enlisted Flyer	51	61	53	Overall		0.979
					M vs. L	0.90 (0.04,22.10)	0.946
					H vs. L	0.74 (0.04,14.77)	0.841
	Enlisted Groundcrew	148	160	132	Overall		****(3)
					M vs. L	****(3)	****(3)
					H vs. L	****(3)	****(3)

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	122	126	120	Overall		0.384
					M vs. L	0.43 (0.13,1.46)	0.175
					H vs. L	0.65 (0.21,1.99)	0.448
Achilles Reflex	Enlisted Flyer	51	60	53	Overall		0.021
					M vs. L	--	--
					H vs. L	0.65 (0.16,2.76)	0.564
	Enlisted Groundcrew	147	160	132	Overall		****(3)
					M vs. L	****(3)	****(3)
					H vs. L	****(3)	****(3)
	Officer	125	127	120	Overall		0.219
					M vs. L	0.19 (0.02,1.66)	0.132
					H vs. L	0.63 (0.14,2.89)	0.548
Tremor	Enlisted Flyer	51	61	53	Overall		0.625
					M vs. L	2.11 (0.19,23.39)	0.542
					H vs. L	2.95 (0.29,30.43)	0.364
	Enlisted Groundcrew	148	160	132	Overall		0.396
					M vs. L	0.91 (0.22,3.66)	0.889
					H vs. L	0.28 (0.03,2.44)	0.248

TABLE 11-12. (continued)

Adjusted Exposure Index Analyses for Neurological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	127	120	Overall		0.483
					M vs. L	0.26 (0.02,3.25)	0.298
					H vs. L	0.89 (0.12,6.76)	0.912
Gait	Enlisted Flyer	51	61	53	Overall		0.188
					M vs. L	0.64 (0.07,6.05)	0.693
					H vs. L	--	--
	Enlisted Groundcrew	148	160	132	Overall		0.576
					M vs. L	0.42 (0.07,2.51)	0.343
					H vs. L	0.88 (0.19,3.99)	0.868
	Officer	125	127	120	Overall		0.123
					M vs. L	0.22 (0.04,1.10)	0.066
					H vs. L	0.57 (0.15,2.10)	0.399
CNS Summary Index	Enlisted Flyer	51	60	53	Overall		0.930
					M vs. L	1.21 (0.25,5.92)	0.818
					H vs. L	0.90 (0.17,4.80)	0.899
	Enlisted Groundcrew	148	160	132	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)

--No abnormal participants present in medium exposure index level for Achilles reflex (or high level for gait) in enlisted flyers.

****(1)Exposure index-by-diabetic class interaction--relative risk and p-value not presented.

****(2)Exposure index-by-insecticide exposure interaction--relative risk, confidence interval, and p-value not presented.

****(3)Exposure index-by-age interaction--relative risk, confidence interval, and p-value not presented.

TABLE 11-13.

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

Variable	Occupation	Covariate	p-Value
CNF Summary Index	Enlisted Groundcrew	Diabetic Class	0.045
Light Touch	Enlisted Flyer	Insecticide Exposure	0.026
Muscle Status	Enlisted Groundcrew	Age	0.026
Achilles Reflex	Enlisted Groundcrew	Age	0.014
CNS Summary Index	Enlisted Groundcrew	Insecticide Exposure	0.010

LONGITUDINAL ANALYSES

Two variables, the modified Romberg sign and the Babinski reflex, were investigated to assess longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables were classified as abnormal or normal. As shown in Table 11-14, 2x2 tables were constructed for each group for each variable. This table shows the number of participants who were abnormal at the Baseline examination and abnormal at the followup examination, abnormal at Baseline and normal at the followup, normal at Baseline and abnormal at the followup, and normal at both Baseline and the followup. The odds ratio is the ratio of the number of participants who were normal at Baseline and abnormal at the followup to the number of participants who were abnormal at Baseline and normal at the followup (the "off-diagonal" elements). The p-value was derived from Pearson's chi-square test of the hypothesis that there was comparable change in the two groups over time.

These data showed no longitudinal difference in the change pattern in the Romberg sign in the two groups, but they did show a significant change in the Babinski reflex. In the Baseline examination, the Ranch Hands had a significantly greater proportion of reflex abnormalities than the Comparisons, but the followup examination showed approximately the same percentage of abnormality in both groups (Est. RR: 1.02, 95% C.I.: [0.27,3.80, p=0.999]).

SUMMARY AND CONCLUSIONS

Interval questionnaire data (1982 through 1985) on neurological illnesses, verified by medical records, revealed no significant group differences. These data were added to verified Baseline historical information to assess possible differences in the lifetime experience of neurological disease. Again, there was no significant difference between the Ranch Hand and Comparison groups.

TABLE 11-14.

Longitudinal Analysis of Romberg Sign and Babinski Reflex:
A Contrast of Baseline and First Followup Examination Abnormalities

Variable	Group	1982 Baseline Exam	1985 Followup Exam: Abnormal	1985 Followup Exam: Normal	Odds Ratio (OR)*	p-Value (OR_{RH} vs. OR_c)
Romberg Sign	Ranch Hand	Abnormal	2	188	0	0.38
		Normal	0	777		
	Comparison	Abnormal	0	250	0.004	
		Normal	1	886		
Babinski Reflex	Ranch Hand	Abnormal	1	7	0.43	0.04
		Normal	3	953		
	Comparison	Abnormal	0	1	5.00	
		Normal	5	1,129		

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

A detailed neurological examination evaluated neurological integrity in three broad areas: cranial nerve function, peripheral nerve function, and central nervous system (CNS) coordination. The summary analytic results for all measurement variables comprising these three functional areas are presented in Table 11-15.

Assessment of the 12 cranial nerves was based on the measurement of 14 variables. Two summary indices were constructed. Both the unadjusted and adjusted analyses did not disclose any statistically significant group differences, although two variables, speech and tongue position, were of borderline significance, with Ranch Hands faring worse than Comparisons. One of the two cranial nerve summary indices was marginally significant, again with the Ranch Hands at a slight detriment.

The unadjusted and adjusted analyses of peripheral nerve function, as measured by eight variables (four reflexes, three sensory determinations, and muscle mass), did not reveal significant group differences.

CNS coordination was evaluated by four measurements and a constructed summary variable. Hand tremor was found to be of borderline significance, with the Ranch Hands faring slightly worse than the Comparisons. The CNS summary index showed a significant detriment to the Ranch Hands.

The exposure analyses for neurological variables with reasonable counts of abnormalities showed only occasional statistically significant results. No consistent pattern with increasing exposure was evident for any occupational category of the Ranch Hand group.

TABLE 11-15.

Overall Summary Results of Unadjusted and Adjusted Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results**
Questionnaire[a] Physical Examination			
Neurological Disease (Interval)	NS[b]	--	
Neurological Disease (History)	NS	--	
Cranial Nerve Function			
Smell	NS	--	
Visual Fields	NS	--	
Light Reaction	NS	--	
Ocular Movements	NS	--	
Facial Sensation	NS	--	
Corneal Reflex	--[c]	--[c]	
Jaw Clench	NS	--	
Smile	NS	--	
Palpebral Fissures	NS	--	
Balance	NS	--	
Gag Reflex	NS	--	
Speech	NS*	--	RH>C
Tongue Position Relative to Midline	NS*	--	RH>C
Palate and Uvula Movement	NS	--	
Neck Range of Motion	NS	NS	
Cranial Nerve Function Index[d]	NS	NS	
Cranial Nerve Function Index[d] (excluding Neck Range of Motion)	NS*	NS*	RH>C
Peripheral Nerve Function			
Pin Prick	NS	****	
Light Touch	NS	NS	
Muscle Status	NS	NS	
Vibratory Sensation	NS	--	
Patellar Reflex	NS	--	
Achilles Reflex	NS	NS	
Biceps Reflex	NS	--	
Babinski Reflex	NS	--	

TABLE 11-15. (continued)

Overall Summary Results of Unadjusted and Adjusted Analyses of Neurological Variables

Variable	Unadjusted	Adjusted	Direction of Results**
Central Nervous System Coordination			
Tremor	NS*	NS*	RH>C
Coordination	NS	--	
Romberg Sign	NS	--	
Gait	NS	NS	
CNS Summary Index[d]	0.036	0.042	RH>C

**RH>C: More abnormalities in Ranch Hand group than in Comparison group.

[a]Disease categories include: inflammatory diseases, heriditary and degenerative diseases, peripheral disorders, disorders of the eye, disorders of the ear, and other disorders.

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

[b]No inflammatory diseases noted; borderline significant ($p=0.069$, RH>C) for other disorders; not significant for remaining categories.

--Analysis not performed because of sparse number of abnormalities.

[c]No abnormalities present.

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

[d]Constructed variable.

****Group-by-covariate interaction.

In a longitudinal analysis of the Romberg sign and the Babinski reflex, only the Babinski reflex revealed a significant difference between the Baseline and followup examination, with the Ranch Hands converting from significant adverse findings at Baseline to favorable nonsignificant findings at the followup examination.

Overall, the followup examination findings are quite similar to the Baseline findings. However, several distinct patterns were evident from the analyses: (1) The followup examination detected substantially fewer abnormalities for almost all measurement variables, (2) the decrease in abnormalities was equivalent in both groups, (3) most of the covariate effects were classical, although exceptions were evident, (4) the adjusted analyses were uniformly similar to the unadjusted analyses, (5) the constructed summary variables were generally statistically significant, or of borderline significance (however some indices were created after the data were examined), and (6) although statistical significance at the pre-assigned α -level of 0.05 was not achieved for any of the measurement variables, abnormalities tended to cluster in the Ranch Hand group.

Of the three group-by-covariate interactions in the adjusted analyses, only one, a borderline group-by-insecticide exposure interaction for hand tremor, where Ranch Hands exposed to insecticides had a marginally significant adverse effect, was of probable biologic (and operational) significance.

In conclusion, none of the 27 neurological variables demonstrated a significant group difference, although several showed an aggregation of abnormalities in the Ranch Hand group, which merits continued surveillance. Historical reporting of neurologic disease was equal in both groups. The clinical sensitivity in detecting neurological deficits varied substantially between the Baseline and the followup examinations, but the number of statistically significant variables remained about the same. None of the exposure analyses revealed dose-response patterns in the Ranch Hand occupational categories. The longitudinal analyses disclosed a favorable reversal of significant Babinski reflex abnormalities at Baseline to nonsignificant findings at the followup examination for the Ranch Hands. The similarity in results between unadjusted and adjusted statistical tests is evidence of group equality for the traditionally important neurological covariates of age, alcohol, and diabetes. Of three group-by-covariate interactions in the adjusted analyses, only the Ranch Hand insecticide interaction with hand tremor was biologically plausible.

CHAPTER 11

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CHAPTER 12

PSYCHOLOGICAL ASSESSMENT

INTRODUCTION

Emotional illnesses or psychological abnormalities are not 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 (see Chapter 11). Higher 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.

Animal studies provide little insight into possible human psychological problems. Animal signs of lethargy, stupor, poor coordination, lack of feeding, and agitation have been observed in multiple studies involving many species. These signs have generally been attributed to the "wasting syndrome" or multi-organ toxicity, rather than primary CNS toxicity.[1] A study of "behavioral" effects in rats following single and weekly doses of 2,4-D showed that the central effects of decreased coordination and lever-pressing behavior were transient and reversible.[2] Further, no latent CNS impairment was detected after a d-amphetamine challenge.

Human studies and case reports have occasionally noted psychological disorders or symptom complexes following exposure to herbicides and TCDD. Complaints included headache, anxiety, malaise, depression, abnormal anger, mood changes, sleep disturbances, decreased libido, and impotence. Scientific confirmation of these symptoms by psychological testing is difficult and exclusion of other plausible causes such as age, preexisting psychological abnormalities, or even motivation for compensation is often impossible. Most studies have merely recorded complaints and have not pursued their validation by indepth functional testing.

Early studies of industrial chemical workers first provided the suggestion of psychological effects. Followup studies from the Nitro, West Virginia, accident in 1949, showed "nervousness," fatigue, irritability, cold intolerance, and decreased libido in many of the workers with chloracne, but most of these symptoms subsided over a 4-year period.[3,4] Two followup studies in 1979, by different investigators of expanded (but slightly different) plant cohorts, noted reports of sexual dysfunction and decreased libido.[5,6] One of these studies noted that these observations (and insomnia) were significantly increased in individuals with chloracne.[5] Neither of these followup efforts conducted neurobehavioral tests to validate the reported symptoms.

Other industrially based studies reported symptoms of fatigue,[7-13] decreased libido,[7] impotence,[8] sleep disturbances,[8,11-13] reduced emotional responses,[8] sensory deficits of smell, taste, and hearing,[9] reading

difficulties,[9] memory loss,[11] and emotional disorders.[12,13] Symptoms of depression and anxiety have been associated with disfiguring chloracne. One study found a relationship between chloracne and hypomania as determined from the MMPI,[14] and another noted that two of three chemists involved in the synthesis of TCDD developed marked personality changes.[15] Although data interpretation problems exist, the Czechoslovakian 10-year followup study cited eight cases of severe dementia in exposed workers and reported that symptoms of anxiety and depression decreased over the followup period.[13]

A contemporary cross-sectional morbidity study of a mobile-home park, environmentally contaminated with dioxin, showed subclinical hepatic, hematologic, immunologic, and psychological changes in exposed residents.[16] Significant abnormalities were recorded in the exposed group for the tension/anxiety and anger/hostility scales of the profile of mood states (POMS) inventory, as well as the vocabulary subtest of the Wechsler adult intelligence scale (WAIS). However, functional testing by the Halstead-Reitan battery (HRB) did not reveal significant group differences. There was no way to differentiate between the primary effects of exposure and the secondary effects of media attention.

In contrast to industrial cohorts, the study of chemically related psychological problems in veterans has proved more difficult because of the confounding effects of combat stress and the post-traumatic stress disorder (PTSD), and the uncertainty of exposure. Of almost 100,000 Vietnam veterans registered in the VA's Agent Orange Registry in 1983, 18 percent complained of "nervousness" and 10 percent cited personality disorders.[17] A psychiatric review of 132 veterans included in the Registry, most of whom had been referred for treatment, disclosed a symptom hierarchy of sleep disorders (53%), mood depression (36%), suicidal thoughts (35%), and irritability (31%).[18] Fifty-three percent of these veterans received the PTSD diagnosis.

In 1980, the American Psychiatric Association established the term "post-traumatic stress disorder" to define a neurosis caused by extreme psychic trauma, e.g., natural disaster, war, imprisonment, or torture.[19] PTSD comprises the symptoms of anxiety, "powder keg" anger, depression, irritability, restlessness, recurrent intrusive dreams, flashbacks, and sleeplessness. Quiescent PTSD may be acutely reactivated in some individuals by specific triggering events (e.g., visiting the Vietnam Memorial).[20] The disorder is equally applicable to civilians following emotionally traumatic experiences. The onset of PTSD may immediately follow the traumatic event or it may occur years afterward. The older war terms shell shock, combat fatigue, and anxiety reaction generally referred to the more immediate symptoms following the trauma although components of PTSD are now recognized in veterans of earlier wars.

The prevalence of PTSD in Vietnam veterans is unknown, and even the qualitative assessments of "common" or "rare" are debatable.[21,22] A 7-month incidence of legal and emotional maladjustments in returning Vietnam veterans occurred at the rate of 23 percent and did not differ significantly from comparable rates in nonveterans.[23] Though a concise definition of PTSD exists, there is controversy as to the best means of diagnosis. Some workers prefer a full and thorough clinical interview[21] while others favor empiric symptom scales.[24] Clearly, each method serves a different, but highly related, purpose: clinical diagnosis in individuals versus an epidemiological/statistical diagnosis in groups.

Risk factors for the development of PTSD may include emotional predisposition, social/ethnic background, parental factors, race, and combat intensity ranging from slight involvement to atrocity behavior.[21,25,26] Parallel conditions to PTSD (or perhaps unrecognized components of PTSD) encompass alcoholism, drug abuse, lawlessness (arrests/felony convictions), personality disorders, and frank psychosis.[21,25-27] This chapter attempts to isolate any psychological disorders attributable to herbicide exposure.

Baseline Summary Results

Extensive psychological parameters were assessed on all participants during the 1982 Baseline questionnaire and physical examination. The expected high degree of concordance between education (college, high school) and military status (officer, enlisted) was observed and validated the sole use of education as a covariate representing socioeconomic status for most analyses.

There were no questionnaire differences for past history of emotional or psychological illnesses between the Ranch Hand and Comparison groups. For the psychological indices of fatigue, anger, erosion, anxiety, and severity of depression (as determined by a modification of the Diagnostic Interview Schedule[28]), no group differences were detected among the college-educated Ranch Hands. However, for the high school-educated stratum, Ranch Hands demonstrated highly significant pathology for fatigue, anger, erosion, and anxiety. An unadjusted analysis of reported depression showed significantly more depression in the Ranch Hands, as did the isolation index adjusted for educational level. Exposure index analyses from the Ranch Hand questionnaire data did not suggest a relationship between exposure and psychological abnormality.

At the time of the physical examination, additional self-reported data were collected with the Cornell Index and the MMPI. The CNS functional testing was conducted by a modified HRB, and intelligence was measured by the WAIS.

The Cornell Index showed a significant increase in psychophysiologic symptoms in the high school-educated Ranch Hands. Six of 10 parameters of the Cornell Index were abnormal in the Ranch Hands (e.g., fear, startle, psychosomatic) as contrasted to the Original Comparisons, and all abnormal responses/parameters were inversely related to education to a statistically significant degree. MMPI results in the high school-educated participants showed differences in the scales of denial, hypochondria, masculinity/femininity, and mania/hypomania as contrasted to the college-educated group. Only the social introversion scale was significant in the college-educated participants. The effect of education was influential ($p<0.01$) in all scales of the MMPI. Race was not a significant covariate. All self-reported data, including those from the in-home questionnaire, were not adjusted for possible group differences in PTSD or combat experience/intensity.

Performance testing by the HRB showed no neuropsychiatric impairment in the Ranch Hands as contrasted to their overall self-administered MMPI and Cornell Index. In fact, Ranch Hand over-reporting was suggested in several parameters, but was not proved. The effect of education on the Halstead-Reitan testing was profound ($p<0.0001$). WAIS intelligence scores revealed very close group similarities in the full-scale and verbal and performance

scales. As expected, the intelligence quotient (IQ) of college graduates was significantly higher than the IQ of high-school graduates. Exposure index analyses of the HRB and WAIS data were negative and disclosed no patterns that suggested an herbicide effect.

Parameters of the 1985 Psychological Assessment

Two of the psychological tests (MMPI, HRB) conducted at the 1982 Baseline examination were repeated at the first followup examination in 1985. Repetitive testing was accomplished for purposes of clinical validation, establishment of comparable longitudinal parameters, and comparable covariate adjustments by concurrently derived PTSD and combat experience indices.

Questions from the Diagnostic Interview Schedule were deleted from the followup questionnaire and were replaced by questions on combat experience in Vietnam. An updated history of mental and emotional disorders was obtained on all participants. A PTSD indicator was derived from a new MMPI subscale[24] and was used for covariate adjustments of non-MMPI psychological data. The WAIS IQ assessment was deleted, but all parameters of the MMPI and HRB were retained. The Cornell Medical Index (CMI)[29] was substituted for the Cornell Index in the 1985 psychological assessment.

The dependent variables and covariates of the followup examination are similar to those analyzed at the Baseline. Longitudinal analyses of the MMPI scales of denial and depression consider the change of psychological test indices between groups.

All statistical analyses are based on 1,016 Ranch Hands and 1,293 Comparisons. No individuals were excluded from the analysis of the psychological data for medical reasons. Sample size differences in the tables below reflect missing data from scale or battery test results, or from relevant covariates. The statistical tests use log-linear models, logistic regression models, Kolmogorov-Smirnov nonparametric tests, Fisher's exact test, and Pearson's chi-square test. Parallel analyses using Original Comparisons are in Tables J-8 through J-18 of Appendix J.

RESULTS AND DISCUSSION

Questionnaire Data

At the followup interview, each participant was asked whether he had ever had a mental or emotional disorder. Whenever possible, the conditions were coded using ICD-9-CM. Reported disorders for which treatment was obtained were subsequently verified by reviews of medical records. Table 12-1 contains a tabulation of the distribution of these psychological illnesses, with information from the Baseline and followup studies combined.

None of the types of illness categories showed statistically significant differences between groups; however, the "other neuroses" category is significant ($p=0.037$), with the Ranch Hands showing more adverse effects, when only Original Comparisons are used (see Table J-8 of Appendix J).

TABLE 12-1.

Unadjusted Analyses for Reported Psychological Illnesses by Group: Baseline and First Followup Studies Combined*

	Group Abnormalities					
	Ranch Hand		Comparison			
Type of Illness	Number	Percent	Number	Percent	Total	p-Value**
Psychoses	14	1.4	9	0.7	23	0.138
Alcohol Dependence	9	0.9	8	0.6	17	0.473
Anxiety	7	0.7	13	1.0	20	0.501
Other Neuroses	72	7.1	74	5.7	146	0.197

*Analyses based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may have had more than one illness.

**Fisher's exact test.

Psychological Examination Data

The MMPI is a self-administered test consisting of 566 questions on various aspects of behavior and personality. The results of the MMPI are numerical scores for 14 scales. The scales are anxiety (psychasthenia), consistency (F-scale), defensiveness (L-scale), denial (K-scale), depression, hypochondria, hysteria, mania/hypomania, masculinity/femininity, paranoia, psychopathic/deviate, schizophrenia, social introversion, and validity. The normal range of scores from 30 to 70 was used to categorize the results as normal or abnormal for all scales except validity. For validity (the number of unanswered questions) categories of 0 or greater than 0 were used. The test was administered to all 2,309 participants. A participant was considered nonresponsive in the MMPI if more than 30 questions (approximately 5%) were unanswered. Due to nonresponse, data on six participants, (two Ranch Hands and four Comparisons) were omitted from the analysis of all variables except validity. Thus, the MMPI analyses were based on 1,014 Ranch Hands and 1,289 Comparisons.

The CMI is a self-administered instrument used to collect a substantial amount of medical and psychiatric data. The 195 questions of the CMI are partitioned into 18 sections (A to R) with the number of questions within a section ranging from 6 to 23. The analysis of the CMI was based on three scores: the total CMI score, an M-R subscore, and an A-H area subscore. The total CMI score is the number of affirmative responses on the entire questionnaire and is analyzed as a continuous variable. The M-R subscore, which deals with mood and feeling patterns, is a useful indicator of

emotional ill-health. This subscore is the total number of affirmative responses to the 51 questions in sections M-R and is trichotomized as 0, 1 to 10, or greater than 10 for the analysis. The A-H area subscore is a measure of the scatter of complaints, indicating a diffuse medical problem, although other interpretations are possible. An abnormal A-H area subscore is defined as the number of sections (of A-H) with three or more affirmative responses. The A-H area subscore, which ranges from 0 to 8, is trichotomized as 0, 1 to 3, or 4 to 8 for the analysis.

Consistent with the 5 percent nonresponse exclusion used for the MMPI, analysis of the total CMI score is based on scores with at least a 95 percent response rate or no more than 10 unanswered items from the total 195. M-R subscores are deleted from the analyses if three or more questions were unanswered from the 51 questions. For the A-H area subscore, participants who failed to answer all items were excluded from the analyses. Using these response criteria, analyses of the total CMI score are based on the scores of 1,000 Ranch Hands (16 deleted) and 1,268 Comparisons (25 deleted); the M-R subscore analyses use the results of 998 Ranch Hands (18 deleted) and 1,267 Comparisons (26 deleted); and the A-H area subscore analyses use 914 Ranch Hands (102 deleted) and 1,148 Comparisons (145 deleted).

The HRB is a neuropsychological test that was administered to all participants to assess the functional integrity of the CNS. The battery consists of seven subtests: category (abstract recognition and analysis), total-time tactile performance, memory tactile performance, localization tactile performance, rhythm, speech, and finger tapping. In addition, other tests were performed (e.g., trailmaking, tests of recent memory) but do not contribute to the impairment index. For each participant who completed all seven subtests, an impairment index, equal to the number of subtests in which the participant scored abnormally, is computed. This variable is dichotomized as normal (impairment index <3) or abnormal (impairment index ≥ 3). Twenty participants (10 in each group) refused or did not complete one or more of the seven subtests. Thus, the analyses of the HRB impairment index are based on data from 1,006 Ranch Hands and 1,283 Comparisons. Fisher's exact test was used to contrast the number of excluded participants between groups. A significant difference was not observed ($p=0.654$).

The analyses of the psychological variables were adjusted for age (born in 1942 or after, born between 1923 and 1941, born in 1922 or before), race (Black, nonblack), education (high school, college), and drink-years (0, greater than 0 to 50, greater than 50). Education was dichotomized into high school and college categories, for purposes of analysis, from the classifications of (1) no high school diploma, (2) high school diploma, (3) attended college, and (4) college diploma. This variable was based on Baseline education levels, and participants with incomplete information were classified as high school educated. In addition, the analyses of the MMPI scales were adjusted for the combat index, a surrogate measure for PTSD. This index was constructed from 15 self-administered questions on combat experiences (see Appendix C, page C-15, AFHS Form 8). Associations of these 15 variables with PTSD, as measured from a subset of the MMPI questions, were examined, and responses to four questions showed statistically significant or marginally significant associations with PTSD. The four questions were (1) flew in aircraft that received battle damage, (2) had a close friend killed in action, (3) encountered mines or booby traps, and (4) wounded. An index, equal to the number of affirmative responses to these four questions, was computed and used as a trichotomized covariate (low, [0; n=708 (30.7%)],

medium [1; n=814 (35.4%)], high [2-4; n= 781 (33.9%)], 6 missing participants, as with MMPI scales) for the analyses of the MMPI scales. While this index was associated with PTSD, it does not necessarily measure stress but does measure combat experience.

The analyses of the CMI and HRB tests were adjusted for PTSD, based on the number of affirmative responses to a subset of 49 questions of the MMPI. For these analyses, PTSD was dichotomized as yes/no using greater than 30 affirmative responses[23] as a positive indicator of PTSD. Sixteen participants (10 Ranch Hands, 6 Comparisons) were classified as having PTSD under this guideline. (Note that this indicator of PTSD was not used as a covariate for the analyses of MMPI scales, because the variable was based on the responses used in the calculation of the MMPI scores.)

Current alcohol use (yes/no) and occupation were examined as potential covariates and are provided in the summary tables for inspection. Current alcohol use was highly correlated with drink-years, which better explained the dependent variables under study. Similarly, occupation was highly correlated with education ($p<0.001$). In this case, education was selected.

Statistical Analysis

Minnesota Multiphasic Personality Inventory (MMPI)

The distributions of the Ranch Hand and Comparison groups for the 14 MMPI variables were contrasted using the Kolmogorov-Smirnov nonparametric tests and stratified by occupation (officer, enlisted flyer, enlisted groundcrew), for a total of 42 tests. Unadjusted analyses were performed using Fisher's exact test. Covariate analyses, using Fisher's exact or Pearson's chi-square test, were conducted for age, race, education, drink-years, combat index, current alcohol use, and occupation. Logistic regression techniques were used to conduct the adjusted analyses. In the adjusted analyses, all covariates were used as discrete variables with the exception of age, which was used as a continuous variable. Current alcohol use and occupation were not used in the adjusted analysis. Using a two-sided α-level of 0.05, and with power of 0.80, the sample sizes are sufficient to detect a 38 percent increase in the rate of abnormal scores for depression, a 61 percent increase in the rate of abnormal scores for denial, and a 119 percent increase in the rate of abnormal scores for social introversion.

Distributional Analyses

The Kolmogorov-Smirnov tests identified no statistically significant differences between the Ranch Hand and Comparison distributions for the 14 MMPI variables at the 0.05 significance level for each occupational category. Only 2 of the 42 tests even approached significance, mania/hypomania (Ranch Hand and Comparison officers, $p=0.092$) and psychopathic/deviate (Ranch Hand and Comparison enlisted flyers, $p=0.088$). Results of the Kolmogorov-Smirnov tests are provided in Tables J-1 to J-3 of Appendix J. It is noted that stratification by occupation reduced the sample size for each test and consequently decreased the power; that is, a larger maximum difference between the Ranch Hand and Comparison distributions is needed to show significance when the sample size is decreased, as is the case when stratification by occupation is performed.

Unadjusted and Adjusted Analyses

The unadjusted results, covariate tests of association, and adjusted results of the analyses for the 14 MMPI variables are summarized in Tables 12-2 to 12-4, respectively. Summary tables, which investigate interactions involving group, are provided in Table J-4 of Appendix J. The results of the tests of association for current alcohol use and occupation are presented in Table 12-3 for inspection, but are not discussed in the text since the measure of total drink-years was more appropriate for use in the analyses.

Anxiety

The unadjusted analysis showed no statistically significant difference in the anxiety scale between the Ranch Hands and the Comparisons ($p=0.311$).

The tests of association with the covariates, using the pooled group categorical data, revealed statistically significant effects for age ($p=0.010$) and education ($p<0.001$). For age, 8.4 percent of the participants born in or after 1942 were scored as abnormal, as were 5.3 percent of those born from 1923 to 1941, and 4.6 percent of those born in or before 1922. The high school subgroup had a higher percentage (8.5%) of abnormalities than the college subgroup (4.4%). For the test of association, drink-years was marginally significant ($p=0.058$), based on the percent of abnormalities for 0, greater than 0 to 50, and greater than 50 drink-years: 10.0 percent, 5.9 percent, and 8.2 percent, respectively.

In the adjusted analysis, there was no statistically significant difference between groups ($p=0.512$). In this analysis, education (EDUC) showed a statistically significant effect ($p<0.001$). The interaction, age-by-combat-index (CI), was also statistically significant ($p=0.008$). A group-(GRP)-by-education interaction was marginally significant ($p=0.057$). Further investigation of this interaction revealed an adjusted relative risk of 1.39 for the high school stratum and 0.68 for the college stratum. However, these relative risks were not significantly different from 1.00 ($p=0.114$, $p=0.233$, respectively). The exploration of this interaction is shown in Table J-4 of Appendix J.

Consistency

The unadjusted test of the MMPI consistency scale revealed no statistically significant difference between the Ranch Hand and Comparison groups ($p=0.222$).

Based on the tests of association, education was statistically significant ($p=0.010$) with 3.9 percent abnormalities in the high school category and 2.0 percent abnormalities in the college category. In addition, the test of association with drink-years was statistically significant ($p=0.021$); the categories 0 and greater than 0 to 50 drink-years each had a percent abnormal frequency of 2.7, whereas there were 5.6 percent abnormalities in the greater than 50 drink-years category.

In the adjusted analysis of the consistency scale, a group-by-education interaction was statistically significant ($p=0.013$). Further analysis of the interaction (shown in Table J-4 of Appendix J) revealed that the high school

TABLE 12-2.

Unadjusted Analyses for MMPI by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Anxiety	n	1,014		1,289			
	Abnormal	73	7.2	79	6.1	1.19 (0.86,1.65)	0.311
	Normal	941	92.8	1,210	93.9		
Consistency	n	1,014		1,289			
	Abnormal	36	3.6	34	2.6	1.36 (0.84,2.19)	0.222
	Normal	978	96.4	1,255	97.4		
Defensiveness	n	1,014		1,289			
	Abnormal	23	2.3	35	2.7	0.83 (0.49,1.42)	0.592
	Normal	991	97.7	1,254	97.3		
Denial	n	1,014		1,289			
	Abnormal	17	1.7	58	4.5	0.36 (0.21,0.63)	<0.001
	Normal	997	98.3	1,231	95.5		
Depression	n	1,014		1,289			
	Abnormal	114	11.2	126	9.8	1.17 (0.89,1.53)	0.272
	Normal	900	88.8	1,163	90.2		
Hypochondria	n	1,014		1,289			
	Abnormal	119	11.7	129	10.0	1.20 (0.92,1.56)	0.198
	Normal	895	88.3	1,160	90.0		
Hysteria	n	1,014		1,289			
	Abnormal	123	12.1	125	9.7	1.29 (0.99,1.67)	0.067
	Normal	891	87.9	1,164	90.3		

TABLE 12-2. (continued)

Unadjusted Analyses for MMPI by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Mania/Hypomania	n	1,014		1,289			
	Abnormal	63	6.2	88	6.8	0.90 (0.65,1.26)	0.611
	Normal	951	93.8	1,201	93.2		
Masculinity/ Femininity	n	1,014		1,289			
	Abnormal	66	6.5	120	9.3	0.68 (0.50,0.93)	0.017
	Normal	948	93.5	1,169	90.7		
Paranoia	n	1,014		1,289			
	Abnormal	31	3.1	28	2.2	1.42 (0.85,2.38)	0.187
	Normal	983	96.9	1,261	97.8		
Psychopathic/ Deviate	n	1,014		1,289			
	Abnormal	120	11.8	149	11.6	1.03 (0.80,1.33)	0.845
	Normal	894	88.2	1,140	88.4		
Schizophrenia	n	1,014		1,289			
	Abnormal	94	9.3	101	7.8	1.20 (0.90,1.61)	0.228
	Normal	920	90.7	1,188	92.2		
Social Introversion	n	1,014		1,289			
	Abnormal	26	2.6	19	1.5	1.76 (0.97,3.20)	0.069
	Normal	988	97.4	1,270	98.5		
Validity	n	1,016		1,293			
	>0	224	22.0	271	21.0	1.07 (0.87,1.30)	0.540
	0	792	78.0	1,022	79.0		

TABLE 12-3.

Association Between MMPI Variables and the Covariates in the Combined Ranch Hand and Comparison Groups

MMPI Scale	Age	Race	Education	Drink-Years	Combat Index	Current** Alcohol Use	Occupation**
Anxiety	0.010	NS	<0.001	NS*	NS	0.001	<0.001
Consistency	NS	NS	0.010	0.021	NS	NS	<0.001
Defensiveness	0.028	0.025	<0.001	<0.001	NS*	0.001	<0.001
Denial	0.037	NS	NS	NS	NS	NS	NS
Depression	NS	NS	<0.001	0.002	NS	NS	<0.001
Hypochondria	0.031	0.025	<0.001	0.041	0.027	0.044	<0.001
Hysteria	0.044	NS	<0.001	0.006	NS	0.027	<0.001
Mania/Hypomania	NS	NS	NS	0.011	0.001	NS	0.022
Masculinity/ Femininity	0.005	NS	<0.001	NS	NS	NS	0.005
Paranoia	0.022	NS	NS	NS	NS	NS*	0.014
Psychopathic/ Deviate	NS	0.001	0.001	<0.001	NS	NS*	<0.001
Schizophrenia	NS	NS	<0.001	0.014	NS	NS*	<0.001
Social Introversion	0.003	NS	NS*	NS	NS	NS*	<0.001
Validity	NS	<0.001	NS	NS	NS*	NS	NS

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

*Borderline significant ($0.05<p\leq0.10$).

**Not used in adjusted analyses.

TABLE 12-4.

Adjusted Analyses for MMPI by Group

Variable	Group: Ranch Hand Total	Group: Comparison Total	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Anxiety	1,012	1,285	1.12 (0.80,1.57)	0.512	EDUC (p<0.001) AGE*CI (p=0.008) GRP*EDUC (marginal: p=0.057)
Consistency	974	1,246	****	****	AGE (p=0.007) DRKYR (p=0.026) CI (p=0.041) GRP*EDUC (p=0.013)
Defensiveness	976	1,250	0.77 (0.45,1.33)	0.347	EDUC (p<0.001) DRKYR (p<0.001)
Denial	1,012	1,285	0.37 (0.21,0.66)	<0.001	EDUC*CI (p=0.044)
Depression	974	1,246	1.10 (0.84,1.45)	0.497	EDUC (p<0.001) DRKYR (p=0.013) GRP*CI (marginal: p=0.055)
Hypochondria	1,012	1,285	1.12 (0.85,1.47)	0.431	AGE (p=0.002) RACE (p=0.026) EDUC (p<0.001) CI (p=0.043)
Hysteria	1,014	1,289	1.27 (0.97,1.66)	0.077	AGE (p=0.003) EDUC (p<0.001)
Mania/Hypomania	974	1,246	0.80 (0.56,1.13)	0.203	DRKYR (p=0.006) AGE*CI (p=0.046)

TABLE 12-4. (continued)

Adjusted Analyses for MMPI by Group

Variable	Group: Ranch Hand Total	Group: Comparison Total	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Masculinity/ Femininity	1,014	1,289	0.69 (0.50,0.95)	0.020	EDUC (p<0.001) RACE*AGE (p=0.008)
Paranoia	1,012	1,285	****	****	AGE*CI (p=0.003) GRP*AGE (p=0.036)
Psychopathic/ Deviate	974	1,246	1.04 (0.79,1.36)	0.780	EDUC (p=0.011) AGE*CI (p=0.003) RACE*DRKYR (p=0.015)
Schizophrenia	976	1,250	****	****	RACE*DRKYR (p=0.017) GRP*EDUC (p=0.010)
Social Introversion	1,012	1,285	****	****	AGE (p=0.004) GRP*CI (p=0.037)
Validity	1,014	1,289	****	****	AGE*CI (p=0.030) GRP*RACE (p=0.012)

*Abbreviations:

EDUC: education
CI: combat index
GRP: group
DRKYR: drink-years of alcohol

****Group-by-covariate interaction -- adjusted relative risk, confidence interval, and p-value are not presented.

Ranch Hand category had a marginally significantly higher percentage of abnormal participants (5.6%) than the high school Comparisons (2.9%) ($p=0.051$). The adjusted relative risk for the high school classification was 1.81 with 95 percent confidence bounds of 1.00 and 3.28. In contrast, the percentage of abnormalities in the Comparison college-educated stratum was higher than the corresponding Ranch Hand subgroup (2.6 percent, 1.4 percent, respectively), but the difference was not statistically significant ($p=0.110$). Age, drink-years (DRKYR), and combat index were also statistically significant ($p=0.007$, $p=0.026$, $p=0.041$, respectively) in the adjusted analyses.

Defensiveness

For the MMPI defensiveness scale, there was no significant difference between groups, based on the unadjusted analysis ($p=0.592$).

The tests of association showed statistically significant differences for all variables except combat index, which was marginally different statistically. The percentage of abnormalities for the age categories (born in or after 1942, born between 1923 and 1941, and born in or before 1922) were 3.3, 1.8, and 4.6, respectively ($p=0.028$). There were 2.3 percent abnormalities for nonblacks as compared to 5.6 percent for Blacks ($p=0.025$). The percent abnormalities for the high school- and college-educated categories were 3.8 and 1.0, respectively ($p<0.001$). For the 0 drink-years category, there were 10.0 percent abnormalities; the percent abnormalities for the greater than 0 to 50 and greater than 50 drink-years were 2.4 and 0.6, respectively ($p<0.001$). For combat index, which was only marginally statistically significant ($p=0.093$), the percent abnormalities were 3.5 for the low, 2.1 for the medium, and 1.9 for the high categorizations.

In the adjusted analysis, there was no significant difference between the Ranch Hand and Comparison groups ($p=0.347$). In this analysis, the covariates of education ($p<0.001$) and drink-years ($p<0.001$) were statistically significant.

Denial

Based on the unadjusted analysis, there was a statistically significant difference between the two groups on the MMPI denial scale ($p<0.001$), with 4.5 percent abnormalities in the Comparison group as contrasted to only 1.7 percent in the Ranch Hand group. The estimated relative risk was 0.36 with a 95 percent confidence interval of 0.21 to 0.63.

The tests of association found only age as a statistically significant covariate ($p=0.037$). Men born in or after 1942 and those born between 1923 and 1941 had 3.0 percent and 3.1 percent abnormalities, respectively, as compared to 8.0 percent abnormalities for those born in or before 1922.

The adjusted analysis showed a statistically significant difference between groups ($p<0.001$). The adjusted relative risk estimate was 0.37 with 95 percent confidence bounds of 0.21 and 0.66. For this analysis, the education-by-combat index interaction was also statistically significant ($p=0.044$).

Depression

The unadjusted analysis of the depression scale revealed no statistically significant difference between the two groups ($p=0.272$).

In the covariate tests of association, education and drink-years showed statistically significant effects ($p<0.001$, $p=0.002$, respectively). There was a higher percentage of abnormalities in the high school-educated category (13.1%) than in the college-educated category (7.2%). For drink-years, the highest rate of abnormality was in the highest category of alcohol use (15.8%), followed by the nondrinker with 10.7 percent abnormalities and the moderate category with 9.4 percent.

In the adjusted analysis, there was no statistically significant difference between groups ($p=0.497$), but there was a marginally significant group-by-combat index interaction ($p=0.055$). This interaction was explored further and is shown in Table J-4 of Appendix J. The analysis of the group-by-combat index interaction revealed a marginal difference within the low (0) category of the combat index ($p=0.055$), but not within the medium and high categories. In contrasting the 192 Ranch Hands and the 490 Comparisons in the 0 category, there were 14.6 percent abnormalities in the Ranch Hand group versus 8.2 percent in the Comparisons ($p=0.039$). The adjusted relative risk for the 0 category of the combat index was 1.73 with a 95 percent confidence interval of 1.03 to 2.91. Education ($p<0.001$) and drink-years ($p=0.013$) also exhibited statistically significant effects in the adjusted analysis.

Hypochondria

There was no statistically significant difference for the MMPI hypochondria scale between the Ranch Hand and Comparison groups ($p=0.198$).

In the covariate tests of association, all five variables were statistically significant. Of men born in or after 1942, 8.8 percent had abnormalities as compared to 12.2 percent and 12.6 percent of those born between 1923 and 1941 and in or before 1922, respectively ($p=0.031$). The rates of abnormalities for Blacks and nonblacks were 16.8 percent and 10.4 percent, respectively ($p=0.025$). There was a highly statistically significant difference for education ($p<0.001$) with the high school-educated category having 13.9 percent abnormalities and the college-educated category having 7.0 percent. There was also a statistically significant difference for drink-years ($p=0.041$). The lowest rate of abnormalities was in the greater than 0 to 50 drink-years category with 9.9 percent; the corresponding percentages for the 0 drink-year and greater than 50 drink-year categories were 12.7 and 14.3, respectively. The percent abnormalities in the low, medium, and high combat index categories were 9.8, 9.4, and 13.2, respectively ($p=0.027$).

The adjusted analysis showed no significant difference between the Ranch Hand and Comparison groups ($p=0.431$). In this analysis, age ($p=0.002$), race ($p=0.026$), education ($p<0.001$), and combat index ($p=0.043$) were statistically significant covariates.

Hysteria

Based on the unadjusted analysis of the MMPI hysteria scale, the difference between the two groups approached statistical significance ($p=0.067$). The percent abnormalities were 12.1 and 9.7 for the Ranch Hand and Comparison groups, respectively. The estimated relative risk was 1.29 with a 95 percent confidence interval of 0.99 to 1.67.

The covariate tests of association showed that there were statistically significant differences for age ($p=0.044$), education ($p<0.001$), and drink-years ($p=0.006$). There were 12.6 percent, 12.1 percent, and 8.9 percent abnormalities in the age categories born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. The high school-educated category had a higher percentage of abnormalities (12.9%) than the college-educated category (8.2%). The drink-years category with the lowest percentage of abnormalities was greater than 0 to 50 with 9.6 percent; the 0 drink-years and the greater than 50 drink-years categories had 14.0 and 14.9 percent abnormalities, respectively.

The adjusted analysis also approached significance ($p=0.077$). The adjusted relative risk was 1.27 with 95 percent confidence bounds of 0.97 and 1.66. Age and education were statistically significant covariates in the adjusted model ($p=0.003$, $p<0.001$, respectively). Drink-years was marginally significant ($p=0.068$) in the presence of other covariates, but was not included in the final adjusted model.

Mania/Hypomania

For the unadjusted analysis of the mania/hypomania scale of the MMPI, there was no statistical difference between the Ranch Hand and the Comparison groups ($p=0.611$).

In the covariate tests of association, there were statistically significant differences for drink-years and combat index ($p=0.011$, and $p=0.001$, respectively). For the mania/hypomania scale, the 0 drink-years category had 6.7 percent abnormalities, the greater than 0 to 50 drink-years category had 5.8 percent, and the greater than 50 drink-years category contained 10.2 percent. The frequencies of abnormalities increased from the low to the high level of the combat index; the percentages were 5.0, 5.3, and 9.4, respectively.

Based on the adjusted analysis, there was no statistically significant difference between the two groups ($p=0.203$). Drink-years was a significant covariate ($p=0.006$), as was the age-by-combat index interaction ($p=0.046$).

Masculinity/Femininity

The masculinity/femininity scale of the MMPI measures the stereotype "macho" attitudes of the test subjects. There was a statistically significant group difference for this scale of the MMPI, unadjusted for covariates ($p=0.017$). There was a higher percentage of abnormalities in the Comparison group (9.3%) than in the Ranch Hand group (6.5%). The estimated relative risk was 0.68, and the 95 percent confidence interval was 0.50 to 0.93.

There was a statistically significant difference detected for age ($p=0.005$) and for education ($p<0.001$), based on the pooled group data in the covariate tests of association. The highest rate of abnormalities was found in men born in or after 1942 (10.2%); whereas those born between 1923 and 1941 had 6.4 percent, and those born in or before 1922 had 8.0 percent. For education, the college-educated category showed an abnormal rate of 10.3 percent versus the high school category with 6.2 percent abnormalities.

The adjusted analysis also showed a statistically significant difference between the two groups ($p=0.020$), with an adjusted relative risk of 0.69 (95% C.I.: [0.50,0.95]). Education and a race-by-age interaction were statistically significant ($p<0.001$, $p=0.008$, respectively). These covariate associations follow expectations.

Paranoia

The unadjusted analysis of the MMPI paranoia scale did not reveal a statistically significant group difference ($p=0.187$).

Based on the pooled group data, the covariate test of association for age was statistically significant ($p=0.022$). There was 3.6 percent abnormalities for men born in or after 1942, 2.0 percent for those born between 1923 and 1941, and no abnormalities for men born in or before 1922. The adjusted analysis revealed a significant group-by-age interaction ($p=0.036$). The age-by-combat index interaction was also statistically significant ($p=0.003$). The group interaction was examined by combining the participants born between 1923 and 1941 with those born in or before 1922, and basing the test on two age categories (born in or after 1942 and born before 1942), due to problems with 0 counts (see Table J-4 of Appendix J). The analysis showed a higher percentage of abnormal Ranch Hands than abnormal Comparisons for participants born before 1942 (2.7% and 1.2%, respectively; $p=0.027$). The relative risk estimate for this age category was 2.63 (95% C.I.: [1.11,6.20]). In contrast, for the stratum born in or after 1942, the frequencies of abnormalities were nearly the same in each group (3.7% for Ranch Hands, 3.5% for Comparisons; $p=0.712$).

Psychopathic/Deviate

No significant difference between the two groups was identified in the unadjusted analysis of this MMPI scale ($p=0.845$).

In the covariate tests of association, there were statistically significant differences for race, education, and drink-years. There were 21.0 percent abnormalities for Blacks as compared to 11.1 percent for non-blacks ($p=0.001$). For education, there were 13.8 percent abnormalities in the high school-educated category and 9.1 percent in the college-educated category ($p=0.001$). The highest rate of abnormalities in the drink-year categories was 20.2 percent for the category of greater than 50 drink-years; the percent abnormalities for the 0 and greater than 0 to 50 categories were 11.3 and 10.1, respectively ($p<0.001$).

Based on the adjusted analysis, there was no significant difference between the Ranch Hand and Comparison groups ($p=0.780$). In this analysis, education ($p=0.011$), the age-by-combat index interaction ($p=0.003$), and the

race-by-drink-year interaction (p=0.015) were statistically significant adjusting variables.

Schizophrenia

The unadjusted tests showed no significant difference between the Ranch Hand and Comparison groups for the MMPI schizophrenia scale (p=0.228).

Based on the pooled group data, the covariate tests of association revealed that education (p<0.001) and drink-years (p=0.014) had statistically significant effects. The high school-educated category had a statistically significant higher rate of abnormalities (11.0%) than the college-educated category (5.4%). For drink-years, the highest percent of abnormalities was in the greater than 50 drink-year category (12.6%), followed by the 0 drink-year category with 8.7 percent, and the greater than 0 to 50 drink-year category, which had 7.7 percent abnormalities.

In the adjusted analysis, the group-by-education interaction was significant (p=0.010) (see Table J-4 of Appendix J). The race-by-drink-year interaction was also statistically significant (p=0.017). Analysis of the high school and college strata showed a higher percentage of abnormal Ranch Hands than abnormal Comparisons in the high school classification (13.4% versus 9.5%, respectively; p=0.033). The relative risk estimate for high school participants was 1.51, with 95 percent confidence bounds of 1.05 and 2.16. The college-educated stratum revealed a nonsignificant group difference, but the Ranch Hands had a lower rate of schizophrenia abnormalities than the Comparison group (4.1% and 6.3%, respectively).

Social Introversion

Based on the unadjusted analysis, the difference between the two groups approached significance (p=0.069). The Ranch Hand group had 2.6 percent abnormalities as contrasted to 1.5 percent abnormalities in the Comparison group. The 95 percent confidence bounds on the estimated relative risk of 1.76 were 0.97 and 3.20.

Age was the only statistically significant covariate (p=0.003). The participants who were born in or after 1942 had a higher percentage of abnormalities (3.1%) than either those born between 1923 and 1941 or those born in or before 1922; both of these latter age categories had a 1.1 percent frequency of abnormalities. Education was of marginal significance (p=0.099) with 2.4 percent of the high school-educated participants scored as abnormal as compared to 1.4 percent of the college-educated participants. The group-by-combat index interaction was statistically significant in the adjusted analysis (p=0.037) (see Table J-4 of Appendix J).

The analysis of the group-by-combat index interaction showed a difference within the low (0) combat index category with the Ranch Hands having a significantly higher percentage of abnormalities than the Comparisons (5.6% and 1.2%, respectively; p=0.002). The adjusted relative risk for this combat index category was 4.86, with a 95 percent confidence interval of 1.77 to 13.36. The medium and high combat index strata showed no statistically significant group differences (p=0.478, p=0.677, respectively). In this adjusted model, age also had a significant effect (p=0.004).

Validity

For the MMPI validity scale, the unadjusted tests showed no significant difference between the Ranch Hand and Comparison groups ($p=0.540$).

The covariate tests of association showed that Blacks had a significantly higher frequency of abnormalities (35.0%) than nonblacks (20.5%) ($p<0.001$). The adjusted analysis revealed a statistically significant group-by-race interaction ($p=0.012$). A covariate interaction, age-by-combat index, was also found to be statistically significant ($p=0.030$). Further investigation of the group interaction disclosed a higher percentage of Black Comparisons with scores greater than 0 than Black Ranch Hands (42.2%, 25.0%, respectively), with an adjusted relative risk of 0.46 ($p=0.038$, 95% C.I.: [0.22,0.96]). In contrast, the nonblack stratum revealed a slightly higher proportion of abnormalities in the Ranch Hands, with an adjusted relative risk of 1.20 (95% C.I.: [0.97,1.49], $p=0.095$) (see Table J-4 of Appendix J).

Cornell Medical Index (CMI)

Three variables derived from the CMI were analyzed: the total CMI, M-R subscore, and the A-H area subscore. The total CMI was analyzed as a continuous variable, using a log (X+1) transformation, where X was the number of affirmative answers. Based on the Kolmogorov-Smirnov test, the distributions of the Ranch Hand and Comparison total CMI scores were contrasted. For this set of analyses, the data were stratified separately by the covariates of age, race, education, current alcohol use, and occupation. The unadjusted analysis of total CMI was based on the two-sample t-test. Analysis of variance and two-sample t-tests were used to analyze the covariates, and the adjusted analysis on the total CMI was based on analysis of covariance techniques, using SAS®-GLM. Age was analyzed as a continuous variable in the adjusted analysis. Using a two-sided α-level of 0.05, and with power of 0.80, the sample sizes were sufficient to detect a 10.2 percent mean shift in the total CMI score relative to the mean observed in the Comparison group.

Pearson's chi-square test was used to conduct the unadjusted analyses and the covariate tests of association of the M-R subscore and the A-H area subscore, which were trichotomized into low, medium, and high classes. The adjusted analyses of these two variables were conducted by log-linear techniques using BMDP®-4F.

In all three CMI variables, a higher score is associated with a higher degree of abnormality.

The results of the unadjusted analysis, covariate tests of association, and the adjusted analyses on the three CMI variables are summarized in Tables 12-5 to 12-7, respectively. As discussed for the MMPI variables, the results of the covariate tests of association for current alcohol use and for occupation are provided in the summary table for information only.

TABLE 12-5.

Unadjusted Analyses for the Cornell Medical Index (CMI) by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Total CMI	n	1,000		1,268			
	Mean[a]	11.74		10.42		--	<0.001
	95% C.I.[a]	(11.17,12.35)		(9.95,10.90)			
M-R Subscore	n	998		1,267		Overall	0.252
	Number/%						
	-0 (Low)	538	53.9%	726	57.3%	Medium vs. Low	
	1-10 (Medium)	408	40.9%	484	38.2%	1.14 (0.96,1.35)	0.146
	>10 (High)	52	5.2%	57	4.5%	High vs. Low	
						1.23 (0.83,1.82)	0.314
A-H Area Subscore	n	914		1,148		Overall	0.003
	Number/%						
	-0 (Low)	360	39.4%	537	46.8%	Medium vs. Low	
	1-3 (Medium)	449	49.1%	504	43.9%	1.33 (1.11, 1.60)	0.003
	4-8 (High)	105	11.5%	107	9.3%	High vs. Low	
						1.46 (1.08,1.98)	0.013

[a]Transformed from log (X+1) scale, where x was the number of questions answered "yes."
--No relative risk given for Total CMI, which was analyzed as a continuous variable.

TABLE 12-6.

Association Between CMI Variables and the Covariates in the Combined Ranch Hand and Comparison Groups

CMI Variable	Age	Race	Education	Drink-Years	PTSD	Current* Alcohol Use	Occupation*
Total CMI	<0.001	NS	<0.001	<0.001	<0.001	<0.001	<0.001
M-R Subscore	<0.001	0.022	<0.001	NS*	<0.001	0.043	<0.001
A-H Area Subscore	<0.001	NS	<0.001	<0.001	<0.001	0.010	<0.001

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

NS*: Borderline significant ($0.05<p\leq0.10$).

**Not used in adjusted analyses.

TABLE 12-7.

Adjusted Analyses for CMI Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Total CMI	n	962	1,229			PTSD (p<0.001) RACE*DRKYR (p=0.039)
	Adj. Mean	****	****	----	****	AGE*EDUC (p=0.005)
	95% C.I.	****	****			GRP*EDUC (p=0.003)
M-R Subscore	n	998	1,265	Overall	0.339	AGE (p<0.001) EDUC (p<0.001)
				Medium vs. Low: 1.14 (0.95,1.35)	0.152 0.598	PTSD (p<0.001) GRP*EDUC
				High vs. Low: 1.12 (0.74,1.70)		(marginal: p=0.067)
A-H Area Score	n	881	1,113	Overall	0.040	AGE (p<0.001)
				Medium vs. Low: 1.27 (1.06,1.53)	0.011 0.190	EDUC (p<0.001) PTSD (p<0.001)
				High vs. Low: 1.24 (0.90,1.71)		DRKYR (p=0.014)

*Additional Abbreviations:

PTSD: Post-Traumatic Stress Disorder

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

----No relative risk given for total CMI, which was analyzed as a continuous variable.

Distributional Analyses

The Kolmogorov-Smirnov tests showed statistically significant differences between the Ranch Hand and Comparison distributions for the total CMI for one category for each of the covariates. For age, the distribution of Ranch Hands born in or after 1942 was statistically different from the corresponding distribution for the Comparisons ($p<0.001$). The distributions of the nonblack Ranch Hand and Comparison responses also differed significantly ($p=0.003$). The contrast of the high school-educated Ranch Hand and Comparison distributions revealed a statistically significant difference ($p<0.001$). The distributions for Ranch Hand and Comparison current drinkers were also statistically different ($p=0.024$). For occupation, the enlisted groundcrew distributions for Ranch Hands and Comparisons were statistically different ($p=0.007$). Except for the covariate age, all significant differences in distributions for each covariate were found in the category having the largest sample size. The results of the 12 Kolmogorov-Smirnov tests are summarized in Table J-5 of Appendix J.

Unadjusted and Adjusted Analyses

Total Cornell Medical Index

Based on the unadjusted analysis, as depicted in Table 12-5, the total CMI means of the Ranch Hand and Comparison groups were statistically different ($p<0.001$). The mean, as transformed from the log (X+1) scale, of the 1,000 Ranch Hands was 11.74 as compared to 10.42 for the Comparisons.

The covariate tests of association identified that age, education, drink-years, and PTSD were highly significant ($p<0.001$ for all). For age, the (transformed) means of the categories showed an increase; the means of those born in or after 1942, between 1923 and 1941, and in or before 1922 were 10.08, 11.49, and 14.53, respectively. The mean of the high school-educated category (12.97) was statistically higher than the mean of the college-educated category (8.99). The mean of the greater than 50 drink-years was 14.49 as compared to means of 10.37 and 10.34 for the 0 and greater than 0 to 50 drink-years, respectively. The mean of the participants with a positive measure of PTSD was 71.77, whereas 10.83 was the mean of those without a positive measure of PTSD.

In the adjusted analysis, there was a significant group-by-education interaction ($p=0.003$). Further analysis of the interaction (see Table J-4 of Appendix J) showed that the high school-educated Ranch Hands had a higher adjusted mean total CMI than the high school-educated Comparisons ($p<0.001$). No significant difference was seen in the college stratum. PTSD was a significant covariate ($p<0.001$). The covariate interactions, race-by-drink-years and age-by-education, were also significant in the adjusted model ($p=0.039$, $p=0.005$, respectively).

M-R Subscore

The results of the unadjusted analysis on the M-R subscore, an indicator of emotional health, revealed no significant difference between groups ($p=0.252$).

The covariate tests of association on the pooled group data showed that age ($p<0.001$), race ($p=0.022$), education ($p<0.001$), and PTSD ($p<0.001$) were statistically significant covariates. For age, participants born in or after 1942 had a higher percentage of scores greater than 0 when compared to the other categories. Blacks had a higher percentage of scores greater than 0 than nonblacks. For education, the college-educated category had a higher percentage of 0 scores. The M-R subscores were distributed differently for participants with and without PTSD. For example, 15 of 16 participants with PTSD had an M-R subscore greater than 10, whereas only 4.2 percent of the participants without PTSD had a similar score. Drink-years showed a marginally significant effect ($p=0.054$); the greater than 50 drink-year category exhibited the largest percentage of participants with scores greater than 0.

No significant difference between the two groups was identified in the adjusted analysis. There was a marginally significant group-by-education interaction ($p=0.067$). Further investigation of this interaction (see Table J-4 of Appendix J) showed a significant difference for the high school-educated stratum ($p=0.030$) but not for the college-educated stratum. This difference results from the contrast of the medium (1 to 10) and low (0) categories, with the Ranch Hands having a higher percentage of participants in the medium category for the M-R subscore than in the low category (Adj. RR: 1.37, 95% C.I.: [1.07,1.75], $p=0.014$). In this analysis, age, education, and PTSD were highly significant adjusting variables ($p<0.001$ for all).

A-H Area Subscore

Based on the unadjusted results, the A-H area subscore--an indicator of diffuse medical problems--revealed a significant difference between the Ranch Hand and Comparison groups ($p=0.003$). This was due to the increased percentage of Ranch Hands over Comparisons in both the medium (1 to 3) and the high (4 to 8) categories ($p=0.003$, $p=0.013$, respectively).

The covariate tests on the A-H area subscore showed that age, education, drink-years, and PTSD were highly significant covariates ($p<0.001$ for all). Older participants (born in or before 1922) had the lowest percentage of 0 scores. The college-educated category had a higher percentage of 0 scores than the high school-educated category. For drink-years, the lowest percentage of 0 scores was in the greater than 50 drink-years category. Twelve of 16 participants with PTSD had scores of 4 to 8, as compared to 9.7 percent of participants without PTSD.

Results of the adjusted analysis were similar to the unadjusted analysis and indicated that the two groups were statistically different ($p=0.040$). The overall group difference was predominately due to an increased adjusted percentage of Ranch Hands over Comparisons in the medium (1 to 3) versus low (0) contrast ($p=0.011$). The adjusted relative risk for this contrast was 1.27 with 95 percent confidence bounds of 1.06 and 1.53. In the adjusted model, age, education, and PTSD were significant covariates ($p<0.001$ for all); drink-years was also statistically significant ($p=0.014$).

Halstead-Reitan Battery (HRB)

The unadjusted analysis of the impairment index, the one variable from the HRB, was performed by using Fisher's exact test. Fisher's exact test and

Pearson's chi-square test were used to conduct the covariate tests of association. The adjusted analysis was based on logistic regression techniques using BMDP®-LR. The results of the analyses of the HRB impairment index are summarized in Table 12-8.

The unadjusted contrast of the 1,006 Ranch Hand scores and the 1,283 Comparison scores for the HRB impairment index revealed no statistically significant group differences ($p=0.533$).

The covariate tests of association showed that age, race, and education were highly significant covariates ($p<0.001$ for all), and drink-years also was statistically significant ($p=0.002$). For age, the highest percent frequency of abnormalities was in the category of participants born in or before 1922 (66.3%); the corresponding frequencies for the participants born between 1923 and 1941 and for those born in or after 1942 were 38.3 percent and 25.1 percent, respectively. Blacks had a significantly higher percentage of abnormal scores, with 57.1 percent as compared to 32.3 percent for non-blacks. The college-educated category had a 22.3 percent frequency of abnormalities versus 43.5 percent for the high school-educated category. With respect to drink-years, the highest percentage of abnormalities (41.2%) was for greater than 50 drink-years; the 0 drink-year and greater than 0 to 50 drink-year categories had 38.0 percent and 32.0 percent, respectively.

There was no significant difference identified between the two groups based on the adjusted analysis ($p=0.697$). Age, race, and education were statistically significant covariates ($p<0.001$ for all).

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group (see Chapter 8 for details on the exposure index). All variables, except the total CMI, were investigated, (unadjusted for any covariates), using Pearson's chi-square test and Fisher's exact test. Analyses of the total CMI were accomplished by t-tests and analysis of variance and covariance techniques. A log transformation was used in both adjusted and unadjusted analyses, and participants with PTSD were deleted. Adjusted analyses were performed using logistic regression, incorporating the covariates of race, age, education, and drink-years, as well as any significant pairwise interactions between the exposure index and these covariates. Age was treated as a continuous variable in the analyses. For the MMPI variables, combat index was also included as a covariate. For the HRB impairment index, participants classified as having PTSD were deleted from the analysis. The M-R subscore and the A-H area subscore were collapsed into 2 categories for analysis: 0 and greater than 0. Participants with PTSD were also deleted from this analysis.

Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts in the proportion of abnormalities between the medium and low exposure levels, and between the high and low exposure levels. Results of the adjusted analyses are presented in Table 12-9, and parallel results for unadjusted analyses are presented in Table J-6 of Appendix J. Results from further study of exposure index-by-covariate interactions are given in Table J-7 of Appendix J.

TABLE 12-8.

Summary Results for the Halstead-Reitan Battery Impairment Index Analyses

Analysis	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est./Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Unadjusted Analysis	n	1,006		1,283				
	Abnormal	348	34.6	427	33.3	1.06 (0.89,1.26)	0.533	N/A
	Normal	658	65.4	856	66.7			
Covariate Tests of Association[a]								AGE (p<0.001) RACE (p<0.001) EDUC (p<0.001) DRKYR (p=0.002) PTSD (p=0.431) ALC (p=0.004) OCC (p<0.001)
Adjusted Analysis	n	1,006		1,283		1.04 (0.86,1.25)	0.697	AGE (p<0.001) RACE (p<0.001) EDUC (p<0.001)

*Additional Abbreviations:
ALC: current alcohol use (yes/no)
OCC: occupation

[a]Based on pooled group data; current alcohol use (ALC) and occupation (OCC) provided for information only.

TABLE 12-9.

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		0.562
						M vs. L	2.46 (0.36,16.82)	0.358
						H vs. L	2.43 (0.35,16.81)	0.367
Anxiety	Enlisted Flyer	n	50	61	53	Overall		0.215
						M vs. L	0.44 (0.12,1.70)	0.235
						H vs. L	0.28 (0.05,1.44)	0.127
	Enlisted Groundcrew	n	148	160	131	Overall		****(1)
						M vs. L	****(1)	****(1)
						H vs. L	****(1)	****(1)
	Officer	n	125	126	120	Overall		0.274
						M vs. L	1.10 (0.14,8.59)	0.925
						H vs. L	----	----
Consistency	Enlisted Flyer	n	50	61	53	Overall		0.425
						M vs. L	0.39 (0.06,2.37)	0.304
						H vs. L	0.30 (0.03,2.93)	0.303
	Enlisted Groundcrew	n	148	160	131	Overall		0.550
						M vs. L	0.87 (0.32,2.34)	0.781
						H vs. L	0.56 (0.18,1.67)	0.296

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		0.518
						M vs. L	----	----
						H vs. L	----	----
Defensiveness	Enlisted Flyer	n	50	61	53	Overall		0.613
						M vs. L	0.17 (0.001,29.09)	0.503
						H vs. L	1.37 (0.02,77.86)	0.878
	Enlisted Groundcrew	n	148	160	131	Overall		0.737
						M vs. L	0.79 (0.23,2.78)	0.719
						H vs. L	1.31 (0.40,4.23)	0.656
	Officer	n	125	126	120	Overall		****(2)
						M vs. L	****(2)	****(2)
						H vs. L	****(2)	****(2)
Denial	Enlisted Flyer	n	50	61	53	Overall		0.234
						M vs. L	1.03 (0.09,11.69)	0.984
						H vs. L	----	----
	Enlisted Groundcrew	n	148	160	131	Overall		0.109
						M vs. L	----	----
						H vs. L	1.41 (0.18,11.09)	0.747

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		0.411
						M vs. L	0.62 (0.20,1.88)	0.393
						H vs. L	1.24 (0.46,3.33)	0.669
Depression	Enlisted Flyer	n	50	61	53	Overall		0.160
						M vs. L	0.55 (0.18,1.67)	0.295
						H vs. L	0.31 (0.09,1.10)	0.070
	Enlisted Groundcrew	n	148	160	131	Overall		****(1)
						M vs. L	****(1)	****(1)
						H vs. L	****(1)	****(1)
	Officer	n	125	126	120	Overall		****(3)
						M vs. L	****(3)	****(3)
						H vs. L	****(3)	****(3)
Hypochondria	Enlisted Flyer	n	50	61	53	Overall		0.195
						M vs. L	0.33 (0.09,1.18)	0.087
						H vs. L	0.74 (0.26,2.14)	0.581
	Enlisted Groundcrew	n	148	160	131	Overall		****(1)
						M vs. L	****(1)	****(1)
						H vs. L	****(1)	****(1)

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		****(3)
						M vs. L	****(3)	****(3)
						H vs. L	****(3)	****(3)
Hysteria	Enlisted Flyer	n	50	61	53	Overall		0.306
						M vs. L	0.55 (0.18,1.74)	0.312
						H vs. L	0.41 (0.12,1.37)	0.148
	Enlisted Groundcrew	n	148	160	131	Overall		****(1)
						M vs. L	****(1)	****(1)
						H vs. L	****(1)	****(1)
	Officer	n	125	126	120	Overall		****(4)
						M vs. L	****(4)	****(4)
						H vs. L	****(4)	****(4)
Mania/ Hypomania	Enlisted Flyer	n	50	61	53	Overall		0.474
						M vs. L	2.51 (0.55,11.53)	0.236
						H vs. L	1.66 (0.35,7.89)	0.527
	Enlisted Groundcrew	n	148	160	131	Overall		0.597
						M vs. L	0.97 (0.38,2.45)	0.945
						H vs. L	0.61 (0.21,1.75)	0.356

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		****(3)
						M vs. L	****(3)	****(3)
						H vs. L	****(3)	****(3)
Masculinity/ Femininity	Enlisted Flyer	n	50	61	53	Overall		0.045
						M vs. L	----	----
						H vs. L	----	----
	Enlisted Groundcrew	n	148	160	131	Overall		0.479
						M vs. L	0.50 (0.16,1.57)	0.234
						H vs. L	0.75 (0.25,2.24)	0.604
	Officer	n	125	126	120	Overall		****(2)
						M vs. L	****(2)	****(2)
						H vs. L	****(2)	****(2)
Paranoia	Enlisted Flyer	n	50	61	53	Overall		****(2)
						M vs. L	****(2)	****(2)
						H vs. L	****(2)	****(2)
	Enlisted Groundcrew (a)	n	148	160	131	Overall		0.789
						M vs. L	1.06 (0.31,3.66)	0.922
						H vs. L	1.47 (0.44,4.92)	0.530

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		0.427
						M vs. L	1.01 (0.34,2.98)	0.985
						H vs. L	1.78 (0.65,4.83)	0.259
Psychopathic/ Deviate	Enlisted Flyer	n	50	61	53	Overall		0.759
						M vs. L	1.20 (0.42,3.41)	0.731
						H vs. L	0.79 (0.24,2.54)	0.689
	Enlisted Groundcrew	n	148	160	131	Overall		****(3)
						M vs. L	****(3)	****(3)
						H vs. L	****(3)	****(3)
	Officer	n	125	126	120	Overall		0.511
						M vs. L	0.72 (0.18,2.97)	0.654
						H vs. L	0.38 (0.07,2.12)	0.269
Schizophrenia	Enlisted Flyer	n	50	61	53	Overall		0.615
						M vs. L	0.70 (0.21,2.35)	0.559
						H vs. L	0.52 (0.14,1.97)	0.338
	Enlisted Groundcrew	n	148	160	131	Overall		0.682
						M vs. L	1.32 (0.66,2.61)	0.429
						H vs. L	1.30 (0.64,2.64)	0.471

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	125	126	120	Overall		0.247
						M vs. L	1.86 (0.16,21.91)	0.620
						H vs. L	----	----
Social Introversion	Enlisted Flyer	n	50	61	53	Overall		0.521
						M vs. L	0.20 (0.01,4.85)	0.321
						H vs. L	0.30 (0.02,5.61)	0.418
	Enlisted Groundcrew	n	148	160	131	Overall		0.394
						M vs. L	0.47 (0.15,1.49)	0.199
						H vs. L	0.87 (0.28,2.67)	0.805
	Officer	n	125	126	120	Overall		0.049
						M vs. L	0.97 (0.53,1.76)	0.920
						H vs. L	0.48 (0.24,0.93)	0.031
Validity	Enlisted Flyer	n	51	61	53	Overall		0.479
						M vs. L	0.67 (0.23,1.94)	0.459
						H vs. L	1.26 (0.47,3.40)	0.649
	Enlisted Groundcrew	n	148	160	131	Overall		0.718
						M vs. L	1.22 (0.71,2.11)	0.470
						H vs. L	1.22 (0.69,2.14)	0.499

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	124	124	120	Overall		****(4)
		Adj. Mean	****(4)	****(4)	****(4)	M vs. L	----	****(4)
		95% C.I.	****(4)	****(4)	****(4)	H vs. L	----	****(4)
Total CMI	Enlisted Flyer	n	48	61	51	Overall		****(3,4)
		Adj. Mean	****(3,4)	****(3,4)	****(3,4)	M vs. L	----	****(3,4)
		95% C.I.	****(3,4)	****(3,4)	****(3,4)	H vs. L	----	****(3,4)
	Enlisted Groundcrew	n	145	154	125	Overall		0.608
		Adj. Mean(b)	13.67	12.48	13.09	M vs. L	----	0.319
		95% C.I.(b)	(11.33, 16.45)	(10.30, 15.09)	(10.81, 15.82)	H vs. L	----	0.655
	Officer	n	123	124	119	Overall		0.301
						M vs. L	0.72 (0.41,1.28)	0.265
						H vs. L	1.11 (0.64,1.93)	0.715
N-R Subscore	Enlisted Flyer	n	48	61	51	Overall		****(4)
						M vs. L	****(4)	****(4)
						H vs. L	****(4)	****(4)
	Enlisted Groundcrew	n	146	152	127	Overall		0.427
						M vs. L	0.82 (0.51,1.31)	0.403
						H vs. L	0.73 (0.44,1.19)	0.201

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

Variable	Occupation	Statistic*	Exposure Index Low	Medium	High	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	n	111	109	112	Overall		0.546
						M vs. L	0.78 (0.44,1.37)	0.383
						H vs. L	0.75 (0.43,1.31)	0.311
A-H Area Subscore	Enlisted Flyer	n	45	57	45	Overall		****(3,4)
						M vs. L	****(3,4)	****(3,4)
						H vs. L	****(3,4)	****(3,4)
	Enlisted Groundcrew	n	129	145	118	Overall		0.427
						M vs. L	0.84 (0.50,1.40)	0.499
						H vs. L	0.92 (0.53,1.59)	0.767
	Officer	n	124	126	118	Overall		0.255
						M vs. L	0.81 (0.43,1.53)	0.512
						H vs. L	0.57 (0.29,1.12)	0.103
HRB Impairment Index	Enlisted Flyer	n	47	61	52	Overall		0.159
						M vs. L	2.28 (0.96,5.44)	0.063
						H vs. L	1.39 (0.58,3.37)	0.461
	Enlisted Groundcrew	n	145	158	127	Overall		****(1)
						M vs. L	****(1)	****(1)
						H vs. L	****(1)	****(1)

TABLE 12-9. (continued)

Adjusted Exposure Index Analyses
for Psychological Variables by Occupation

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*n: represents total sample size for variable in given occupational stratum.

(a): marginal exposure index by race interaction (p=0.055) -- relative risk, confidence interval, and p-value presented, and additional information provided in interaction summaries.

(b): converted from log (X+1) scale, where X was the number of questions answered yes.

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

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

****(3): exposure index-by-education interaction -- relative risk, confidence interval, and p-value not presented.

****(4): exposure index-by-drink-year interaction -- relative risk/adjusted mean, confidence interval, and p-value not presented.

****(3,4): exposure index-by-education and exposure index-by-drink-year interaction -- relative risk/adjusted mean, confidence interval, and p-value not presented.

----: no relative risk given for Total CMI, which was analyzed as a continuous variable.

Unadjusted analyses revealed a borderline significant difference between the high and low exposure levels for masculinity/femininity in officers (Est. RR: 2.38, 95% C.I.: [0.94,6.06], p=0.075), and for the total CMI in officers (low mean: 7.99, high mean: 10.04, p=0.018; overall p-value: 0.049). These data supported an increase in the proportion of abnormalities with increasing exposure levels. Other significant or marginally significant results were associated with a decrease in the proportion of abnormalities with an increase in exposure level.

The frequency of abnormalities for the different exposure index levels exhibited no graduated pattern across exposure levels. Within the officer stratum, five variables demonstrated an increasing dose-response relationship, although usually nonsignificant; however, four variables showed the opposite pattern, that is, a decreasing proportion of abnormalities with increasing exposure levels.

Few significant results were observed in the adjusted analysis, as in the unadjusted analysis. The medium level of the HRB impairment index for enlisted flyers showed an increased relative risk over the low level (Adj. RR: 2.28, 95% C.I.: [0.96,5.44], p=0.063). Many exposure index-by-covariate interactions were present, however, which prevented a direct comparison.

Interactions were present for 13 of the 18 variables, but no occupational stratum was predominant. A summary of these interactions is presented in Table 12-10.

TABLE 12-10.

Summary of Exposure Index-by-Covariate Interactions in Adjusted Analyses of Psychological Variables

Variable	Occupation	Covariate	p-Value
Anxiety	Enlisted Groundcrew	Race	0.020
Denial	Officer	Age	0.048
Depression	Enlisted Groundcrew	Race	0.050
Hypochondria	Officer	Education	0.005
Hypochondria	Enlisted Groundcrew	Race	0.033
Hysteria	Officer	Education	0.018
Hysteria	Enlisted Groundcrew	Race	0.007
Mania/Hypomania	Officer	Drink-Years	0.015
Masculinity/Feminity	Officer	Education	0.018
Paranoia	Officer	Age	0.044
Paranoia	Enlisted Flyer	Age	0.004
Paranoia	Enlisted Groundcrew	Race	0.055 (marginal)
Psychopathic/Deviate	Enlisted Groundcrew	Education	0.040
Total CMI	Officer	Drink-Years	0.034
Total CMI	Enlisted Flyer	Education	0.027
Total CMI	Enlisted Flyer	Drink-Years	0.021
M-R Subscore	Enlisted Flyer	Drink-Years	0.042
A-H Area Subscore	Enlisted Flyer	Education	0.009
A-H Area Subscore	Enlisted Flyer	Drink-Years	0.004
HRB Impairment Index	Enlisted Groundcrew	Race	0.031

Significant or borderline significant results in these interactions, suggestive of a dose-response relationship (i.e., increasing abnormalities or more abnormal means as exposure increases), were as follows:

(1) Hysteria in college-educated officers, overall p-value = 0.025; high versus low contrast (Adj. RR: 3.49, 95% C.I.: [1.17,10.32], p=0.024); increase in the proportion of abnormalities with increasing exposure levels.

(2) Mania/Hypomania in officers with greater than 50 drink-years, high versus low contrast, p=0.067; analysis affected by sparse cell sizes, however.

(3) Masculinity/Femininity in college-educated officers, medium versus low contrast (Adj. RR: 3.05, 95% C.I.: [1.01,9.08], p=0.048); increase in the proportion of abnormalities with increasing exposure levels.

(4) Total CMI in high school-educated, nondrinking, enlisted flyers, medium versus low contrast, p=0.018.

(5) Total CMI in college-educated, nondrinking, enlisted flyers, overall p-value =0.060; analysis affected by sparse cell sizes, however.

(6) M-R subscore in nondrinking, enlisted flyers, overall p-value = 0.060; analysis affected by sparse cell sizes, however.

(7) A-H area subscore in high school-educated, nondrinking, enlisted flyers, overall p-value = 0.007; analysis affected by sparse cell sizes, however.

(8) HRB impairment index in nonblack enlisted groundcrew, medium versus low contrast (Adj. RR: 1.88, 95% C.I.: [1.09,3.25], p=0.024).

All other significant interaction results were not consistent with a dose-response relationship.

In summary, no consistent or strong patterns of increasing dose-response relationship were evident throughout the psychological exposure index analyses.

LONGITUDINAL ANALYSES

Two scales for the MMPI, depression and denial, were significantly different by group at Baseline and were investigated to assess the longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables are scores and were classified as abnormal or normal according to criteria given previously. These variables have been stratified by education level. As shown in Table 12-11, 2x2 tables were constructed for each group for each variable. These tables show the number of participants who were abnormal at Baseline and abnormal at followup, abnormal at Baseline and normal at followup, normal at Baseline and abnormal at followup, and normal at both Baseline and followup examinations.

TABLE 12-11.

Longitudinal Analysis of Depression and Denial:
A Contrast of Baseline and First
Followup Examination Abnormalities

Variable	Education	Group	1982 Baseline Exam	1985 Followup Exam		Odds Ratio (OR)*	p-Value (OR_{RH} vs/OR_C)
				Abnormal	Normal		
Depression	High School	Ranch Hand	Abnormal	59	48	0.65	
			Normal	31	570		0.04
		Comparison	Abnormal	44	43	1.21	
			Normal	52	695		
	College	Ranch Hand	Abnormal	11	9	1.11	
			Normal	10	227		0.73
		Comparison	Abnormal	7	11	1.36	
			Normal	15	276		
Denial	High School	Ranch Hand	Abnormal	2	5	2.20	
			Normal	11	690		0.56
		Comparison	Abnormal	6	10	3.20	
			Normal	32	786		
	College	Ranch Hand	Abnormal	0	3	1.67	
			Normal	5	249		0.32
		Comparison	Abnormal	5	3	4.33	
			Normal	13	288		

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

The odds ratio given is the ratio of the number of participants who were normal at the Baseline and abnormal at the followup to the number of participants who were abnormal at the Baseline and normal at the followup (the "off-diagonal" elements). The changes in normal/abnormal status within each group are contrasted between the Ranch Hand and Comparison groups, and the p-value is derived from Pearson's chi-square test of the hypothesis that the pattern of change in the two groups is the same.

The data showed a significant difference ($p=0.04$) in the depression scores in the two groups between examinations for the high school-educated stratum: significantly more Comparisons developed depression in the interval. The percentage of Ranch Hands with abnormalities for depression decreased from the Baseline examination to the followup examination, in contrast to the Comparison group, which showed an increase in depression abnormalities. No significant difference in the pattern of change for depression was found in the college-educated stratum, nor were any significant differences observed for denial.

DISCUSSION

The MMPI is a comprehensive, self-administered questionnaire containing 566 questions that broadly assess behavior, personality, and validity and consistency indicators of the responses. The MMPI data are divided into 14 scales that are not mutually exclusive for specific questions. In this study, an additional MMPI scale for the characterization of PTSD is used to identify highly correlated combat experiences of the participants. Four combat questions were selected as a surrogate measure of PTSD, and an index of these questions is used as a covariate in all of the adjusted analyses of the MMPI subscales.

Distributional testing for the 14 scales of the MMPI, stratified by occupation, yielded no significant differences or discernible patterns between the two groups. In contrast, both unadjusted and adjusted analyses showed significant group differences for the denial and masculinity/femininity scales, with the Comparisons having higher proportions of abnormalities than the Ranch Hands. Also, borderline significant associations ($0.05<p\leq 0.10$) were observed for the hysteria and social introversion scales, with the Ranch Hands having slightly higher proportions of abnormalities than the Comparisons. The discrepancy in results between Kolmogorov-Smirnov distributional testing and the refined statistical models was also noted in the 1984 Baseline Report.

The unadjusted and adjusted results were completely comparable with respect to group differences when direct contrast was possible, i.e., when no group-by-covariate interactions were present. Of the seven group interactions noted in the adjusted analyses, three involved the covariate of education, with the high school-educated Ranch Hands faring worse than high school-educated Comparisons. Further, the high school strata usually exhibited a higher frequency of abnormalities than the college-educated strata. Overall education showed a profound effect either as a main effect or by an interaction with another covariate. The strong influence of education was also detected in the Baseline data. Analyses using only the Original Comparisons often showed stronger group differences than the analyses based upon the total Comparison group (see Tables J-13 to J-18 of Appendix J).

A direct comparison of the MMPI results between the Baseline and followup examinations is hampered by the small change in cohorts and the difference in statistical models. In general, at the followup the Ranch Hands manifested more MMPI scale abnormalities than the Comparisons, as judged by the number of relative risks greater than one. However, the highly significant results for the denial scale, with the Comparisons having a higher proportion of abnormalities than the Ranch Hands, suggested that the Comparisons may be underreporting on all of the MMPI scales, and consequently more relative risks greater than one would be expected. A contrast of the adjusted Baseline MMPI results to the adjusted (and unadjusted results where interactions are noted in the adjusted tests) results of the followup suggest a relatively consistent pattern of narrowing group differences over time (e.g., hypochrondria, depression, hysteria, schizophrenia scales), either by a decrease in Ranch Hand abnormalities or an increase of Comparison abnormalities. This trend was also suggested in the longitudinal analysis of two scales (depression and denial) although only the "favorable" Ranch Hand change in depression for the high school stratum reached statistical significance. Overall, the followup MMPI data suggested a subtle, but consistent, decrease in reporting of concerns (or strength of concerns) in the Ranch Hands.

Only 16 participants were identified as possibly having PTSD by the MMPI subscale. Further, only 4 of 15 combat experience questions manifested strong correlation to these possible PTSD cases. Most PTSD surveys have focused on U.S. Army ground personnel, obscuring direct comparisons to U.S. Air Force personnel because of inherent differences in combat experience, education, proportion of officers, and career motivation.

The CMI revealed a significant group difference for the total score and the A-H area subscore, with the Ranch Hands exhibiting higher mean scores or higher frequencies of abnormal scores. There was no group difference for the M-R subscore. These results differed slightly from the distributional tests which showed one statistically significant stratum, where the Ranch Hand mean was greater than the Comparison mean, for each covariate (see Table J-5 of Appendix J). Because the Baseline CMI was in a different format, direct comparison of each psychological parameter to the followup CMI is not feasible. However, the Baseline CMI noted statistically significant group differences for 5 of 10 parameters, which is in approximate accord with the magnitude and direction of the results found at the followup examination. This analysis of the total CMI analyzed at followup has sufficient statistical power to detect a mean difference of one response out of 195 questions (0.5% difference, at power=0.8) between the groups. Education showed the same profound effect on the adjusted analyses as was noted at Baseline.

The functional integrity of the CNS, as measured by the HRB impairment index, showed no significant group differences. There was similarity (Adj. RR: 1.04, 95% C.I.: [0.86,1.25], p=0.697) in results of the impairment index. As in the Baseline analysis, education was a major covariate in the followup examination; the additionally strong effects of age and race were also noted at the followup examination. Although valid differences exist between groups for some measures, there is no indication that these differences are manifest or confirmed by impaired CNS function, a reasonable medical expectation for chemically induced neurobahavioral pathology. Adjustment of the HRB results for PTSD (not feasible at the Baseline analysis) suggests that some group differences lack organic basis.

SUMMARY AND CONCLUSIONS

Questionnaire data (verified by medical record reviews) for the lifetime events of psychotic illness, alcohol dependence, anxiety, or other neuroses disclosed no significant differences between groups for these conditions.

Analyses of the followup psychological examination emphasized 14 scales from the Minnesota Multiphasic Personality Inventory (MMPI), 3 parameters of the Cornell Medical Index (CMI), and the Halstead-Reitan Battery (HRB) impairment index.

The similarity of the group distribution for the 14 MMPI variables, each stratified by the 3 occupational categories, was examined, and only 2 of the 42 tests approached statistical significance. The group distributions of the total CMI score were similarly contrasted, with separate analyses performed with stratification by the five covariates of age, race, occupation, education, and current drinking status. For one stratum of each of these covariates, a significant difference in the distribution of the Ranch Hand and Comparison scores was found. In all cases for the CMI, the Ranch Hand mean was greater than the Comparison mean. Distributional analyses using Original Comparisons generally reflected the same results as those involving the total Comparison group.

Results of unadjusted and adjusted analyses on all of the 18 psychological variables are given in Table 12-12.

The unadjusted analyses showed a significant difference for the MMPI scales of denial ($p<0.001$) and masculinity/femininity ($p=0.017$), the total CMI ($p<0.001$), and the Section A-H area subscore ($p=0.003$). A borderline significant difference was observed for the MMPI scales of hysteria ($p=0.067$) and social introversion ($p=0.069$). Comparisons had a greater percentage of abnormal scores for the denial and masculinity/femininity scales, whereas Ranch Hands showed adverse findings for the other four variables. The overall MMPI results have been interpreted in light of the significant increased denial in the Comparison group.

The covariates age, education, drink-years, current alcohol use, and occupation had pronounced effects on the psychological variables, with a significant association or a borderline significant association with at least two-thirds of the 18 psychological variables. Many dependent variables in this chapter were affected by age in an expected pattern. Very few variables exhibited this pattern of consistency with drink-years. The intermediate category of greater than 0 to 50 drink-years often had the smallest proportion of abnormalities. The post-traumatic stress disorder (PTSD) variable, derived from a subset of the MMPI, was strongly associated with the CMI measures, but not with the HRB Impairment Index. Race and the Vietnam combat index (used for the MMPI subscales) had significant associations with a lesser amount of the psychological variables (6 of 18 variables and 3 of 14 variables, for race and combat index, respectively).

The adjusted analyses were generally quite similar to the unadjusted analyses with respect to group differences, although a direct comparison of these analyses was often clouded by the presence of a substantial number of interactions (six group-by-covariate interactions were significant, and three interactions approached significance [$0.05<p\leq0.10$]). The MMPI scales of denial and masculinity/femininity were statistically significant in both the

TABLE 12-12.

Overall Summary Results of Adjusted and Unadjusted Analyses of Psychological Variables

Variable	Unadjusted	Adjusted	Direction of Results[a]
Questionnaire:			
Psychological Illness	NS	--	
Psychological Examination:			
MMPI			
Anxiety	NS	NS	
Consistency	NS	****	
Defensiveness	NS	NS	
Denial	<0.001	<0.001	C>RH
Depression	NS	NS	
Hypochondria	NS	NS	
Hysteria	NS*[b]	NS*[b]	RH>C
Mania/Hypomania	NS	NS	
Masculinity/Femininity	0.017	0.020	C>RH
Paranoia	NS	****	
Psychopathic/Deviate	NS	NS	
Schizophrenia	NS	****	
Social Introversion	NS*[b]	****	RH>C
Validity	NS	****	
CMI			
Total CMI	<0.001	****	RH>C
M-R Subscore	NS	NS	
A-H Area Subscore	0.003	0.040	RH>C
HRB			
Impairment Index	NS	NS	

[a]RH>C - more abnormalities in Ranch Hands; C>RH - more abnormalities in Comparisons.

[b]Illnesses include psychosis, alcohol dependence, anxiety, and other neuroses.

--Analysis not performed.

NS: Not significant.

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

****Interaction involving group.

adjusted and unadjusted analyses, where Comparisons showed an adverse effect over Ranch Hands. The A-H area subscore of the CMI (suggesting diffuse medical problems) was also significant, where the Ranch Hands had higher mean scores than the Comparisons, suggesting the Ranch Hands had more illness. Education was often involved in significant group interactions with high school-educated Ranch Hands demonstrating a higher percentage of abnormal scores than high school-educated Comparisons. No group differences were observed in the college-educated stratum. The M-R subscore of the CMI, a broad indicator of emotional health, was not statistically different between the two groups.

The HRB impairment index, a measure of central nervous system (CNS) functional integrity, did not differ significantly between the Ranch Hand and Comparison groups. Strong covariates in the adjusted analysis were age, race, and education.

Because of alternate statistical models and slightly different psychological testing parameters, a direct contrast between the psychological results of the Baseline and followup examinations was not always possible. However, several broad patterns were observed: (1) the discordance between distributional tests and results from traditional statistical models of the MMPI variables was noted with data from both examinations; (2) there was a narrowing of group differences at the followup examination for most subjective variables, either by a decrease in Ranch Hand reporting, or by an increase in Comparison reporting; and (3) as at the Baseline, functional CNS testing, as measured by the HRB impairment index, showed no group differences, and did not support an organic basis for differences in self-reported symptomatology. The longitudinal analysis of two MMPI scales, depression and denial, showed a significant reversal of depression seen at Baseline in the high school-educated Ranch Hands.

The determination of PTSD in both Air Force cohorts by a relatively new MMPI scale showed a prevalence rate of less than 1 percent. This low rate is strongly influenced by characteristics of the study population (e.g., age, education, and officer ratio).

Unadjusted exposure index analyses did not reveal any patterns consistent with a dose-response relationship. For the adjusted exposure analyses, approximately one-third presented exposure interactions with the covariates of race, education, and age, but no consistent pattern could be identified.

In conclusion, some test measures of psychological health (MMPI and CMI) did not show substantial adverse effects for either group. Significant test results were present in both groups or were noted in specific subgroups of a covariate. Educational level, age, and alcohol use showed strong effects on the psychological scales and scores in this psychological assessment. There was a subtle but consistent trend for more favorable subjective test results at the followup examination for the Ranch Hands relative to the Comparisons. Testing of the CNS by the HRB demonstrated an almost identical prevalence of pathology in both groups.

CHAPTER 12

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CHAPTER 13

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. The liver is a major target organ for single high-dose and continued low-dose exposure to chlorophenols and TCDD. Peptic/stomach ulcer disease and porphyria cutanea tarda (PCT) are suspected clinical endpoints following moderate- to high-level exposures.

A variety of experimental animal studies[1-5] have demonstrated hepatic dysfunction and porphyria following a wide range of exposures to TCDD. The effects of exposure, as measured by enzymatic change, however, generally appear to be more related to species than to dose and route of administration.

Gross organ pathology in the digestive system and associated clinical symptoms have been observed following TCDD oral administration to (or accidental ingestion by) animals. Pathological lesions have included gastric ulcers, metaplasia of the gastric mucosa, ileitus, hepatic hypertrophy and degeneration, hepatic parenchymal cell necrosis, and hepatic lipid accumulation.

Scientific interest has centered on changes in hepatic enzymes following TCDD administration. Clearly, TCDD has proved to be an exceptional inducer of hepatic enzymes and mixed function oxidases, and a powerful inhibitor of other enzymes. Specifically, the induction of cytochrome P-450, a ferrocytochrome enzyme, by TCDD has been demonstrated in many species and most of their tissues. Further, marked increases in cytochrome P-450 have been implicated in the mechanism of hepatotoxicity, although other factors, such as genetic susceptibility via the Ah locus, iron levels, and lipid peroxidation (but not vitamin A), are also contributory.[6-8]

TCDD has also been shown to produce hepatic porphyria in animals by a reduction in uroporphyrinogen decarboxylase, possibly due to the activation of the P-450 enzyme.[9,10] The porphyriogenic effect of TCDD has also been influenced by genetic susceptibility, iron levels, sex, and ambient temperature.[11,12] In correlation with some human studies, hexachlorobenzene was found to be more porphyriogenic than TCDD.[11]

Numerous morbidity studies, predominantly from the industrial sector, have noted significant abnormal liver function in exposed workers, with and without the presence of clinical hepatic disease. Abnormal liver function test results have been found for direct bilirubin, alkaline phosphatase, triglycerides, cholesterol, serum glutamic-oxaloacetic transaminase (SGOT), gamma-glutamyl transpeptidase (GGTP), urine d-glucaric acid, etc.[13-26] The consistent finding of elevated cholesterol levels may have predictive significance with respect to future heart disease (see Chapter 15), but at present there is no evidence for this.

Contemporary studies have focused on two indirect measures of hepatic microsomal activity, GGTP and urine d-glucaric acid. In the study of the English industrial incident, several Seveso investigations, and the two studies of the Monsanto plant in Nitro, West Virginia, there was modest agreement in observing elevated GGTP and urine d-glucaric acid levels in exposed individuals.[18,19,21,22] Common to all studies was the observation that individuals with chloracne manifested significantly more abnormal liver function tests than exposed individuals without chloracne or unexposed individuals, suggesting a link to TCDD exposure.

Several industrial studies have shown altered porphyrin excretion patterns (predominantly an increase in uroporphyrin) or clinical evidence of PCT, particularly in chronically exposed workers.[27-29] Individuals with low chronic exposure or high acute exposure (Seveso) have not shown these signs. Further, detailed reviews of the suspected association have identified the following scientific study design and interpretive problems: (1) multiple etiologies of PCT or abnormal porphyrin excretion patterns (chemical exposure, genetic makeup, alcohol consumption), (2) misdiagnosis of PCT, and (3) confounding of chemical exposures for the industrial cohorts.

Some investigators believe that the PCT cases found in the early U.S. and European studies were more likely caused by exposure to chlorobenzenes than to TCDD.[30] Overall, the evidence at present is inconclusive to establish a causal association between PCT and TCDD exposure.

A recent industrial study based on questionnaire data has suggested an association of stomach/peptic ulcers with exposure to TCDD.[22] This finding at the Monsanto plant differs from similar research using a slightly different cohort at the same plant which produced a negative conclusion on peptic ulcer disease.[31] The gastric ulcer-TCDD association has not been reported in other cohort dioxin morbidity studies, but ulcer disease has generally not been a major research focus. The preliminary gastric ulcer-TCDD association is fortified somewhat by studies that have shown significant gastric mucosal damage in monkeys following oral administration of TCDD.[2]

Baseline Summary Results

The 1982 AFHS examination conducted an extensive evaluation of hepatic status by questionnaire, physical examination, and laboratory testing. The questionnaire elicited data on liver conditions, liver disease, and symptoms compatible with PCT, as well as detailed information on PCT risk factors (e.g., alcohol consumption, chemical exposures). The physical examination measured hepatomegaly when present and determined liver function and porphyrin patterns by a comprehensive battery of 12 laboratory tests.

The questionnaire showed that Ranch Hands reported more miscellaneous liver conditions (verified by medical record reviews) and more skin changes compatible with PCT than their Comparisons. Although the PCT-reported data were statistically significant, no cases of PCT were diagnosed at examination in either cohort.

The physical examination detected a twofold increase in hepatomegaly in the Ranch Hands, but the numbers were small and not statistically significant. Many of the laboratory test results demonstrated statistical interactions with the covariates. These interactions can be interpreted as being

suggestive of an herbicide effect. Ranch Hands had slightly higher GGTP and lactic dehydrogenase (LDH) results and lower cholesterol levels; no differences were found for bilirubin or alkaline phosphatase levels.

SGOT, serum glutamic-pyruvic transaminase (SGPT), and LDH results in the Ranch Hands interacted with the covariates alcohol, degreasing chemicals, and industrial chemicals differently than they did in the Comparisons. All of these two-factor interactions were statistically significant ($p<0.05$). There were no significant group differences in uroporphyrin, coproporphyrin, or d-aminolevulinic acid levels, nor did any test set support a diagnosis of PCT. Exposure analyses were essentially negative.

The comprehensive hepatic evaluation did not reveal any consistent pattern of significant liver damage in the Ranch Hand group. Nevertheless, because of subtle profile differences in conjunction with questionnaire results and recent literature citations, the gastrointestinal system continues to be targeted for intensive examination throughout all phases of the followup effort.

Parameters of the 1985 Gastrointestinal Assessment

The 1985 AFHS examination continued the emphasis on hepatic function and expanded the porphyrin test battery to six assays. In addition, new components were added to the questionnaire to assess past and current diagnosed peptic ulcer disease, along with a series of screening questions to assess possible undiagnosed disease. Covariate data on aspirin usage, blood group, and family history of peptic ulcer were likewise obtained. Additional probes on intestinal parasites, gallbladder disease, and other liver conditions were also added. Because of the known profound effects of alcohol ingestion on hepatic function, a detailed alcohol consumption history was obtained by questionnaire.

Thus, the dependent variables and covariates in the analyses below reflect a substantial enhancement over those assessed in the 1982 Baseline examination. Because of the effects of increased body temperature and past/current hepatitis B on some liver function tests, participants with a fever of 100 or more degrees Fahrenheit and/or a positive hepatitis B surface antigen (HB_sAg) test were excluded from the analyses. Categorization of continuous clinical variables to dichotomous variables was largely accomplished by use of normal test values from the SCRF laboratory. Minor numeric differences in the tables that follow are due to an occasionally missing value.

The analyses are generally based on 1,009 Ranch Hands and 1,289 total Comparisons after removal of the febrile and positive HB_sAg participants. The statistical analyses relied largely on general linear models (SAS®-GLM), logistic regression techniques (BMDP®-LR), and log-linear models (BMDP®-4F). Parallel analyses using Original Comparisons are found in Tables K-7 to K-16 of Appendix K.

RESULTS AND DISCUSSION

This chapter, entitled "Evaluation of Hepatic Status" in the Baseline Report, incorporates the new elements of peptic ulcer disease and mortality from diseases of the digestive system; hence, the chapter name change to "Gastrointestinal Assessment."

Because of the importance of gastrointestinal disorders, numerous historical and laboratory variables were chosen for evaluation. The analyses are reported in the following order: questionnaire data, mortality data, physical examination findings, laboratory results, exposure index analyses, and representative longitudinal analyses.

Questionnaire Data: Liver Disorders

At the followup examination, each participant was asked whether he had developed hepatitis, jaundice, cirrhosis, or other liver disorders during the interval 1982 to 1985. Affirmative responses were subsequently subject to verification by medical record reviews.

Since the Baseline interview, eight Ranch Hands and five Comparisons cited a verified history of hepatitis ($p=0.264$); four Ranch Hands and five Comparisons reported a subsequently verified history of enlarged liver ($p=0.999$); one from each group noted a verified symptom of jaundice; one Ranch Hand cited a confirmed interval history of cirrhosis; and six Ranch Hands and six Comparisons gave verified histories of seven miscellaneous liver disorders ($p=0.774$). Table 13-1 presents the ICD code and descriptive diagnosis of the miscellaneous liver disorders by group.

Because the number of respondents with new liver disorders was small and precluded meaningful analyses, the verified interval history was added to the verified Baseline history to assess possible lifetime differences for liver disease. These combined results are presented in Table 13-2.

On the basis of combined data, the verified questionnaire responses for historic hepatitis, jaundice, cirrhosis, enlarged liver, and miscellaneous liver disorders did not vary significantly between the Ranch Hand and Comparison groups. The results for miscellaneous liver disorders differed from the Baseline findings. At Baseline, significantly more Ranch Hands than Original Comparisons had a verified liver disorder other than jaundice, hepatitis, or cirrhosis (13/1,045 versus 1/773; $p=0.006$). Subsequent to Baseline, the status of one additional Ranch Hand disorder and one more Original Comparison disorder was verified. Including these two new verified conditions with the data from replacement and shifted Comparisons, the group contrast at Baseline would have been of borderline significance (14/1,045 versus 7/1,224; $p=0.077$). Combining these Baseline data with the followup data resulted in nonsignificant lifetime results. However, the combined Baseline and interval analysis contrasting the Ranch Hands and the Original Comparisons was marginally significant ($p=0.065$) due to the contribution of the significant Baseline results.

The verification status of reported liver symptoms and diseases is presented in Table 13-3. The data reflect the proportions of historic reporting that were verified by medical record reviews, and are contrasted by group for each variable. These data showed that the proportion of verified disease was not statistically significant between groups except for the category of enlarged liver which showed a higher confirmation rate in the Comparison group. Thus, over-reporting or symptom/disease misclassification by the participants was not a function of group membership.

TABLE 13-1.

Number of Other Liver Conditions Reported
by Study Participants at Followup by Group
(Verified by Medical Record Review)

ICD* Code (Meaning)	Group	
	Ranch Hand	Comparison
5713 (Alcoholic Liver Damage)	1	1
57420 (Calculus of Gallbladder without Mention of Cholecystitis)	0	1
7891 (Hepatomegaly)	1	1
7904/7905 (Enzyme Elevation)	3	0
7948 (Abnormal Liver Scan)	1	1
E9426 (Adverse Effect of Drug)	0	1
M81406 (Adenocarcinoma)	0	1
Total	6	6

*ICD = International Classification of Diseases.

TABLE 13-2.

Unadjusted Analyses for Baseline and Interval History of Liver Disease by Group (Verified by Medical Record Review)

		Group					
		Ranch Hand		Comparison			
Disease	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Hepatitis (Viral and Alcoholic)	n	1,016		1,293			
	Yes	37	3.6	43	3.3	1.10 (0.70,1.72)	0.731
	No	979	96.4	1,250	96.7		
Jaundice	n	1,016		1,293			
	Yes	20	2.0	28	2.2	0.91 (0.51,1.62)	0.771
	No	996	98.0	1,265	97.8		
Cirrhosis	n	1,016		1,293			
	Yes	3	0.5	2	0.2	1.91 (0.32,11.46)	0.660
	No	1,013	99.5	1,291	99.8		
Enlarged Liver	n	1,016		1,293			
	Yes	17	1.7	24	1.9	0.90 (0.48,1.68)	0.874
	No	999	98.3	1,269	98.1		
Miscel-laneous Liver Disorders	n	1,016		1,293			
	Yes	17	1.7	13	1.0	1.68 (0.81,3.47)	0.195
	No	999	98.3	1,280	99.0		

TABLE 13-3.

Medical Record Verification of Reported Liver Symptoms and Diseases by Group (Baseline and Interval Questionnaires Combined)

Variable	Verification Status	Group		p-Value
		Ranch Hand	Comparison	
Hepatitis	Number Reported	47	53	
	Medical Records Reviewed	44	48	
	Medical Records Pending or Not Released	3	5	
	Number Verified	37	43	
	Percent Verified	78.7	81.1	0.806
Jaundice	Number Reported	43	59	
	Medical Records Reviewed	23	35	
	Medical Records Pending or Not Released	20	24	
	Number Verified	20	28	
	Percent Verified	46.5	47.5	0.999
Cirrhosis	Number Reported	7	3	
	Medical Records Reviewed	5	3	
	Medical Records Pending or Not Released	2	0	
	Number Verified	3	2	
	Percent Verified	42.9	66.7	0.999
Enlarged Liver	Number Reported	30	29	
	Medical Records Reviewed	29	29	
	Medical Records Pending or Not Released	1	0	
	Number Verified	17	24	
	Percent Verified	56.7	82.8	0.047
Miscellaneous Liver Disorders	Number Reported	21	14	
	Medical Records Reviewed	20	14	
	Medical Records Pending or Not Released	1	0	
	Number Verified	17	13	
	Percent Verified	94.4	92.9	0.627

Peptic Ulcer Diseases

The primary purpose of these analyses was to compare the ulcer disease experience of the Ranch Hand and Comparison groups. Since blood type has been reported to affect the incidence of peptic ulcer disease, blood type was used as a covariate in these analyses. The military medical and personnel records of the 2,309 study participants were reviewed to determine the blood type as recorded in these sources. The distribution of blood types in the two groups is shown in Table 13-4.

TABLE 13-4.

Unadjusted Analysis of Blood Type by Group

	Blood Type								
	O		A		B		AB		
Group	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total*
Ranch Hand	378	45.4	334	40.1	87	10.5	33	4.0	832
Comparison	504	46.4	425	39.1	125	11.5	33	3.0	1,087
				p=0.60					

*184 Ranch Hands and 206 Comparisons missing from blood type analysis.

The blood type distribution was not significantly different in the two groups (p=0.60), and was similar to the distribution of blood types in the general U.S. white male population (p=0.57).

Both physical examination diagnoses and questionnare responses to questions concerning ulcers were used as sources of data on the occurrence of ulcer disease. A total of 58 participants was diagnosed as having ulcer disease at the time of the examination; however, 13 had to be deleted from the analyses of physical examination data and 15 from the analyses of questionnaires due to missing data on blood type. On questionnaires, 42 reported currently having ulcers and an additional 126 reported having had ulcers in the past. These data are summarized in Table 13-5.

A three-factor log-linear analysis (group, ulcer, blood type) of data from the physical examination showed a significant three-factor interaction, with the Ranch Hand rate being higher in blood types AB and O, and lower for types A and B (p=0.03). Stratified analyses of each blood type were conducted and did not reveal any statistically significant group differences. These data are shown in Table 13-6.

TABLE 13-5.

Frequency of Diagnosed and Reported Ulcer Disease by Group

		Group				
		Ranch Hand		Comparison		
Variable	Statistic	Number	Percent	Number	Percent	Total
Diagnosed Disease	n	832		1,087		1,919
(Physical	Yes	19	2.3	26	2.4	45
Examination Data)	No	813	97.7	1,061	97.6	1,874
Reported Disease	n	832		1,085		1,917
(Questionnaire	Current	22	2.6	20	1.8	44
Data)	Past	53	6.4	73	6.7	126
	None	757	91.0	992	91.4	1,749

A three-factor log-linear analysis of questionnaire data was also performed. This analysis looked at current and past history of ulcer disease. No significant group differences or multifactor interactions were seen, with all p-values being greater than 0.10.

These analyses demonstrated overall group equivalence within the Ranch Hand and Comparison groups with respect to blood type and present and past ulcer disease.

Mortality Count Data

Linkage of digestive system mortality to observed historic or examination morbidity has not been explored in this report; the linkage process, with the use of the Comparison replacement strategy, remains an open research issue. From a broader perspective, however, review of mortality count data in conjunction with current morbidity data may be useful in identifying disease pattern(s) with respect to group membership, organ-specific disease, and important covariates. For these purposes, the latest mortality count data (as of 31 December 1985) are summarized in Table 13-7.

These data showed a large mortality contribution (approximately 50%)from liver disease in both groups and a relative excess in Ranch Hands as contrasted to Comparisons. For malignant neoplasms, there was a relative excess in the Comparison group. There is also the suggestion that alcohol is an important risk factor. The relative excess of malignant neoplasms in the Comparison group is also striking. Overall, the slight excess of digestive system mortality in the Ranch Hands and the differences in distribution of

TABLE 13-6.

Unadjusted Analyses of Peptic Ulcer Disease by Blood Type by Group

		Group					
		Ranch Hand		Comparison			
Blood Type	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
O	n	378		504			
	Yes	13	3.4	11	2.2	1.60 (0.70,3.60)	0.37
	No	365	96.6	493	97.8		
A	n	334		425			
	Yes	4	1.2	12	2.8	0.42 (0.14,1.29)	0.21
	No	330	98.8	413	97.2		
B	n	87		125			
	Yes	0	0.0	3	2.4	--	0.27[a]
	No	87	100.0	122	97.6		
AB	n	33		33			
	Yes	2	6.1	0	0.0	--	0.49[a]
	No	31	93.9	33	100.0		

--Estimated relative risk and confidence interval not calculated due to zero count in a cell.

[a]Fisher's exact test.

TABLE 13-7.

Frequency of Digestive System Mortality by Group

ICD Code	Deaths, by Group	
	Ranch Hand	1:5 Comparison
Pancreatitis (5770)	1	2
Alcoholic cirrhosis (5712)	0	6
Nonalcoholic cirrhosis (5715)	3	5
Nonalcoholic fatty liver (5718)	0	1
Chronic liver disease (5728)	1	1
Alcoholic liver disease (5711)	1	0
Duodenal ulcer (5325)	0	1
Malignant neoplasm (150-159)	2	15
Total	8	31

deaths by cause in the two groups raise the issue of competing mortality. Interpretation of the analyses in this report of hepatic function and liver disease, with alcohol consumption taken into account, should be reviewed in the light of these mortality data.

Physical Examination Data

Gastrointestinal dysfunction was not a major focus of the physical examination except for a comprehensive biochemical profile of the liver. Consequently, only data on hepatomegaly were analyzed, and results of the analysis are shown in Table 13-8.

The analysis showed a marginally significant excess (eight cases versus three) of hepatomegaly in the Ranch Hands ($p=0.069$). These results were in relative contrast to the Baseline examination findings of 1.56 percent and 0.78 percent in the Ranch Hand and Comparison groups, respectively ($p=0.138$), in the sense that fewer abnormalities were detected at the followup, although at both examinations the difference favored the Comparisons.

The group data for hepatomegaly were pooled and compared to the covariates of age, race, occupation, current alcohol use (one or less drinks per day, more than one to four drinks per day, and more than four drinks per day), lifetime exposure to industrial chemicals, and lifetime exposure to degreasing chemicals. Only age and occupation showed significant associations with hepatomegaly ($p=0.018$, $p=0.026$, respectively). Because of sparse data, an adjusted analysis was not conducted.

General Laboratory Examination Data

As in the Baseline Report, the followup examination emphasized evaluation of laboratory data, particularly for hepatic function. Thus, this

TABLE 13-8.

Unadjusted Analysis of Enlarged Livers
Diagnosed at Physical Examination by Group*

	Enlarged Liver					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	8	0.8	1,002	99.2	1,010	0.069
Comparison	3	0.2	1,287	99.8	1,290	

*Excludes participants with positive HB_sAg.

section reports on nine laboratory tests of hepatic function and on two tests reflecting porphyrin metabolism. Normal ranges for these 11 variables as determined by the SCRF and the Mayo Clinic Laboratories are presented in Table 13-9. Only values greater than the normal range were considered important in the assessment of dysfunction.

Analyses of the nine hepatic variables were adjusted for the covariates of age, race, occupation (OCC), current alcohol use (ALC), days of exposure to industrial chemicals (IC), and days of exposure to degreasing chemicals (DC). For the two porphyrin analyses, blood urea nitrogen was used as a covariate. Because the hepatic test variables encompass acute to chronic effects, there was no "ideal" alcohol covariate (e.g., drink-years, current alcohol consumption in drinks per day).

The covariate alcohol use was obtained from questionnaire data, centering on daily alcohol consumption (beer, wine, liquor) for those participants who reported drinking at least one drink in the 2 weeks preceding the examination. Thus, the alcohol covariate measures recent drinking intensity and may be more useful in adjustment of acute variables (e.g., GGTP, SGPT) than variables related to chronic liver dysfunction (e.g., bilirubin determinations, alkaline phosphatase).

Exposure to industrial chemicals and degreasing chemicals was measured in cumulative days of unprotected exposure, and was derived from the 1982 and 1985 questionnaires. These data, therefore, represent lifetime exposure.

Exclusion categories consisted of fever (over 100 degrees Fahrenheit) and positive HB_sAg tests, because of the known effects of these conditions on liver function tests. Three participants (two Ranch Hands, one Comparison) were excluded because of fever, and eight (five Ranch Hands, three Comparisons) because of a positive HB_sAg test (seven positive, one missing). In addition, due to missing alcohol data, nine other individuals (six Ranch Hands, three Comparisons) were deleted from the analyses when current alcohol use was found to be a significant covariate.

TABLE 13-9.

Laboratory Norms for Nine Hepatic Function Variables and Two Porphyrin Determinations

Variable	Unit	SCRF Normal	SCRF Abnormal
SGOT	U/L	27-47	≥48
SGPT	U/L	3-36	≥37
GGTP	U/L	15-85	≥86
Alkaline Phosphatase	U/L	50-136	≥137
Total Bilirubin	mg/dl	≤1.5	>1.5
Direct Bilirubin	mg/dl	≤0.36	≥0.37
LDH	U/L	100-190	≥191
Cholesterol[a]	mg/dl	≤260	≥261
Triglycerides[a]	mg/dl	≤320	≥321
Uroporphyrin[b]	mg/24 hrs	≤46	≥47
Coproporphyrin[b]	mg/24 hrs	≤96	≥97

[a] SCRF provides age-dependent normal ranges; these values represent the maximum normal limits for those older than 40.

[b] Performed at the Mayo Clinic.

Statistical Analyses

The nine dependent variables from the hepatic battery were subjected to three types of basic analyses: (1) a continuous dependent variable adjusted by continuous covariates (CC), (2) a continuous dependent variable adjusted by discrete covariates (CD), and (3) a discrete (categorical) dependent variable adjusted by discrete covariates (DD), except for current alcohol use, which was left as a continuous variable for model-fitting and power purposes. General linear models (SAS®) were used for the CC and CD analyses, and BMDP®-LR was used for the DD analyses.

As noted in Chapter 7, Statistical Methods, all adjustments were carried out with the simplest model, including all significant covariates and two- and three-way interactions. The log transformation was used for the nine hepatic variables and for uroporphyrin, while a square root transformation was employed for the coproporphyrin variable. Since some direct bilirubin values were 0, the value 0.10 was added prior to log transformation.

The sample sizes were sufficient to detect a 1.93-fold increase in the frequency of abnormal values for alkaline phosphatase and a 1.42-fold increase in the frequency of abnormal values for SGPT, using a (two-sided) α-level of 0.05 and power 0.80. Further, the sample sizes were sufficient to detect a 0.7 percent mean shift in alkaline phosphatase, a 1.8 percent mean shift in SGPT, and a 2.8 percent mean shift in uroporphyrin values.

The results of the analyses on the 11 dependent variables are presented in the following summary tables (Tables 13-10 through 13-12), followed by descriptive narrative text. The summary tables are in the following logical order: unadjusted results, covariate tests of association, and adjusted results. Tables K-1 and K-2 of Appendix K summarize interactions from the statistical analyses. All analytic information on any given variable can be obtained by scanning the summary tables.

The following discussion condenses the key information on each dependent variable. Group-by-covariate interactions are narratively presented. The variables are organized in the same order as given in the tables.

Serum Glutamic-Oxaloacetic Transaminase (SGOT)

The unadjusted continuous (group means) and categorical (percent abnormalities) tests showed no statistically significant differences between groups ($p=0.298$ and $p=0.999$, respectively).

Tests of association with the covariates using pooled group categorical data demonstrated the significant effect of race (a higher percentage of abnormalities in Blacks than nonblacks, 13.5% versus 7.6%; $p<0.022$) and current alcohol use (21.2% abnormal values associated with more than four drinks per day, 9.0% abnormals for more than one to four drinks per day, and 5.8% for one or less drinks per day; $p<0.001$). Similarly, the mean SGOT levels differed significantly between races ($p<0.001$) and by current alcohol use ($p<0.001$).

The CC adjusted model showed no significant group differences ($p=0.309$). Significant covariates were race, an interaction of current alcohol use-by-degreasing chemicals, and an interaction of current alcohol use-by-age (all

TABLE 13-10.

Unadjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
SGOT	n	1,009	1,289		
	Mean	33.5	33.0		0.298
	95% C.I.	(32.8,34.1)	(32.5,33.5)		
	Number/%				
	Normal	929 92.1%	1,187 92.1%	1.00 (0.74,1.36)	0.999
	High	80 7.9%	102 7.9%		
SGPT	n	1,009	1,289		
	Mean	21.6	22.5		0.051
	95% C.I.	(20.9,22.3)	(21.9,23.1)		
	Number/%				
	Normal	872 86.4%	1,102 85.5%	0.93 (0.73,1.17)	0.546
	High	137 13.6%	187 14.5%		
GGTP	n	1,009	1,289		
	Mean	32.8	32.4		0.632
	95% C.I.	(31.4,34.3)	(31.2,33.6)		
	Number/%				
	Normal	919 91.1%	1,172 90.9%	0.98 (0.74,1.31)	0.942
	High	90 8.9%	117 9.1%		
Alkaline Phospha-tase	n	1,009	1,289		
	Mean	91.8	89.3		0.009
	95% C.I.	(90.4,93.3)	(88.1,90.6)		
	Number/%				
	Normal	953 94.5%	1,236 95.9%	1.37 (0.93,2.01)	0.114
	High	56 5.6%	53 4.1%		
Total Bilirubin	n	1,009	1,289		
	Mean	0.74	0.75		0.576
	95% C.I.	(0.73,0.76)	(0.74,0.76)		
	Number/%				
	Normal	982 97.3%	1,250 97.0%	0.88 (0.54,1.45)	0.706
	High	27 2.7%	39 3.0%		

TABLE 13-10. (continued)

Unadjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Direct Bilirubin	n	1,009	1,289		
	Mean	0.18	0.18		0.981
	95% C.I.	(0.17,0.18)	(0.17,0.18)		
	Number/%				
	Normal	971 96.2%	1,246 96.7%	1.13 (0.73,1.77)	0.649
	High	38 3.8%	43 3.3%		
LDH	n	1,009	1,289		
	Mean	123.5	123.9		0.655
	95% C.I.	(122.2,124.8)	(122.7,125.2)		
	Number/%				
	Normal	999 99.0%	1,272 98.7%	0.75 (0.34,1.64)	0.560
	High	10 1.0%	17 1.3%		
Cholesterol	n	1,009	1,289		
	Mean	214.3	215.0		0.688
	95% C.I.	(211.8,216.8)	(212.8,217.2)		
	Number/%				
	Normal	863 85.5%	1,082 83.9%	0.88 (0.70,1.11)	0.322
	High	146 14.5%	207 16.1%		
Triglycerides	n	1,009	1,289		
	Mean	118.5	117.3		0.719
	95% C.I.	(113.8,123.3)	(113.4,121.4)		
	Number/%				
	Normal	941 93.3%	1,210 93.9%	1.11 (0.79,1.55)	0.549
	High	68 6.7%	79 6.1%		
Uroporphyrin	n	1,006	1,286		
	Mean	16.9	17.9		0.048
	95% C.I.	(16.2,17.7)	(17.3,18.6)		
Copropor-phyrin	n	1,008	1,287		
	Mean	119.1	115.6		0.081
	95% C.I.	(116.2,122.0)	(113.0,118.2)		

TABLE 13-11.

Association Between Nine Hepatic Function Variables and Two Porphyrin Determinations and Six Covariates in the Combined Ranch Hand and Comparison Groups

Variable	Analysis*	Age	Race	Occupation	Alcohol	Industrial Chemicals	Degreasing Chemicals
SGOT	C	NS	<0.001	NS	<0.001	NS	NS
	D	NS	0.022	NS	<0.001	NS	NS
SGPT	C	<0.001	NS	NS	<0.001	NS	0.017
	D	0.001	NS	NS	<0.001	NS	NS
GGTP	C	0.012	<0.001	0.032	<0.001	NS	NS
	D	NS	0.021	NS	<0.001	NS	NS
Alkaline Phosphatase	C	NS	NS	<0.001	<0.001[a]	<0.001	0.010
	D	NS	NS	0.003	NS*[a]	0.030	NS*
Total Bilirubin	C	NS*	NS	0.011	0.008	NS	NS
	D	NS	<0.001	NS	NS	NS	NS
Direct Bilirubin	C	NS	NS*	NS	<0.001	NS	NS
	D	NS	0.015	NS	NS	NS	NS
LDH	C	<0.001	0.006	NS	NS	NS	NS
	D	NS	NS	NS	NS	NS	NS
Cholesterol	C	<0.001	NS	0.002	<0.001	NS	NS
	D	0.010	NS	0.008	0.018	NS	NS
Triglycerides	C	<0.001	<0.001	0.013	0.030	NS*	0.019
	D	NS	0.031	NS	NS	NS*	NS
Uroporphyrins	C	NS	NS	NS	NS	NS	NS
Coproporphyrins	C	0.003	NS	NS	<0.001	NS	NS

*Continuous (C)/Discrete (D).

NS: Not significant ($p>0.10$)

NS*: Borderline significant ($.05<p\leq 0.10$).

[a]Wine consumption.

TABLE 13-12.

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
SGOT	CC	n	1,003	1,286	—	0.309	ALC*DC(p<0.001) AGE*ALC(p<0.001) RACE(p<0.001)
		Adj. Mean	34.8	34.3			
		95% C.I.	(33.8,35.7)	(33.4,35.3)			
	CD	n	1,003	1,286	—	****	GRP*ALC(p=0.048) ALC*IC(p=0.008) DC(p=0.019), RACE(p<0.001)
		Adj. Mean	****	****			
		95% C.I.	****	****			
	DD	n	1,003	1,286	1.03 (0.75,1.41)	0.868	AGE*ALC(p<0.001) OCC*ALC(p<0.001) RACE (p=0.026)
SGPT	CC	n	1,003	1,286	—	0.048	ALC*DC(p=0.008), RACE*DC(p=0.015) AGE*ALC(p=0.001), RACE*IC(p=0.017)
		Adj. Mean	21.4	22.2			
		95% C.I.	(20.4,22.4)	(21.3, 23.3)			
	CD	n	1,003	1,286	—	0.029	ALC*DC(p=0.032), AGE*ALC(p=0.022) OCC*AGE(p=0.026), IC(p=0.049)
		Adj. Mean	21.9	22.9			
		95% C.I.	(20.2,23.8)	(21.1,24.8)			
	DD	n	1,003	1,286	0.93 (0.73,1.18)	0.531	AGE*ALC(p=0.004)
GGTP	CC	n	1,003	1,286	—	0.575	AGE*ALC(p<0.001),RACE*IC(p=0.011) ALC*DC(p<0.001), AGE*DC(p=0.009)
		Adj. Mean	37.5	37.0			
		95% C.I.	(35.2,40.1)	(34.7,39.3)			
	CD	n	1,003	1,286	—	0.668	AGE*ALC(p=0.023), OCC*ALC(p=0.044) RACE(p<0.001)
		Adj. Mean	44.1	43.6			
		95% C.I.	(40.0,48.6)	(39.6,47.9)			
	DD	n	1,003	1,286	1.00 (0.74,1.34)	0.971	AGE*ALC(p<0.001), RACE(p=0.016)

TABLE 13-12. (continued)

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
	CC	n	1,003	1,285			AGE*IC(p=0.010), RACE*IC(p=0.007)
		Adj. Mean	91.6	89.1	—	0.008	OCC(p<0.001), WINE(p<0.001)
		95% C.I.	(89.4,93.9)	(87.0,91.2)			
Alkaline Phosphatase	CD	n	1,003	1,285			GRP*IC(p=0.011), AGE*IC(p=0.019)
		Adj. Mean	****	****	—	****	RACE*IC(p=0.002), OCC(p<0.001)
		95% C.I.	****	****			WINE (p<0.001)
	DD	n	1,003	1,285	1.44 (0.97,2.13)	0.070	WINE*DC(p=0.006), AGE*IC(p=0.005)
							RACE*IC(p=0.004), OCC*IC(p=0.016)
	CC	n	1,003	1,286			AGE*DC(p=0.039)
		Adj. Mean	0.78	0.78	—	0.599	RACE*ALC(p=0.007)
		95% C.I.	(0.75,0.81)	(0.75,0.81)			RACE*OCC(p=0.001)
Total Bilirubin	CD	n	1,003	1,286			RACE*ALC(p=0.004)
		Adj. Mean	0.83	0.83	—	0.598	OCC*ALC(p=0.034)
		95% C.I.	(0.79,0.87)	(0.80,0.87)			OCC*RACE(p=0.002)
	DD	n	1,009	1,289	0.89 (0.54,1.47)	0.648	RACE(p<0.001)
	CC	n	1,003	1,286			
		Adj. Mean	0.18	0.18	—	0.972	RACE*ALC(p=0.025)
		95% C.I.	(0.17,0.20)	(0.17,0.19)			
Direct Bilirubin	CD	n	1,003	1,286			DC*IC(p=0.025), ALC*DC(p=0.012)
		Adj. Mean	0.21	0.20	—	0.830	RACE*ALC(p=0.019), OCC*ALC(p=0.002)
		95% C.I.	(0.19,0.22)	(0.19,0.22)			
	DD	n	1,003	1,286	****	****	GRP*IC(p=0.012), RACE(p=0.014)
							ALC(p=0.026)

TABLE 13-12. (continued)

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Realtive Risk (95% C.I.)	p-Value	Covariate Remarks*
	CC	n	1,003	1,286			GRP*AGE(p=0.018), OCC*IC(p=0.014)
		Adj. Mean	****	****	—	****	RACE*IC(p=0.024)
		95% C.I.	****	****			
LDH	CD	n	1,003	1,286			RACE(p<0.001), AGE(p<0.001)
		Adj. Mean	130.0	130.5	—	0.671	DC(p=0.016)
		95% C.I.	(127.3,132.8)	(127.8,133.1)			
	DD	n	1,009	1,289	0.75 (0.34,1.64)	0.560	
	CC	n	1,003	1,286			RACE*DC(p=0.021), RACE*OCC(p=0.005)
		Adj. Mean	219.5	220.4	—	0.604	IC(p=0.043), ALC(p<0.001)
		95% C.I.	(214.5,224.7)	(215.5,225.4)			AGE(p<0.001)
Cholesterol	CD	n	1,003	1,286			RACE*OCC(p=0.027), ALC(p<0.001)
		Adj. Mean	223.8	224.9	—	0.548	AGE(p<0.001)
		95% C.I.	(217.7,230.1)	(218.9,231.0)			
	DD	n	1,003	1,286	0.85 (0.68,1.08)	0.181	RACE*ALC(p=0.012), AGE(p=0.029)
							OCC(p=0.039)
	CC	n	1,003	1,286			GRP*AGE(p=0.015), ALC*DC(p=0.005)
		Adj. Mean	****	****	—	****	RACE*ALC(p=0.031), OCC(p<0.001)
		95% C.I.	****	****			
Triglycerides	CD	n	1,003	1,286			OCC(p<0.001), RACE(p<0.001)
		Adj. Mean	112.5	112.1	—	0.905	AGE(p<0.001), ALC(p=0.038)
		95% C.I.	(103.7,121.9)	(103.7,121.2)			
	DD	n	1,009	1,289	****	****	GRP*OCC(p=0.027), RACE (p=0.026)
							IC(p=0.038)

TABLE 13-12. (continued)

Adjusted Continuous and Categorical Analyses for Hepatic Function Variables and Two Porphyrin Determinations by Group

Variable	Analysis	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Uroporphyrin	CC	n	1,000	1,283			GRP*BUN(p=0.015)
		Adj. Mean	****	****	—	****	DC*OCC(p=0.005)
		95% C.I.	****	****			ALC(p=0.026)
Coproporphyrin	CC	n	1,002	1,284			AGE*ALC(p=0.003)
		Adj. Mean	119.3	115.7	—	0.065	BUN(p<0.001)
		95% C.I.	(116.4,122.2)	(113.2,118.2)			

*Abbreviations:
GRP: group
OCC: occupation
ALC: current alcohol use
WINE: wine consumption
DC: exposure to degreasing chemicals
IC: exposure to industrial chemicals
BUN: blood urea nitrogen

— No relative risk or confidence interval given for continuous analyses.
**** Group-by-covariate interaction—adjusted mean/relative risk, confidence interval, and p-value are not presented.

with p<0.001). The CD analysis revealed a significant group (GRP)-by-current alcohol use interaction (p=0.048), precluding a direct group contrast. Exploration of the interaction disclosed that the Ranch Hands had a significantly higher (p=0.010) mean SGOT for the more than one to four drinks per day category, whereas there were no significant group differences for the one or less drinks per day or more than four drinks per day categories (see Table K-1 of Appendix K). Other significant covariate effects included degreasing chemicals (p=0.019), race (p<0.001), and a current alcohol use-by-industrial chemical (IC) interaction (p=0.008). The DD SGOT analysis showed no significant group differences (p=0.868). Covariates making significant contributions were race (p=0.026), an age-by-current alcohol use interaction (p<0.001), and an occupation (OCC)-by-current alcohol use interaction (p<0.001).

Serum Glutamic-Pyruvic Transaminase (SGPT)

The unadjusted categorical analysis was not significant (p=0.546), but the comparison of group means showed a borderline significant result, with the Comparisons having a higher mean SGPT than the Ranch Hands (p=0.051).

Covariate associations with the pooled categorical Ranch Hand and Comparison group data showed an inverse relationship (p=0.001) between SGPT levels and age, with 17.1 percent abnormalities for those born in or after 1942, 12.3 percent for those born between 1923 and 1941, and 8.1 percent for those born in or before 1922. The relationship with current alcohol use was also profound (p<0.001), with 23.4 percent abnormals noted for more than four drinks per day, 15.3 percent abnormals for more than one to four drinks per day, and 12.4 percent for one or less drinks per day. The direction and magnitude of the covariate effects of age and alcohol were quite similar for the tests of association with the mean SGPT level of both groups (p<0.001 for both covariates).

No significant group interactions were detected in either the discrete or the continuous analyses. The CC-adjusted analysis yielded a significant group difference, with the Comparisons having a higher group mean than the Ranch Hands (p=0.048). The model was adjusted by the interactions of current alcohol use-by-degreasing chemicals (p=0.008), current alcohol use-by-age (p=0.001), race-by-degreasing chemicals (p=0.015), and race-by-industrial chemicals (p=0.017). The CD model also showed a significantly elevated mean SGPT in the Comparison group (p=0.029). The analysis was adjusted for exposure to industrial chemicals (p=0.049), and the interactions of age-by-occupation (p=0.026), age-by-current alcohol use (p=0.022), and current alcohol use-by-degreasing chemicals (p=0.032). A borderline significant interaction (p=0.0505) between group and current alcohol use was found, but because of modeling strategy, this interaction was not included in the final model. (This interaction is explored further in Table K-1 in Appendix K, however.) The DD-adjusted analysis, like the unadjusted discrete analysis, disclosed a nonsignificant group difference (p=0.531). The model was adjusted for an age-by-current alcohol use interaction (p=0.004).

Gamma-Glutamyl Transpeptidase (GGTP)

The unadjusted contrasts of both mean levels of GGTP and the frequency of abnormalities showed no significant differences between the Ranch Hand and Comparison groups (p=0.632 and p=0.942, respectively).

For discrete covariate associations, significance was noted for race, with 14.9 percent abnormals in Blacks and 8.6 percent for nonblacks ($p=0.021$), and current alcohol use, with 26.1 percent abnormals for more than four drinks per day, 10.5 percent for more than one to four drinks per day, and 6.2 percent for one or less drinks per day use ($p<0.001$). While the mean level of GGTP was similarly affected by race and current alcohol ($p<0.001$ for both covariates), it was also influenced by age (30.3 U/L for those born in or before 1922, 33.9 U/L for those born between 1923 and 1941, and 31.1 U/L for those born in or after 1942; $p=0.012$) and occupation (31.5 U/L for officers, 35.2 U/L for enlisted flyers, and 32.5 U/L for enlisted groundcrew; $p=0.032$).

Each of the three adjusted analyses consistently produced nonsignificant group differences (CC: $p=0.575$; CD: $p=0.668$; DD: $p=0.971$). None of the three models was affected by a group-by-covariate interaction. The CC analysis was adjusted by four covariate interactions: age-by-current alcohol use ($p<0.001$), race-by-industrial chemicals ($p=0.011$), current alcohol use-by-degreasing chemicals ($p<0.001$), and age-by-degreasing chemicals ($p=0.009$). The CD model was adjusted by race ($p<0.001$), by an age-by-current alcohol use interaction ($p=0.023$), and by an occupation-by-current alcohol use interaction ($p=0.044$). The DD analysis was adjusted by race ($p=0.016$) and by an age-by-current alcohol use interaction ($p<0.001$).

Alkaline Phosphatase

The analysis of group mean values showed a significantly higher ($p=0.009$) Ranch Hand mean (91.8 U/L) than that observed in the Comparison group (89.3 U/L). The unadjusted categorical analysis revealed a higher percentage of Ranch Hand abnormalities (5.6%) than Comparison abnormalities (4.1%), but this difference was not significant (Est. RR=1.37, 95% C.I.: [0.93,2.01], $p=0.114$).

With pooled group data, significant covariate associations were found between the proportion of abnormal values and occupation ($p=0.003$), industrial chemicals ($p=0.030$), and marginally significant associations with wine consumption ($p=0.056$) and degreasing chemicals ($p=0.091$). The mean value of alkaline phosphatase depended significantly on all four of these covariates.

The CC-adjusted analysis also showed a significantly higher mean value of alkaline phosphatase in the Ranch Hand group ($p=0.008$). The model was adjusted by the significant covariates of wine consumption (WINE) ($p<0.001$), occupation ($p<0.001$), and the interactions of age-by-industrial chemicals ($p=0.010$) and race-by-industrial chemicals ($p=0.007$). Wine consumption was used as a covariate instead of alcohol intensity since wine showed a very strong negative association with alkaline phosphatase. This effect masked a very weak positive association between beer or liquor consumption and alkaline phosphatase.

In the CD model a significant group-by-industrial chemicals interaction was found ($p=0.011$). Specifically, in those individuals exposed to industrial chemicals, the Ranch Hands had a significantly higher mean value than the Comparisons ($p<0.001$), whereas in the unexposed stratum, the mean values were not significantly different between groups ($p=0.973$; see Table K-1 of Appendix K). The CD analysis was also adjusted by wine consumption ($p<0.001$), occupation ($p<0.001$), and the interactions of age-by-industrial chemicals ($p=0.019$) and race-by-industrial chemicals ($p=0.002$).

The DD model revealed a marginally significant group difference (Adj. RR: 1.44, 95% C.I.: [0.97,2.13], p=0.070) following adjustment by four significant interactions of wine-by-degreasing chemicals (p=0.006), age-by-industrial chemicals (p=0.005), race-by-industrial chemicals (p=0.004), and occupation-by-industrial chemicals (p=0.016).

Total Bilirubin

Both the continuous and categorical unadjusted analyses found no significant differences in total bilirubin values between groups (p=0.576 and p=0.706, respectively).

The covariate associations for both groups showed a significant effect of race (8.5% abnormal in Blacks versus 2.5% in nonblacks; p<0.001). Significant differences in mean total bilirubin levels were found between occupational groups (0.76 mg/dl for officers, 0.72 mg/dl for enlisted flyers, and 0.75 mg/dl for enlisted groundcrew; p=0.011), and with increasing levels of current alcohol use (0.80 for more than four drinks per day, 0.75 for more than one to four drinks per day, and 0.74 for one or less drinks per day; p=0.008). Further, increasing levels of total bilirubin were marginally associated with age (p=0.093).

The CC model, adjusted for the interactions of age-by-degreasing chemicals (p=0.039), race-by-current alcohol use (p=0.007), and race-by-occupation (p=0.001), revealed no significant differences in total bilirubin means between groups (p=0.599). Similarly, the CD analysis found no difference between group means (p=0.598) after adjustment for the interactions of race-by-current alcohol use (p=0.004), occupation-by-current alcohol use (p=0.034), and occupation by race (p=0.002). The DD model, adjusted for race (p<0.001), also failed to detect significant group differences in the proportion of total bilirubin abnormalities (p=0.648).

Direct Bilirubin

Neither the continuous nor the categorical unadjusted tests disclosed significant differences between the Ranch Hand and Comparison groups (p=0.981 and p=0.649, respectively).

A covariate association with the categorical data combined from both groups was noted for race, with 7.8 percent abnormalities found in Blacks as contrasted to 3.3 percent in nonblacks (p=0.015). There was a significant association between mean values of direct bilirubin and current alcohol use (0.21 mg/dl, 0.17 mg/dl, and 0.17 mg/dl for more than four drinks per day, more than one to four drinks per day, and one or less drinks per day, respectively; p<0.001) and a marginally significant difference due to race (0.20 mg/dl for Blacks versus 0.18 mg/dl for nonblacks; p=0.059).

For both the CC and CD analyses, no significant group differences were found (p=0.972 and p=0.830, respectively). The CC model was adjusted for a race-by-current alcohol use interaction (p=0.025), and the CD model was adjusted for the significant interactions of race-by-current alcohol use (p=0.019), occupation-by-current alcohol use (p=0.002), current alcohol use-by-degreasing chemicals (p=0.012), and degreasing chemicals-by-industrial chemicals (p=0.025). The DD analysis revealed a group-by-industrial chemical

exposure interaction (p=0.012). For participants exposed to industrial chemicals, the Ranch Hands had a higher proportion with abnormal values than the Comparisons (5.3% abnormal versus 2.9%, respectively; p=0.035), whereas there was no group difference for participants not exposed to industrial chemicals (p=0.144). Each stratum of the interaction was adjusted for race (p=0.014) and current alcohol use (p=0.026). The biological relevance of this interaction is unclear at this time.

Lactic Dehydrogenase (LDH)

No significant differences were found between the groups, either in the proportion of abnormal values (p=0.560) or in the mean levels of LDH (p=0.655). Significant effects for age (121.6 U/L, 124.6 U/L, 135.3 U/L for those born in or after 1942, between 1923 and 1941, and in or before 1922, respectively; p<0.001) and race (129.5 U/L for Blacks versus 123.4 U/L for nonblacks; p=0.006) were found in the tests of mean LDH levels.

The CC analysis revealed a group-by-age interaction (p=0.018), although no significant adjusted group differences were found for any of the three age strata. The model was also adjusted for the significant interactions of occupation-by-exposure to industrial chemicals (p=0.014) and race by exposure to industrial chemicals (p=0.024). The CD model revealed no significant group differences after adjustment by age (p<0.001), race (p<0.001), and degreasing chemicals (p=0.016). Similarly, the DD analysis found no significant group differences, and no covariates made a significant contribution to the model.

Cholesterol

No significant differences were found between groups, either in the proportion of abnormal cholesterol levels (p=0.322) or in mean values of cholesterol (p=0.688) by unadjusted tests. However, in contrast, analysis of the Ranch Hand group versus the Original Comparisons (see Table K-9 of Appendix K) showed that the Comparisons had a significantly higher proportion of abnormal levels than the Ranch Hands (18.3% versus 14.5%, respectively; Est. RR: 0.76, 95% C.I.: [0.60,0.96], p=0.023). This observation was also found at Baseline. Significant covariate associations were noted between the proportion of participants with abnormally high cholesterol levels and age (12.7% for those born in or after 1942, 17.2% for those born between 1923 and 1941, and 18.4% for those born in or before 1922; p=0.010), occupation (14.9% for officers, 20.5% for enlisted flyers, and 13.9% for enlisted groundcrew; p=0.008), and current alcohol use (14.1% for one or less drinks per day, 16.4% for more than one to four drinks per day, and 21.7% for more than four drinks per day; p=0.018). For the associations between mean cholesterol levels and age, occupation, and current alcohol use, the significance of the covariate effects was greater than for the discrete analyses (p<0.001, p=0.002, and p<0.001, respectively).

The CC results showed no significant group difference (p=0.604). The model was adjusted by age (p<0.001), current alcohol use (p<0.001), industrial chemical exposure (p=0.043), and the race-by-degreasing chemicals (p=0.021) and race-by-occupation (p=0.005) interactions. The CD analysis was negative for significant group differences (p=0.548). The analysis included the covariate contributions made by age (p<0.001), current alcohol use

($p<0.001$), and a race-by-occupation interaction ($p=0.027$). The DD analysis also showed no significant difference between groups for adjusted proportions of participants with abnormal cholesterol levels ($p=0.181$). Contributing covariates included age ($p=0.029$), occupation ($p=0.039$), and a race-by-current alcohol use interaction ($p=0.012$). In all of the discrete cholesterol analyses, the cutpoint of 260 mg/dl was used.

Triglycerides

In the unadjusted analyses, no significant differences in the proportion of participants with abnormal triglyceride levels or in mean values were found between the Ranch Hand and Comparison groups ($p=0.549$ and $p=0.719$, respectively).

The covariate tests of association for percent abnormal triglycerides disclosed the significant effect of race (2.1% for Blacks and 6.7% for nonblacks; $p=0.031$) and a marginally significant association for industrial chemical exposure ($p=0.073$). For mean triglyceride levels, significant associations for age ($p<0.001$), race ($p<0.001$), occupation ($p=0.013$), current alcohol use ($p=0.030$), and degreasing chemicals ($p=0.019$) were noted, in addition to a marginally significant association with exposure to industrial chemicals ($p=0.077$).

The CC analysis revealed a significant group-by-age interaction ($p=0.015$), which showed a significantly elevated mean triglyceride level in Ranch Hands ($p=0.039$) born in or before 1922 as compared to similarly aged Comparisons (see Table K-1 of Appendix K). There were no significant differences for the other two age strata. A significant adjusting covariate was occupation ($p<0.001$); in addition, the current alcohol use-by-degreasing chemicals ($p=0.005$) and race-by-current alcohol use ($p=0.031$) interactions were used for adjustment. The CD-adjusted analysis found no significant group differences ($p=0.905$). The model was adjusted by age ($p<0.001$), race ($p<0.001$), occupation ($p<0.001$), and current alcohol use ($p=0.038$).

The DD analysis found a significant group-by-occupation interaction ($p=0.027$). Stratification by occupation revealed a significant increase in the proportion of abnormal triglyceride levels for Ranch Hand officers (Adj. RR: 1.77, 95% C.I.: [1.04,3.01], $p=0.035$) but no significant group differences were discerned for the enlisted flyer or enlisted groundcrew strata. The models were adjusted by race ($p=0.026$) and industrial chemical exposure ($p=0.038$). A cutpoint of 320 mg/dl was used to distinguish abnormal from normal.

Uroporphyrin

The uroporphyrin variable was analyzed only in the continuous form. The unadjusted analysis revealed a significant difference between group means (Comparisons 17.9 mg/24 hrs, Ranch Hands 16.9 mg/24 hrs; $p=0.048$).

A CC model found a significant group-by-blood urea nitrogen (BUN) interaction ($p=0.015$; see Table K-1 of Appendix K). To interpret the interaction, BUN was dichotomized at the median value of 14 mg/dl. Stratifying by BUN levels revealed a significantly greater ($p<0.001$) uroporphyrin mean for Comparisons than for Ranch Hands for BUN levels of 14 or less mg/dl and a non-significant but greater Ranch Hand mean for participants with BUN levels of

more than 14 mg/dl. The stratified model was adjusted for current alcohol use ($p=0.026$) and the occupation-by-degreasing chemicals ($p=0.005$) interaction.

Coproporphyrin

As with the uroporphyrin variable, coproporphyrin was analyzed only as a continuous variable. The unadjusted analysis revealed a borderline significant difference in the mean coproporphyrin levels (119.1 mg/24 hrs for Ranch Hands and 115.6 mg/24 hrs for Comparisons; $p=0.081$).

The covariate tests of association detected the significant effects of age ($p=0.003$) and current alcohol use ($p=<0.001$).

A CC model, adjusted by BUN ($p<0.001$) and an age-by-current alcohol use interaction ($p=0.003$) revealed a borderline significant group difference ($p=0.065$) similar to the unadjusted analysis. The adjusted coproporphyrin means were 119.3 mg/24 hrs and 115.7 mg/24 hrs for the Ranch Hands and Comparisons, respectively.

Discussion

The results from the nine hepatic and two porphyrin analyses were not totally consistent with the Baseline findings. Several analytical reasons may possibly explain some of these differences, i.e., the adjusted analyses herein used the additional covariates of age, race, and occupation (the matching variables), and all two-way covariate interactions. However, as the Baseline data were not reanalyzed with the model process and total Comparison group used in this report, the contribution of analytic technique versus a true change in hepatic status is unknown.

The Baseline Report noted a significantly lower mean cholesterol level in the Ranch Hands (opposite of an expected dioxin effect) and slight tendencies for higher GGTP and LDH values in the Ranch Hands. In this chapter, the analyses have shown equivalent group cholesterol levels, an increased SGPT mean in the Comparisons, an increased mean alkaline phosphatase in the Ranch Hands, an increased uroporphyrin mean in the Comparisons, and a borderline increased coproporphyrin mean in the Ranch Hands. The individual hepatic assay results were not suggestive of a pattern of significant hepatic damage in the Ranch Hands that might be supportive of an herbicide effect. Further, there was no consistent group-by-covariate interaction that suggests a detriment to a specific subcategory of the Ranch Hands.

For those covariates used in both the Baseline study and this followup study, the direction and magnitude of their effects were relatively consistent between the studies. However, an unexpected association between wine drinking and alkaline phosphatase lacks a plausible explanation, particularly considering the inverse relationship, i.e., increasing alkaline phosphatase levels with decreasing wine consumption. These findings suggested the association between wine and alkaline phosphatase may be due to imprecision in data collection.

None of the categorical (normal/abnormal categories) analyses was statistically significant, whereas all of the significant results were

generated by the more powerful contrasts of continuously distributed hepatic data.

Both porphyrin analyses showed group associations and are in distinct contrast to the otherwise largely negative hepatic findings. The significantly elevated uroporphyrin mean value in the Comparisons was directly opposite to that expected if dioxin-induced PCT were prevalent in the Ranch Hands. The primary biochemical defect in PCT is the reduced activity of uroporphyrinogen decarboxylase, an enzyme that metabolizes uroporphyrin. This defect leads to increased levels of uroporphyrin and coproporphyrin.

Questionnaire-Laboratory Correlations: Porphyria Cutanea Tarda

In the interval questionnaire all participants were asked whether their skin manifested "patches," excessive bruises, or sensitivity. These questions were deemed important in order to bound the maximum prevalence of cutaneous disorders compatible with a diagnosis of PCT. These historical data are given in Table 13-13.

TABLE 13-13.

Unadjusted Analysis for Interval History of Skin Bruises, Skin Patches, and Skin Sensitivity by Group

	Bruises, Patches, or Sensitivity					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	265	26.2	746	73.8	1,011	0.001
Comparison	260	20.2	1,029	79.8	1,289	

These data revealed that the Ranch Hands reported significantly more cutaneous symptoms (26.2%) than the Comparisons (20.2%). However, these data were substantially less than those reported at the Baseline in-home questionnaire, which also showed a statistically significant excess in the Ranch Hands.

To determine if the skin histories might be related to PCT, the historic data were compared to the porphyrin test results. The abnormal/normal cut-point of the coproporphyrin assays was reset to the 95th percentile because the normal range of the laboratory overclassified the proportion of abnormals. Table 13-14 gives the tabular display of both porphyrin test results by the reporting history of skin disorders.

TABLE 13-14.

Unadjusted Analyses for Porphyrin Abnormalities by Group and Skin Patch, Bruise, or Sensitivity Reported at Followup Questionnaire

Group	Skin Patch, Bruise, or Sensitivity Reported	Abnormal Porphyrin Findings for a Participant: 0 Number	0 Percent	1 Number	1 Percent	2 Number	2 Percent	Total	p-Value*
Both Groups	Yes	472	90.1	48	9.2	4	0.8	524	0.789
	No	1,593	90.2	165	9.3	9	0.5	1,767	
Ranch Hand	Yes	239	90.5	24	9.1	1	0.4	264	0.950
	No	670	90.3	70	9.4	2	0.3	742	
Comparison	Yes	233	89.6	24	9.2	3	1.2	260	0.742
	No	923	90.1	95	9.3	7	0.7	1,025	

*Chi-square test, 2 d.f.

The data from both groups combined suggest that there is no relationship between a history of cutaneous disorders and porphyrin test positivity. The group-specific data in the table also show a lack of a statistically significant association between the reporting of skin patches, bruises, or sensitivity and the presence of an abnormal porphyrin test result. However, in both the Ranch Hand and Comparison groups, participants who had abnormal tests for both uroporphyrins and coproporphyrins were more likely to have reported cutaneous disorders than participants with normal findings for both tests. Consequently, the data were retabulated, focusing only upon uroporphyrin abnormalities (absolutely required for a diagnosis of PCT) and reporting of cutaneous disorders. These data are summarized in Table 13-15.

These data suggest that the relative risk of increased uroporphyrin abnormalities for Ranch Hands is independent of whether or not a study participant reported skin patches, bruises, or sensitivities at the followup questionnaire (Breslow-Day test of homogeneity of odds ratio, p=0.791). In each instance (reported/not reported), the estimated relative risk was nonsignificant and less than 1, and in both the Ranch Hand group and the Comparison group there was a higher percentage of uroporphyrin abnormalities for participants who did not report skin patches, bruises, or sensitivity than for participants who did report these conditions.

Thus, the sequential displays of Tables 13-13 through 13-15 show excessive reporting of PCT-like cutaneous symptoms in the Ranch Hand group that was not related to test abnormalities for both uroporphyrin and coproporphyrin abnormal test results, or for uroporphyrin abnormalities alone. These analyses were consistent with the clinical observation that

TABLE 13-15.

Unadjusted Analyses for Uroporphyrin Abnormalities by Group and Skin Patch, Bruise, or Sensitivity Reported at Followup Questionnaire

Variable	Stratification	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Group: Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
		n	264		260			
	Skin Patch, Bruise, or Sensitivity Reported	Abnormal	12	4.5	12	4.6	0.98 (0.43,2.23)	0.999
		Normal	252	95.5	248	95.4		
Uroporphyrin								
		n	742		1,025			
	Skin Patch, Bruise, or Sensitivity Not Reported	Abnormal	42	5.7	66	6.4	0.89 (0.62,1.28)	0.547
		Normal	700	94.3	959	93.6		

only one differential diagnosis at the examination entertained the diagnosis of PCT. Based on all of these observations, PCT was a rare, if not non-existent, condition in the Ranch Hands.

EXPOSURE INDEX ANALYSES

Both unadjusted and adjusted exposure index analyses were carried out for the nine laboratory tests of hepatic function and the two porphyrin metabolite tests. The porphyrin variables were analyzed only as continuous variables, while the others were analyzed both as continuous variables and discretized variables. Five covariates were included in the adjusted analyses: age, race, current alcohol use, exposure to degreasing chemicals (yes/no), and exposure to industrial chemicals (yes/no). Current alcohol use was treated as a continuous variable for all adjusted analyses, and age was treated as a continuous variable for the continuous adjusted analyses. Age was trichotomized (born in or after 1942, born between 1923 and 1941, and born in or before 1922) for the discrete adjusted analyses. In addition, the covariate BUN was used in the porphyrin analyses.

For each variable, exposure level frequencies and percents are presented in Table K-3 of Appendix K along with the results of the unadjusted discrete

analyses using Pearson's chi-square test to reflect overall exposure index differences and Fisher's exact test to investigate medium versus low and high versus low exposure level contrasts. Unadjusted means for each exposure level are presented in Table K-4 of Appendix K, along with the results of the unadjusted continuous analyses (using an F-test for an overall group assessment) and t-tests to examine medium versus low and high versus low exposure index contrasts. Results of the adjusted categorical and adjusted continuous analyses are presented in Tables 13-16 and 13-17, respectively. These results are presented in the context of a main effects model containing exposure index and all five covariates. Additional adjusted continuous analyses were conducted to examine pairwise interactions involving the exposure index and the covariates. Unadjusted and adjusted results for each variable are discussed in sequence.

SGOT

Within each occupation cohort, the low exposure level had the lowest percentage of abnormalities and the lowest mean. A marginally significant overall exposure level relationship (p=0.065) was found in the unadjusted discrete analysis for the enlisted groundcrew. This association was statistically significant in the adjusted analysis (p=0.023), exhibiting a dose-response effect; medium versus low (Adj. RR: 2.14, 95% C.I.: [0.77,5.99], p=0.147) and high versus low (Adj. RR: 3.64, 95% C.I.: [1.36,9.72], p=0.010). A nonsignificant dose-response relationship was observed in the corresponding unadjusted and adjusted continuous analyses (p=0.418 and p=0.409, respectively), with unadjusted means of 32.9 U/L, 33.2 U/L, and 34.4 U/L for the low, medium, and high exposure levels, respectively. No significant results were found for enlisted flyers and officers.

SGPT

Within the enlisted groundcrew and enlisted flyer cohorts the low exposure level had the lowest percentage of abnormalities and the lowest mean value. This situation was reversed for the officers who exhibited the highest percentage of abnormal measurements and highest mean value in the low exposure categories. A significant overall result was found for enlisted flyers in the adjusted discrete analysis (p=0.036; medium versus low, Adj. RR: 6.55, 95% C.I.: [1.25,34.43], p=0.026); high versus low, Adj. RR: 4.29, 95% C.I.: [0.75,24.35], p=0.101). In the corresponding adjusted continuous analyses, a marginally significant dose-response relationship was observed (p=0.058) with adjusted means 18.1 U/L, 21.4 U/L, and 21.8 U/L for the low, medium, and high exposure levels, respectively. No significant results were found for officers or enlisted groundcrew.

GGTP

No significant or marginally significant results were found. A non-significant dose-response relationship was seen for enlisted flyers and officers in the continuous analyses but, conversely, a nonsignificant decreasing dose-response relationship was seen in the enlisted groundcrew.

TABLE 13-16.

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Medium Total	High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	129	120	Overall		0.508
					M vs. L	1.60 (0.64,3.98)	0.312
					H vs. L	1.02 (0.38,2.77)	0.963
SGOT	Enlisted Flyer	55	65	57	Overall		0.108
					M vs. L	7.79 (0.77,79.20)	0.083
					H vs. L	5.38 (0.49,59.50)	0.170
	Enlisted Groundcrew	152	160	140	Overall		0.023
					M vs. L	2.14 (0.77,5.99)	0.147
					H vs. L	3.64 (1.36,9.72)	0.010
	Officer	125	129	120	Overall		0.768
					M vs. L	0.97 (0.48,1.97)	0.933
					H vs. L	0.77 (0.37,1.64)	0.504
SGPT		Enlisted	55	65	57	Overall	0.036
	Flyer				M vs. L	6.55 (1.25,34.43)	0.026
					H vs. L	4.29 (0.75,24.35)	0.101
	Enlisted Groundcrew	152	160	140	Overall		0.457
					M vs. L	1.53 (0.77,3.01)	0.223
					H vs. L	1.18 (0.57,2.48)	0.655

TABLE 13-16. (continued)

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index Low Total	Medium Total	High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	129	120	Overall		0.987
					M vs. L	1.02 (0.38,2.72)	0.968
					H vs. L	0.94 (0.35,2.54)	0.906
GGTP	Enlisted Flyer	55	65	57	Overall		0.798
					M vs. L	1.51 (0.41,5.65)	0.536
					H vs. L	1.46 (0.37,5.78)	0.586
	Enlisted Groundcrew	152	160	140	Overall		0.760
					M vs. L	0.74 (0.34,1.64)	0.462
					H vs. L	0.89 (0.40,1.97)	0.776
	Officer	126	129	120	Overall		0.272
					M vs. L	2.44 (0.65,9.05)	0.184
					H vs. L	0.91 (0.19,4.36)	0.926
Alkaline Phosphatase	Enlisted Flyer	54	64	56	Overall		0.191
					M vs. L	4.84 (0.52,44.80)	0.165
					H vs. L	5.34 (0.58,49.06)	0.139
	Enlisted Groundcrew	153	160	141	Overall		0.431
					M vs. L	1.35 (0.50,3.59)	0.552
					H vs. L	1.82 (0.72,4.59)	0.202

TABLE 13-16. (continued)

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Total Bilirubin	Officer	125	129	120	Overall		0.851
					M vs. L	0.67 (0.10,4.51)	0.677
					H vs. L	1.10 (0.18,6.61)	0.915
	Enlisted Flyer[a]	54	65	57	--	--	--
	Enlisted Groundcrew	152	160	140	Overall		0.332
					M vs. L	0.41 (0.10,1.65)	0.208
					H vs. L	1.02 (0.32,3.23)	0.971
Direct Bilirubin	Officer	125	129	120	Overall		0.354
					M vs. L	2.69 (0.46,15.82)	0.274
					H vs. L	3.10 (0.56,17.25)	0.196
	Enlisted Flyer	55	65	57	Overall		0.466
					M vs. L	2.97 (0.48,18.38)	0.241
					H vs. L	1.79 (0.24,13.43)	0.571
	Enlisted Groundcrew	152	160	140	Overall		0.767
					M vs. L	1.61 (0.43,6.06)	0.480
					H vs. L	1.40 (0.36,5.51)	0.628

TABLE 13-16. (continued)

Adjusted Categorical Exposure Index Analyses (Main Effects Model) Results for Hepatic Function Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	125	129	120	Overall		0.107
					M vs. L	0.54 (0.27,1.09)	0.085
					H vs. L	0.50 (0.25,1.03)	0.060
Cholesterol	Enlisted Flyer	55	65	57	Overall		0.972
					M vs. L	1.02 (0.38,2.73)	0.962
					H vs. L	1.12 (0.42,3.02)	0.822
	Enlisted Groundcrew	152	160	140	Overall		0.417
					M vs. L	1.20 (0.57,2.55)	0.630
					H vs. L	1.61 (0.78,3.30)	0.194
	Officer	125	129	120	Overall		0.721
					M vs. L	0.97 (0.38,2.45)	0.946
					H vs. L	1.35 (0.55,3.32)	0.514
Triglycerides	Enlisted Flyer	55	65	57	Overall		0.379
					M vs. L	2.66 (0.62,11.39)	0.189
					H vs. L	2.06 (0.44,9.60)	0.358
	Enlisted Groundcrew	152	160	140	Overall		0.363
					M vs. L	0.44 (0.14,1.42)	0.173
					H vs. L	0.60 (0.19,1.86)	0.375

[a]No analysis done since there were only three abnormal (one medium, two high).

TABLE 13-17.

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
SGOT	Officer	n	125	129	120	Overall	0.718
		Adj. Mean	33.6	34.7	33.8	M vs. L	0.450
						H vs. L	0.904
	Enlisted Flyer	n	55	65	57	Overall	0.276
		Adj. Mean	30.3	32.8	32.7	M vs. L	0.144
						H vs. L	0.184
	Enlisted Groundcrew	n	152	160	140	Overall	0.409
		Adj. Mean	33.5	34.1	35.0	M vs. L	0.595
						H vs. L	0.183
SGPT	Officer	n	125	129	120	Overall	0.695
		Adj. Mean	20.1	20.0	19.1	M vs. L	0.969
						H vs. L	0.451
	Enlisted Flyer	n	55	65	57	Overall	0.058
		Adj. Mean	18.1	21.4	21.8	M vs. L	0.047
						H vs. L	0.030
	Enlisted Groundcrew	n	152	160	140	Overall	0.581
		Adj. Mean	20.2	21.4	21.0	M vs. L	0.309
						H vs. L	0.492

TABLE 13-17. (continued)

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
GGTP	Officer	n	125	129	120	Overall	0.828
		Adj. Mean	30.9	32.2	32.4	M vs. L	0.611
						H vs. L	0.580
	Enlisted Flyer	n	55	65	57	Overall	0.286
		Adj. Mean	36.6	42.6	44.6	M vs. L	0.230
						H vs. L	0.132
	Enlisted Groundcrew	n	152	160	140	Overall	0.299
		Adj. Mean	36.9	36.6	33.1	M vs. L	0.914
						H vs. L	0.159
Alkaline Phosphatase	Officer	n	126	129	120	Overall	0.843
		Adj. Mean	82.3	82.9	83.8	M vs. L	0.808
						H vs. L	0.561
	Enlisted Flyer	n	54	64	56	Overall	0.127
		Adj. Mean	90.7	99.3	97.7	M vs. L	0.053
						H vs. L	0.122
	Enlisted Groundcrew	n	153	160	141	Overall	0.576
		Adj. Mean	91.5	94.0	93.5	M vs. L	0.318
						H vs. L	0.444

TABLE 13-17. (continued)

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
Total Bilirubin	Officer	n	125	129	120	Overall	0.439
		Adj. Mean	0.77	0.75	0.79	M vs. L	0.504
						H vs. L	0.545
	Enlisted Flyer	n	55	65	57	Overall	0.070
		Adj. Mean	0.69	0.76	0.79	M vs. L	0.128
						H vs. L	0.023
	Enlisted Groundcrew	n	152	160	140	Overall	0.240
		Adj. Mean	0.73	0.74	0.78	M vs. L	0.838
						H vs. L	0.117
Direct Bilirubin	Officer	n	125	129	120	Overall	0.567
		Adj. Mean	0.20	0.19	0.21	M vs. L	0.517
						H vs. L	0.689
	Enlisted Flyer	n	55	65	57	Overall	0.724
		Adj. Mean	0.18	0.19	0.19	M vs. L	0.471
						H vs. L	0.498
	Enlisted Groundcrew	n	152	160	140	Overall	0.550
		Adj. Mean	0.17	0.19	0.18	M vs. L	0.277
						H vs. L	0.670

TABLE 13-17. (continued)

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
LDH	Officer	n	125	129	120	Overall	0.232
		Adj. Mean	134.0	131.3	128.9	M vs. L	0.373
						H vs. L	0.088
	Enlisted Flyer	n	55	65	57	Overall	0.101
		Adj. Mean	114.4	112.4	120.9	M vs. L	0.619
						H vs. L	0.129
	Enlisted Groundcrew	n	152	160	140	Overall	0.092
		Adj. Mean	125.3	125.3	129.7	M vs. L	0.997
						H vs. L	0.055
Cholesterol	Officer	n	125	129	120	Overall	0.049
		Adj. Mean	236.7	225.0	224.2	M vs. L	0.039
						H vs. L	0.029
	Enlisted Flyer	n	55	65	57	Overall	0.214
		Adj. Mean	213.2	208.1	220.6	M vs. L	0.492
						H vs. L	0.343
	Enlisted Groundcrew	n	152	160	140	Overall	0.945
		Adj. Mean	209.6	211.1	210.1	M vs. L	0.742
						H vs. L	0.927

TABLE 13-17. (continued)

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
	Officer	n	125	129	120	Overall	0.739
		Adj. Mean	110.0	108.5	116.3	M vs. L	0.886
						H vs. L	0.558
Triglycerides	Enlisted Flyer	n	55	65	57	Overall	0.981
		Adj. Mean	112.5	111.2	113.7	M vs. L	0.919
						H vs. L	0.927
	Enlisted Groundcrew	n	152	160	140	Overall	0.922
		Adj. Mean	110.9	109.9	107.9	M vs. L	0.890
						H vs. L	0.690
	Officer	n	125	129	120	Overall	0.856
		Adj. Mean	17.49	16.69	17.45	M vs. L	0.621
						H vs. L	0.977
Uroporphyrin	Enlisted Flyer	n	54	65	57	Overall	0.703
		Adj. Mean	18.58	16.96	18.27	M vs. L	0.438
						H vs. L	0.890
	Enlisted Groundcrew	n	151	160	139	Overall	0.644
		Adj. Mean	16.39	16.54	15.45	M vs. L	0.903
						H vs. L	0.451

TABLE 13-17. (continued)

Adjusted Continuous Exposure Index Analyses (Main Effects Model) for Hepatic Function Variables and Two Porphyrin Determinations by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
	Officer	n	125	129	120	Overall	0.901
		Adj. Mean	127.65	128.84	130.26	M vs. L	0.833
						H vs. L	0.649
Coproporphyrin	Enlisted Flyer	n	55	65	57	Overall	0.669
		Adj. Mean	108.67	115.31	109.81	M vs. L	0.408
						H vs. L	0.890
	Enlisted Groundcrew	n	151	160	140	Overall	0.325
		Adj. Mean	115.28	115.71	122.88	M vs. L	0.935
						H vs. L	0.177

Alkaline Phosphatase

For the enlisted groundcrew and the enlisted flyers, the lowest abnormal prevalence rate and lowest mean value were found in the low exposure category. A nonsignificant increasing dose-response relationship was seen within these occupations for the discrete analyses. In both unadjusted and adjusted continuous analyses, a marginally significant medium versus low contrast was found for enlisted flyers ($p=0.086$ and $p=0.053$, respectively), with unadjusted means of 88.9 U/L, 96.3 U/L, and 95.2 U/L for the low, medium, and high exposure levels, respectively.

Total Bilirubin

Discrete analyses revealed no significant findings; adjusted discrete analyses for enlisted flyers were not done due to sparse data. Continuous analyses revealed a significant overall effect ($p=0.045$, unadjusted) for enlisted flyers, which was marginally significant after adjustment ($p=0.070$). In both unadjusted and adjusted analyses, the high versus low mean contrast was significant ($p=0.014$ and $p=0.023$, respectively), with unadjusted means of 0.66 mg/dl, 0.73 mg/dl, and 0.76 mg/dl for the low, medium, and high exposure levels, respectively.

Direct Bilirubin

There were no significant exposure findings in either the continuous or discrete analyses, although within each occupational cohort, the lowest abnormal prevalence rate was found in the low exposure group.

LDH

The unadjusted discrete analyses revealed no significant or marginally significant results. No adjusted discrete analyses were done due to sparse data. The unadjusted continuous analyses for the enlisted groundcrew showed a significant overall relationship with the exposure index ($p=0.031$), with mean values of 123.1 U/L, 122.3 U/L, 127.9 U/L for the low, medium, and high exposure levels; the high versus low contrast was significant ($p=0.037$). After adjustment, the continuous analyses for enlisted groundcrew revealed marginally significant results ($p=0.092$, overall; $p=0.055$, high versus low). No significant or marginally significant results were seen for enlisted flyers or officers. Enlisted flyers and enlisted groundcrew had the largest mean values for their highest exposure category, which is reversed in the officers, who exhibited a nonsignificant decreasing dose-response relationship with exposure level.

Cholesterol

Significant or marginally significant results were found for officers in the direction of a decreasing dose-response relationship in both the adjusted continuous (overall $p=0.049$, medium versus low $p=0.039$, high versus low $p=0.029$) and adjusted discrete (medium versus low $p=0.085$, high versus low $p=0.060$) analyses. Neither of the enlisted cohorts demonstrated a similar decreasing response.

Triglycerides

No significant or marginally significant results were found.

Uroporphyrins and Coproporphyrins

No significant or marginally significant results were found.

EXPOSURE INDEX ANALYSES

Additional continuous analyses were done to examine pairwise interactions involving exposure level and the covariates. Ten exposure group-by-covariate interactions were found at $p \leq 0.05$. All interactions were found in the enlisted flyer and enlisted groundcrew occupations. Eight of the interactions involved current alcohol consumption, one involved age, and one involved race. The interactions are summarized in Tables K-5 and K-6 of Appendix K. In Table K-5 of Appendix K, the slope of the continuous covariate with respect to the dependent variable is provided for each of the three exposure levels. Table K-6 of Appendix K presents the mean level of direct bilirubin for each of the three exposure levels by race. The interactions involving current alcohol consumption are mainly due to a nonsignificant dependent variable response to increasing alcohol consumption in the low exposure group in contrast to a significant positive response for the medium and high groups. The SGOT, SGPT, and GGTP interaction results for the enlisted groundcrew provide support for an interpretation of herbicide effect.

In summary, the nine hepatic function variables and two porphyrin metabolite variables showed no conclusive evidence of a dose-response relationship at the followup examination. Five overall exposure group differences were found. Only two of these (SGOT for enlisted groundcrew, and total bilirubin for enlisted flyers) supported a dose-response relationship.

LONGITUDINAL ANALYSES

Three hepatic enzyme variables, SGOT, SGPT, and GGTP, were chosen for longitudinal analysis, spanning the spectrum of intermediate to acute effects. These test variables were chosen because both the Baseline and the followup assays were performed by the high-precision ACA 500® DuPont technology. The data from these three hepatic variables are arrayed in Table 13-18.

The SGOT and SGPT data showed slight but uniform increases from the Baseline examination. These increases were proportionately the same for both the Ranch Hand and Comparison groups. These changes may reflect an aging effect or are due to laboratory variation. As indicated by the equality-of-difference p-values, none of the three hepatic variables showed a statistically significant difference in the changes from Baseline to followup between groups.

TABLE 13-18.

Longitudinal Analyses for SGOT, SGPT, and GGTP:
A Contrast of Baseline and First Followup Examination Test Means

Variable	Group	Total	Means 1982 Baseline	Means 1985 Followup	p-Value* (Equality of Difference)
SGOT	Ranch Hand	971	32.91	33.73	0.61
	Comparison	1,139	32.97	33.73	
SGPT	Ranch Hand	971	20.08	21.82	0.72
	Comparison	1,139	20.51	22.44	
GGTP	Ranch Hand	971	39.26	33.16	0.63
	Comparison	1,139	38.64	32.35	

*Analyzed in log units.

SUMMARY AND CONCLUSIONS

The interval questionnaire revealed sparse reporting of liver disorders from 1982 to 1985 that was not significantly different between groups. Historical liver disease was verified by medical records, and these data were added to the verified Baseline history to assess possible lifetime differences. No significant differences were found. The medical record verification process showed that the historical data were generally correctly reported and classified between groups, except for the category of enlarged liver which showed a higher verification rate in the Comparison group.

Digestive system mortality showed an overall nonsignificant excess in the Ranch Hands, but a relative nonsignificant excess of malignant neoplasms in the Comparisons.

No differences were found for past or current peptic ulcer disease for the Ranch Hand and Comparison groups, adjusted for standard covariates as well as blood type.

The physical examination disclosed a borderline significant increase of hepatomegaly in the Ranch Hand group. Emphasis was placed on nine laboratory test variables measuring liver function, i.e., serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase, total and direct bilirubin, lactic dehydrogenase (LDH), cholesterol, and triglycerides. In addition, uroporphyrin and coproporphyrin measurements were obtained to assess liver function and the likelihood of porphyria cutanea tarda (PCT). The nine hepatic variables were subjected to continuous and categorical statistical tests, and were adjusted for the covariates age, race, occupation, current alcohol consumption, and unprotected exposure to both industrial chemicals and degreasing chemicals. Final statistical models used only

the significant covariates and two-way interactions for adjustment. The two porphyrin measurements were analyzed only in the continuous form. The overall summary results of the analyses of these 11 variables are given in Table 13-19.

The results showed a significantly lower mean SGPT level, a greater mean alkaline phosphatase level, a lower mean uroporphyrin level for Ranch Hands as contrasted with Comparisons, and a marginally significant greater mean coproporphyrin level. Only in the instance of alkaline phosphatase did the discrete analysis approach statistical significance. No group differences were noted for SGOT, GGTP, total and direct bilirubin, LDH, cholesterol, or triglycerides. However, an analysis using only the Original Comparisons revealed a significantly greater mean cholesterol level in the Comparison group. A review of the covariate effects in the adjusted statistical models revealed that all covariates behaved as expected with the exception of alcohol consumption for the alkaline phosphatase analysis, which showed an inverse relationship with wine consumption.

Exploration of group-by-group covariate interactions for alkaline phosphatase, direct bilirubin, triglycerides, SGOT, and uroporphyrins revealed significant group differences within specific covariate strata. In particular, Ranch Hands exposed to industrial chemicals had a significantly higher adjusted mean level of alkaline phosphatase and a significantly higher abnormal prevalence rate of direct bilirubin than similarly exposed Comparisons. For triglycerides, Ranch Hands born in or before 1922 had a significantly higher adjusted mean level than similar aged Comparisons, while Ranch Hand officers exhibited a significantly higher abnormal prevalence rate than Comparison officers. For SGOT, Ranch Hand moderate current drinkers (more than one to four drinks per day) had a significantly higher mean level than corresponding Comparisons. In the opposite direction, Comparisons with a mean BUN level less than or equal to 14 (median for all participants) were found to have a significantly higher adjusted mean uroporphyrin level than similar Ranch Hands. These results did not disclose any common pattern detrimental to the Ranch Hand group.

These findings were generally consistent with the 1982 Baseline data, which disclosed a significantly increased mean cholesterol level in the Comparisons and nonsignificant Ranch Hand mean elevations for GGTP and LDH. Slight differences in analytic results are probably due to the use of more fully adjusted models used for the followup examination data.

Overall, the followup examination laboratory data showed no adverse clinical or exposure patterns in either group. Further, the detection of significant mean shifts (still within normal range) by the continuous statistical tests, not mirrored by the categorical tests, suggests a circumstance of statistical power rather than findings of biological relevance.

Of the five significant or marginally significant results that were found in the adjusted exposure index analyses, four exhibited a trend suggestive of an increasing dose-response relationship. In the enlisted flyer cohort, the percentages of SGPT abormalities were significantly different and increased from the low to the high exposure categories. The corresponding mean values were marginally significantly different among exposure levels. Also, the mean levels of total bilirubin were marginally significantly different among exposure levels, increasing with exposure level. For enlisted groundcrew, the percentage of SGOT abnormalities significantly differed among

TABLE 13-19.

Overall Summary Results of Unadjusted and Adjusted Analyses of Nine Hepatic Function Variables and Two Porphyrin Metabolite Tests

Variable	Unadjusted		Adjusted*			Direction of Results**
	Mean	Categorical	Mean		Categorical	
			CC	CD	DD	
Questionnaire						
Liver Disease (Lifetime History)						
Hepatitis	--	NS	--	--	--	
Jaundice	--	NS	--	--	--	
Cirrhosis	--	NS	--	--	--	
Enlarged Liver	--	NS	--	--	--	
Miscellaneous Liver Disorders	--	NS	--	--	--	
Peptic Ulcer Disease	--	NS	--	--	NS[a]	
Physical Examination						
Hepatomegaly	--	NS*	--	--	--	RH>C
Laboratory Testing						
SGOT	NS	NS	NS	****	NS	
SGPT	NS*	NS	0.048	0.029	NS	C>RH
GGTP	NS	NS	NS	NS	NS	
Alkaline Phosphate	0.009	NS	0.008	****	NS*	RH>C
Total Bilirubin	NS	NS	NS	NS	NS	
Direct Bilirubin	NS	NS	NS	NS	****	
LDH	NS	NS	****	NS	NS	
Cholesterol	NS	NS	NS	NS	NS	
Triglycerides	NS	NS	****	NS	****	
Uroporphyrin	0.048	--	****	--	--	C>RH
Coproporphyrin	NS*	--	NS*	--	--	RH>C
Questionnaire-Laboratory Correlation						
Skin Bruises, Patches, and Sensitivity	--	0.001	--	--	--	RH>C

*C: Continuous
D: Discrete

**RH>C: more abnormalities, or higher mean value, in Ranch Hands.
C>RH: more abnormalities, or higher mean value, in Comparisons.

[a]Adjusted for blood type.

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

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

--Analysis not performed.

****Group-by-covariate interaction.

exposure levels. Within the enlisted flyer cohort, all nine laboratory tests of hepatic function had the lowest percentage of abnormalities in the low exposure category; correspondingly, six of the nine mean levels were lowest for the low exposure category. Of the ten group-by-covariate interactions that were found, three (SGOT, SGPT, and GGTP) supported a dose-response relationship in the enlisted groundcrew cohort. Exploration of these interactions revealed a trend that showed an increasing association between current alcohol consumption and the dependent variables for increasing exposure levels.

Longitudinal analyses for SGOT, SGPT, and GGTP disclosed no statistically significant group differences in the mean shifts from the Baseline to the followup examination.

Interval reporting of PCT-like symptoms of skin patches, bruises, and sensitivity was significantly increased in the Ranch Hands ($p=0.001$). However, when these historic data were contrasted to both uroporphyrin and coproporphyrin abnormalities, no correlation was apparent, nor were there any significant group differences. Since an elevation in the uroporphyrin level is required for a diagnosis of PCT, the historic data were retabulated with only uroporphyrin abnormalities; again, no group differences were apparent, and, in fact, uroporphyrin abnormalities in both groups were higher in those participants without a history of skin disorders than in those participants with such a history. The likelihood of bona fide PCT among study participants, and particularly among the Ranch Hands, appears to be remote.

In conclusion, the followup examination disclosed more statistically significant findings for tests of liver function than the Baseline examination, but they were equally divided between the two groups and did not demonstrate clinical, statistical, or exposure patterns consistent with an herbicide-related effect on health. No evidence was found to suggest an increased likelihood of PCT among the Ranch Hand group.

CHAPTER 13

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CHAPTER 14

DERMATOLOGICAL EVALUATION

INTRODUCTION

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

Since the association between chlorinated chemicals and chloracne was first noted in 1957,[1,2] a variety of animal experiments have shown the dermal sensitivity of rabbits, monkeys, and hairless mice to TCDD, 2,4,5-T (contaminated with TCDD), and other chlorinated dibenzo compounds, furans, or their brominated analogs.[1-7] Chloracne is not associated with exposure to 2,4-D.[8] Accidental exposure to waste oils containing TCDD has caused significant dermal symptoms, including loss of hair, ulcerative dermatitis, and inflamed mucous membranes in horses, dogs, cats, and mice.[9,10] Studies have suggested that the chloracnegens induce a series of pathological skin changes in target cells of the epithelial lining of sebaceous glands via the Ah receptor.[11] Hyperkeratinization of these cells eventually leads to the formation of the comedone characteristic of acne.

In humans, development of the hallmark rash, chloracne, is generally acknowledged to represent substantial topical or systemic exposure to one or more chloracnegens.[1,5,6,12-18] Acute fulminant chloracne is characterized by a maculopapular rash of active comedones, conforming to an eyeglass or facial butterfly distribution, often accompanied by chest, back, or eyelid lesions.[5,18]

The severity of the chloracne appears to be generally dose related, but may also depend on the route of administration, age, genetic predisposition, and/or the existence of acne vulgaris or other skin disorders.[5,15,18] Occasionally, exposure, via contaminated clothes of an industrial worker, has been associated with chloracne in family members.[19] Sequelae from severe chloracne include actinic elastosis, acne scars, disfigurement, excessive hair growth, and Peyronie's disease.[5,16] Severe chloracne is often accompanied by acute effects in other organ systems. In contrast, low to moderate exposure to chloracnegens generally produces mild chloracne with few, if any, attendant systemic signs and symptoms.

The clinical diagnosis of acute chloracne is easier than the diagnosis of subacute and chronic chloracne. In the latter instances, a history of exposure to chloracnegens is essential in the diagnosis, particularly if the individual has experienced adolescent acne. Chronic chloracne has been clinically observed more than 30 years after onset,[16] but a biopsy is often necessary to confirm these cases.[18] Mild or transient cases of chloracne may be confused with persistent adolescent acne or other skin conditions.

As noted in the AFHS Baseline Morbidity Report, over one-half of the veteran complaints in the Veterans Administration Herbicide Registry involved dermatological conditions, a fact sometimes alluded to as "evidence" of exposure to Agent Orange. In actuality, skin disease was a major medical problem among American troops serving in Vietnam. Forty-seven percent of the combat-days lost in the 9th Infantry Division from July 1968 to June 1969 were due to dermatological conditions.[19] These diseases were directly related to the tropical climate and terrain. Only in rare cases has the Veterans Administration made a diagnosis of chloracne in a Vietnam combat veteran. The natural history of chloracne suggests that most cases should have been diagnosed while in Vietnam, but a dermatological survey failed to reveal any cases.[20]

Most recognized chloracne cases have been diagnosed in chemical plant workers or in victims of industrial accidents. Thousands of cases were recorded in the 1930-1940 era, and earlier descriptions of chloracne-like disease were found in 1897 to 1901.[21] Industrial exposure to chloracnegens has been generally characterized as moderate-prolonged or severe-acute. In the setting of casual-sporadic exposure, as in the typical cases of the contaminated housing areas in Times Beach, Missouri, and the Quail Run Trailer Park, chloracne is virtually unknown.[22,23]

A number of dioxin morbidity studies have shown a clustering of abnormal laboratory tests in individuals with chloracne.[13,15-17,24-27] This has led some investigators to believe that long-term sequelae to dioxin exposure will be found only in people with chloracne.[16] Other investigators feel that this belief is not consistent with normal spectrum-of-illness concepts and that effects may occur in the absence of chloracne.[28]

Baseline Summary Results

The 1982 Baseline clinical examination revealed an unexpected significant excess ($p=0.03$) of basal cell carcinoma in the Ranch Hand group. Risk factor data (e.g., sun exposure, host factors of tannability, complexion) were not collected in 1982.

The 1982 examination focused on the diagnosis of chloracne both in historical terms by a detailed questionnaire and in contemporary terms via a comprehensive clinical assessment. The questionnaire data did not demonstrate anatomic, incidence, or onset-time patterns of acne in the Ranch Hand group that might support an inference of past chloracne, nor did the physical examination detect a single case. Fourteen biopsies from 11 participants also failed to document a chloracne diagnosis. A dermatology index (the number of clinically detected skin abnormalities per individual) was virtually identical between the Ranch Hand and Comparison groups, and was associated with the history of past acne in both groups. No exposure level associations were noted in any occupational category of the Ranch Hand group. The comprehensive dermatological assessment did not reveal evidence of past or current chloracne in the Ranch Hand group.

Parameters of the 1985 Dermatological Evaluation

Questionnaire data recaptured many of the acne parameters of the 1982 questionnaire, and the physical examination parameters were similar to the

1982 Baseline examination. Particular emphasis was given to the diagnosis of basal cell carcinoma and to the collection of risk factor data, e.g., skin color, reaction to sun, ethnicity (see Chapter 10, Malignancy).

Thus, the dependent variables and covariates of the analyses below closely approximated those previously conducted on the Baseline examination and questionnaire data. The adjusted statistical analyses were based on logistic regression (BMDP®-LR) and log-linear models (BMDP®-4F), and the unadjusted analyses primarily use Pearson's chi-square test and Fisher's exact test. In addition, an empiric Venn diagram was used to explore the potential of historic chloracne. Parallel analyses using only Original Comparisons are presented in Tables L-3 through L-11 of Appendix L.

RESULTS AND DISCUSSION

General

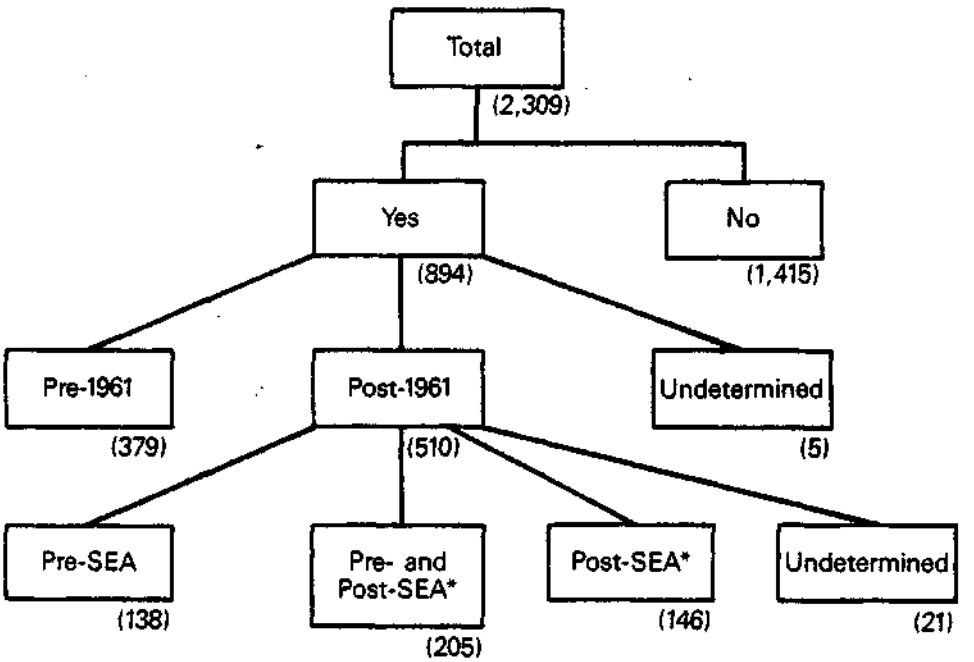
Detailed dermatological data were obtained by standard physical examination techniques. Numeric differences in summary tables reflect missing dependent variable and undeterminable covariate information. One participant refused the dermatology examination; consequently, all skin disorder analyses were based on 2,308 participants. Data were collected on 22 skin disorders, which were in turn reduced to eight variables for analysis: comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, hyperpigmentation, other abnormalities, and the dermatology index. Descriptions of skin biopsies, which were also conducted at the physical examination, are given in this chapter. Followup questionnaire information regarding the presence, time, and location of acne was also analyzed. The analyses in this chapter first investigate questionnaire information on acne, and subsequent analyses center upon the eight skin disorder variables and the skin biopsies.

Four covariates were included in this analysis: age, race, occupation, and presence of acne before duty in Southeast Asia. Age is used in its continuous form for all adjusted logistic regression analyses, but age is trichotomized (born in 1942 or after, born between 1923 and 1941, and born in 1922 or before) for presentation in summary tables and for use in dependent variable and covariate association analyses and log-linear models. Participants were categorized as either Black or nonblack. Occupation was divided into the three classifications of officer, enlisted flyer, and enlisted groundcrew. Sample size differences in subsequent adjusted analyses reflect missing dependent variable data or missing data on the presence of acne before duty in Southeast Asia.

Questionnaire Data

The acne status of each participant was determined by Baseline and followup questionnaire information. In particular, the occurrence of acne and the dates for acne occurrence have been determined and analyzed. Additionally, the analysis of the location of acne is presented for a subset of the participants who have had acne.

Figure 14-1 below is a diagram explaining the occurrence of acne by time determination for the 2,309 participants, along with frequencies and an explanation of terms.



Yes to Acne — Reported acne on both/either Baseline and/or followup study.

No to Acne — Never had acne.

Pre-1961 Acne — Participants with acne who had last occurrence of acne in or before 1961.

Post-1961 Acne — Participants with acne who had an occurrence of acne sometime after 1961.

Undetermined — Time reference not determinable from date information available.

Pre-SEA Acne — Participants with post-1961 acne who had all occurrences of acne before the start of first Southeast Asia (SEA) tour (as determined from military records).

Post-SEA Acne — Participants with post-1961 acne who had all occurrences of acne after the start of first SEA tour.

Pre- and Post-SEA Acne — Participants with post-1961 acne who had multiple occurrences, both before and after the start of first SEA tour, or a case of acne that began before the start of first SEA tour and that ended after starting SEA tour.

*: Analysis of location of acne performed for these participants.

Figure 14-1.
Occurrence of Acne by Time for First Followup Participants

The distinction was made between pre-1961 and post-1961, since herbicide missions in Vietnam commenced in 1962. Responses of 2,309 participants indicated that 1,415 individuals never had acne, 379 had acne before 1961, 138 had acne after 1961 but before duty in SEA, 205 had acne both before and after duty in SEA, 146 had acne only after SEA duty, and 26 participants could not be specifically classified.

Occurrence of Acne

The reported occurrence of acne, as determined by Baseline and followup questionnaires, is displayed in Table 14-1. The analysis showed that the Ranch Hand group reported slightly more acne than the Comparison group, although the difference is nonsignificant (p=0.111). Analyses using Original Comparisons only showed a borderline significance (p=0.071) found in Table L-3 of Appendix L.

The participants who responded "yes" to acne were categorized according to whether their acne occurred before or after 1961. The distribution of pre-1961 versus post-1961 acne is given in Table 14-2.

TABLE 14-1.

Unadjusted Analysis for Reported Historical Occurrence of Acne by Group

	Acne					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	412	40.6	604	59.4	1,016	Est. RR: 1.15
Comparison	482	37.3	811	62.7	1,293	95% C.I.: (0.97,1.36)
						p-Value: 0.111
Total	894		1,415		2,309	

TABLE 14-2.

Unadjusted Analysis for Reported Historical Occurrence of Acne Relative to 1961 by Group*

Group	Occurrence of Acne: Post-1961 Number	Post-1961 Percent	Pre-1961 Number	Pre-1961 Percent	Total	Summary Statistics
Ranch Hand	239	58.3	171	41.7	410	Est. RR: (for post-1961 cases): 1.07 95% C.I.: (0.82, 1.04) p-Value: 0.634
Comparison	271	56.6	208	43.4	479	
Total	510		379		889	

*Five participants deleted due to missing data at time of occurrence.

As shown, no significant difference in the distribution of post-1961 versus pre-1961 acne existed between Ranch Hands and Comparisons (p=0.634).

Cases of post-1961 acne were classified to SEA tour(s) of duty, as determined by military records. The distribution of post-1961 acne cases relative to SEA is shown in Table 14-3.

This marginal significance (p=0.058) was due primarily to a larger percentage of Ranch Hands in the post-SEA category, as contrasted with the Comparisons (35.1% versus 25.3%).

Duration of Acne

The approximate duration of acne was examined among the three SEA categories by group using a two-factor analysis of variance. The calculation of acne duration for participants with multiple occurrences in overlapping time periods counted time periods only once. A square root transformation was used to normalize the duration data. Results from duration of acne analyses are given in Table 14-4.

TABLE 14-3.

Unadjusted Analysis for Reported Historical Occurrence of Acne Relative to SEA Tour of Duty for Post-1961 Acne by Group*

	Post-1961 Acne							
	Pre-SEA		Post-SEA		Pre- and Post-SEA			
Group	Number	Percent	Number	Percent	Number	Percent	Total	p-Value
Ranch Hand	58	25.4	80	35.1	90	39.5	228	0.058
Comparison	80	30.7	66	25.3	115	44.1	261	
Total	138		146		205		489	

*Twenty-one post-1961 participants with acne deleted due to missing data on time of occurrence.

TABLE 14-4.

Adjusted Analysis for Duration of Acne (in Years) for Post-1961 Acne by Group*

Group	Total	Adjusted Mean**	95% C.I.**	p-Value	Covariate Remarks
Ranch Hand	219	8.18	(7.43,8.96)	0.189	Time Reference to
Comparison	252	7.49	(6.82,8.19)		SEA ($p<0.001$)
Total	471				

*Eighteen participants deleted due to missing data on time of occurrence.
**Converted from square root scale.

This adjusted analysis showed no significant effect due to group ($p=0.189$), but a highly significant effect due to SEA category ($p<0.001$), with the pre- and post-SEA category having higher mean durations than the pre-SEA or post-SEA categories, which were nearly identical. No interaction was present between group and SEA category ($p=0.314$). A categorical analysis was performed, in which duration was categorized into 5-year increments (five duration categories, the last being greater than 20 years). There was no significant difference between groups (pre-SEA, $p=0.520$; post-SEA, $p=0.776$; pre- and post-SEA, $p=0.880$).

Location of Acne

The location of acne for participants classified as post-SEA or pre- and post-SEA (351 participants) was analyzed. Spatial distribution of acne with

primary emphasis on acne on the temples, around the eyes, or on the ears was determined from the questionnaire; these data are presented in Figures 14-2 and 14-3. Figure 14-2 shows the distribution of acne for Ranch Hands and Comparisons, for post-SEA and pre- and post-SEA participants combined, whereas Figure 14-3 represents a similar distribution for only post-SEA participants. If more than one episode of acne occurred, cases involving the temples, eyes, or ears took precedence. Also, multiple-site involvement took precedence over single-site involvement.

The Ranch Hand and Comparison Venn diagrams were contrasted by chi-square analysis of a 2x8 table, and no difference in the spatial distribution was noted for the combination of pre- and post-SEA and post-SEA groups ($p=0.706$), or for the analysis of only the post-SEA group ($p=0.699$). Sparse data cells were present in the analysis of both figures. Differences in spatial distributions were also not evident when the "other sites" classification was deleted ($p=0.770$ and $p=0.664$, respectively). If the intersection of the circles in these figures (i.e., temples, ears, and eyes) is contrasted with the rest of the locations of acne, no significant difference is seen ($p=0.189$ and $p=0.627$ for the combination of post-SEA and pre- and post-SEA groups and for only the post-SEA group, respectively).

Physical Examination Data

Twenty-two skin disorders were assessed at the dermatological examination (page C-9 of Appendix C). These disorders were combined into eight variables for analytic purposes. Comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, and hyperpigmentation were analyzed separately. The remaining 16 conditions were grouped to form a broad variable called "other abnormalities." Analysis of skin cancer is included in the malignancy chapter and will not be discussed here. Additionally, comedones, acneiform lesions, acneiform scars, and inclusion cysts were grouped to construct a dermatology index, which summed the number of abnormalities for these four conditions for each participant. Logistic regression techniques, with the use of BMDP®-LR, were utilized for adjusted analysis of all these variables except the dermatology index, which used BMDP®-4F. The sample sizes were sufficient to detect a 27-percent increase in the prevalence rate for comedones, a 30 percent increase in the prevalence rate for acneiform scars, and a 12 percent increase in the prevalence of at least one abnormality for the dermatology index, using a two-sided α-level of 0.05 with a power of 0.80. No cases of chloracne were chemically diagnosed.

Preliminary Dependent Variables and Covariate Relationships

The association of the eight skin disorder variables in both groups and the covariates of age (born in or after 1942, born between 1923 and 1941, born in or before 1922), race (Black or nonblack), occupation, and presence of pre-SEA acne (yes/no) was assessed using Pearson's Chi-square test and Fisher's exact test. Table 14-5 is a summary of the associations of the dependent variables with these four covariates. Seven additional participants, who were initially classified as "undetermined," were reclassified as having acne before duty in SEA, based on data gathered by telephone. Nineteen participants were omitted from analyses involving presence of pre-SEA acne, because historical information on the date of onset of acne was not available.

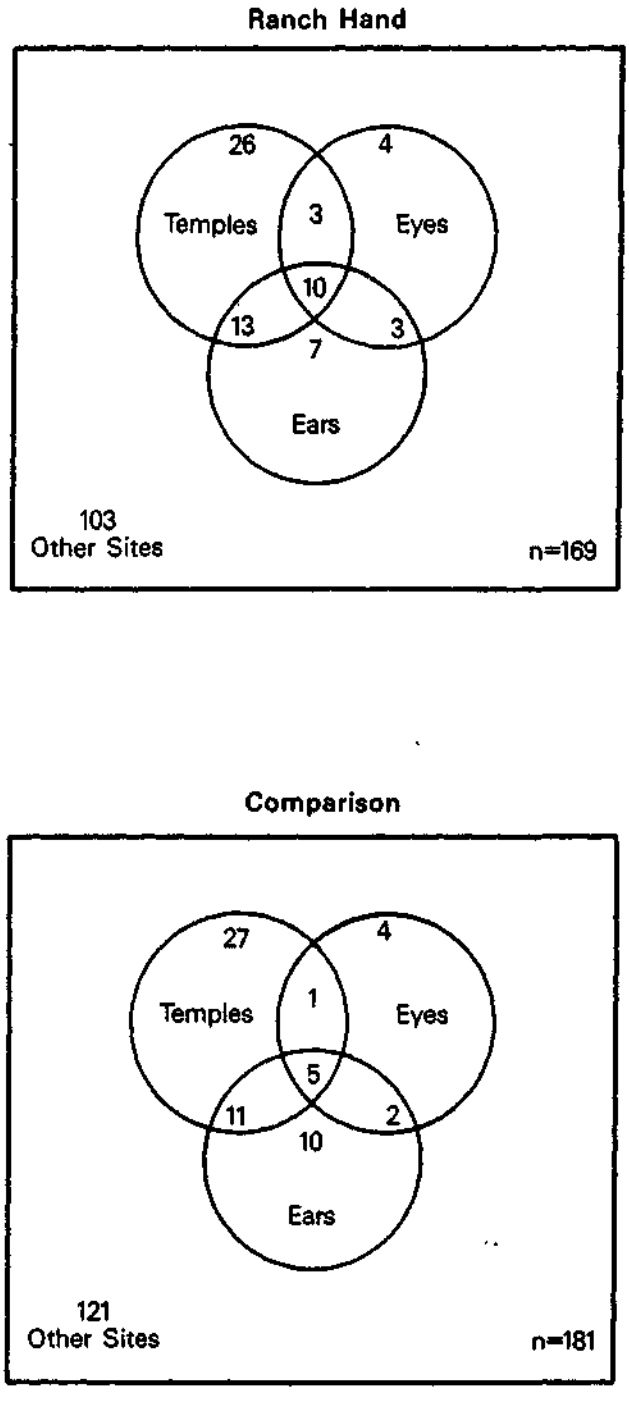


Figure 14-2.
Location of Post-SEA and Pre- and Post-SEA Acne by Group

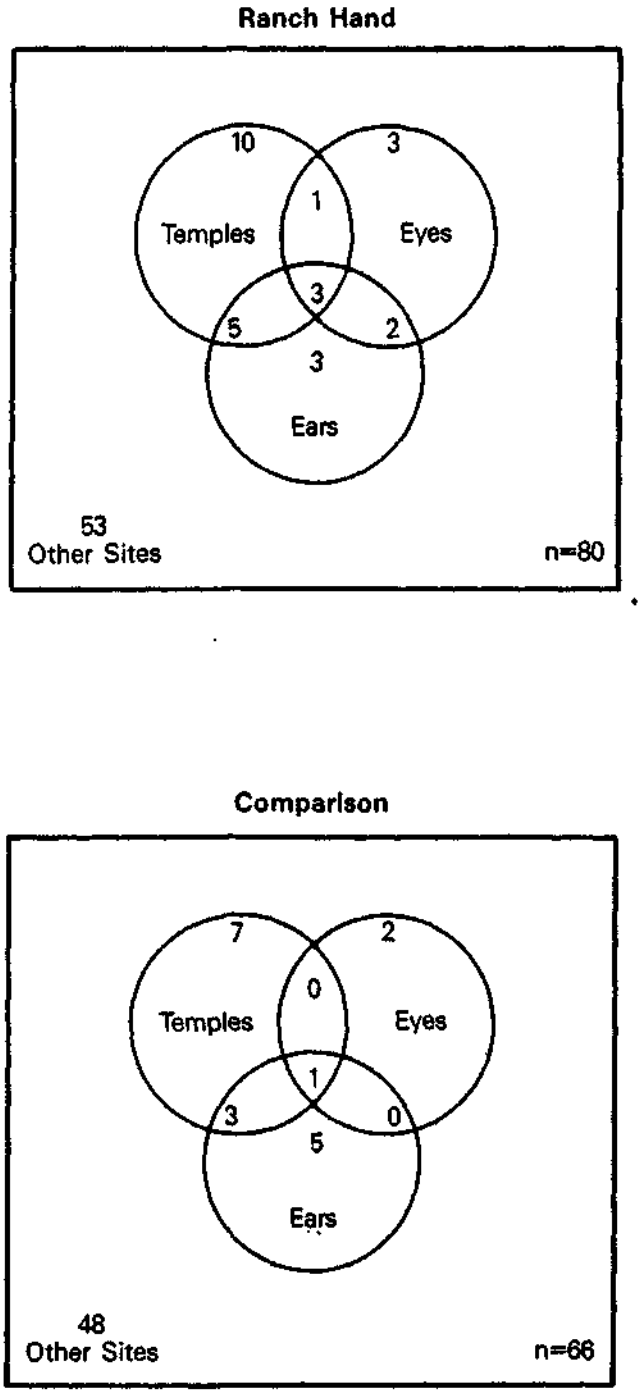


Figure 14-3.
Location of Post-SEA and Acne by Group

TABLE 14-5.

Association Between Dermatological Variables and Age, Race, Occupation, and Pre-SEA Acne in the Combined Ranch Hand and Comparison Groups

Variable	Age	Race	Occupation	Pre-SEA Acne
Comedones	<0.001	<0.001	<0.001	NS
Acneiform Lesions	<0.001	NS*	NS*	<0.001
Acneiform Scars	<0.001	<0.001	<0.001	<0.001
Depigmentation	NS	0.009	NS	NS
Inclusion Cysts	NS	NS	0.036	NS
Hyperpigmentation	NS	<0.001	<0.001	0.003
Other Abnormalities	<0.001	<0.001	<0.001	NS*
Dermatology Index	NS	NS	0.010	<0.001

NS: Not significant ($p>0.10$)

NS*: Borderline significant ($0.05<p\leq0.10$) effect with variable.

Age had a significant effect on four of the variables. Prevalence rates for comedones and other abnormalities were highest for older participants (born in or before 1922). On the other hand, the prevalence of acneiform lesions and acneiform scars was higher in the younger participants (born in or after 1942).

Nonblacks had a significantly higher prevalence of comedones and other abnormalities and a marginally significant increase ($p=0.055$) in acneiform lesions. Blacks had a significantly higher prevalence rate for acneiform scars, depigmentation, and hyperpigmentation.

Occupation had a significant or marginally significant effect on seven of the eight variables, with either enlisted flyers or enlisted groundcrew generally having a higher percentage of abnormalities.

Participants with pre-SEA acne had a significantly higher prevalence rate for acneiform lesions and acneiform scars, and a higher percentage with at least one abnormality in the dermatology index. Participants without acne pre-SEA had a significantly higher prevalence rate for hyperpigmentation, and a marginally significantly higher prevalence rate ($p=0.084$) for other abnormalities.

Analyses of Individual Dependent Variables

Comedones

As reflected in Table 14-6, there was not a significant difference ($p=0.361$) between the proportion of participants with comedones in the Ranch Hand and Comparison groups, unadjusted for any covariates.

TABLE 14-6.

Unadjusted Analysis for Comedones by Group

Group	Comedones: Present Number	Comedones: Present Percent	Comedones: Absent Number	Comedones: Absent Percent	Total	Summary Statistics
Ranch Hand	250	24.6	766	75.4	1,016	Est. RR: 0.91
Comparison	340	26.3	952	73.7	1,292	95% C.I.: (0.76,1.10) p-Value: 0.361

Tests of association between the presence of comedones in both groups and the four covariates indicated that there was not a significant effect due to the presence of pre-SEA acne ($p=0.355$), but that there were significant effects due to occupation ($p<0.001$), age ($p<0.001$), and race ($p<0.001$). The proportion of participants with comedones increased with age (18.9% for participants born in or after 1942, 29.8% for participants born between 1923 and 1941, and 37.9% for participants born in or before 1922). Significantly more nonblacks had comedones than Blacks (26.5% versus 11.9%), and enlisted flyers had more than enlisted groundcrew or officers (34.4%, 24.8%, and 22.6%, respectively).

An adjusted analysis of the proportion of participants with comedones was performed using logistic regression techniques. Results are presented in Table 14-7.

TABLE 14-7.

Adjusted Analysis for Comedones by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	0.89 (0.74,1.09)	0.260	Occupation ($p<0.001$) Presence of Pre-SEA Acne ($p=0.038$) Race-by-Age ($p=0.046$)

Again, no significant differences were found between groups (p=0.260). Occupation, pre-SEA acne, and a race-by-age interaction were significant (p<0.001, p=0.038, and p=0.046, respectively).

Compared to Baseline findings, the percentage of participants with comedones increased in the Comparison group but decreased in the Ranch Hand group. Estimated and adjusted relative risks were both less than 1.0 in the followup study, while the estimated relative risk in the Baseline study was slightly greater than 1.0 (RR=1.05, with Original Comparisons used), but statistically nonsignificant.

Acneiform Lesions

As shown in Table 14-8, there was not a significant difference between the proportion of participants with acneiform lesions in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.624).

TABLE 14-8.

Unadjusted Analysis for Acneiform Lesions by Group

	Acneiform Lesions					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	188	18.5	828	81.5	1,016	Est. RR: 1.06
Comparison	228	17.6	1,064	82.4	1,292	95% C.I.: (0.86,1.31)
						p-Value: 0.624

Tests of association between the presence of acneiform lesions in both groups and the four covariates revealed marginally significant effects due to race (p=0.055) and occupation (p=0.064), and significant effects for age (p<0.001) and presence of pre-SEA acne (p<0.001). Nonblacks had a marginally significantly higher proportion of participants with acneiform lesions than Blacks (18.4% versus 11.9%). The proportion of participants with lesions was greatest for enlisted groundcrew (20.1%), as compared to the other occupations (officers, 16.4%; enlisted flyers, 16.0%). The proportion of participants with acneiform lesions decreased with age (born in or after 1942, 23.0%; born between 1923 and 1941, 14.8%; born in or before 1922, 10.3%). A significantly higher proportion of participants with acne present before SEA had lesions (22.4%), as compared with those not having acne before SEA (16.0%).

An adjusted analysis of the proportion of participants with acneiform lesions was performed using logistic regression techniques. Results of this analysis are summarized in Table 14-9.

TABLE 14-9.

Adjusted Analysis for Acneiform Lesions by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	1.08 (0.87,1.34)	0.512	Age (p<0.001) Race (p=0.014) Presence of Pre-SEA Acne (p=0.008)

The results showed no significant differences between groups (p=0.512). Age (p<0.001), race (p=0.014), and presence of pre-SEA acne (p=0.008) were significant adjusting variables in this analysis. The Baseline and followup results for acneiform lesions were nearly identical with respect to group differences.

Acneiform Scars

Table 14-10 shows no significant difference between the proportion of participants with acneiform scars in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.720).

TABLE 14-10.

Unadjusted Analysis for Acneiform Scars by Group

	Acneiform Scars					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	150	14.8	866	85.2	1,016	Est. RR: 1.05
Comparison	183	14.2	1,109	85.8	1,292	95% C.I.: (0.83,1.33)
						p-Value: 0.720

Tests of association between the presence of acneiform scars in both groups and the covariates disclosed significant effects due to the four variables (p<0.001). As age increased, the proportion of participants with

acneiform scars decreased (17.9% for participants born in or after 1942, 12.4% for participants born between 1923 and 1941, and 5.7% for participants born in or before 1922). Significantly more Blacks had scars than nonblacks (28.0% and 13.5%, respectively), and enlisted personnel had more than officers (enlisted groundcrew, 16.9%; enlisted flyers, 16.5%; and officers, 10.4%). The pre-SEA acne classification had a significantly higher proportion of participants with acneiform scars than the non pre-SEA acne classification.

An adjusted analysis of the proportion of participants with acneiform scars was performed using logistic regression techniques. Results are given in Table 14-11.

TABLE 14-11.

Adjusted Analysis for Acneiform Scars by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	1.07 (0.84,1.36)	0.584	Age (p=0.006) Race (p<0.001) Occupation (p=0.016) Presence of Pre-SEA Acne (p<0.001)

No significant group differences were found (p=0.584). As in the covariate analysis with acneiform scars, significant effects in the adjusted analysis were observed due to all four covariates (age, p=0.006; race, p<0.001; occupation, p=0.016; presence of pre-SEA acne, p<0.001). The results for acneiform scars, as with the acneiform lesions, were quite similar in the followup and Baseline studies.

Depigmentation

Table 14-12 shows the contrast between the proportion of participants with depigmentation in the Ranch Hand and Comparison groups, unadjusted for any covariates. The proportion of participants with depigmentation was greater in the Comparison than in the Ranch Hand group; however, the difference between groups was nonsignificant (p=0.143).

TABLE 14-12.

Unadjusted Analysis for Depigmentation by Group

Group	Depigmentation: Present Number	Depigmentation: Present Percent	Depigmentation: Absent Number	Depigmentation: Absent Percent	Total	Summary Statistics
Ranch Hand	102	10.0	914	90.0	1,016	Est. RR: 0.82
Comparison	155	12.0	1,137	88.0	1,292	95% C.I.: (0.63,1.07)
						p-Value: 0.143

Tests of association between the presence of depigmentation in both groups and the four covariates determined a significant effect due to race (p=0.009), but showed nonsignificant effects for age, occupation, and presence of pre-SEA acne.

An adjusted analysis of the proportion of participants with depigmentation was performed using logistic regression techniques. The statistics are presented in Table 14-13.

TABLE 14-13.

Adjusted Analysis for Depigmentation by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,016	1,292	0.82 (0.63,1.07)	0.144	Race (p=0.010)

No significant difference was observed between groups (p=0.144). Race was the only significant covariate in this adjusted analysis (p=0.010). Depigmentation was not analyzed in the Baseline study.

Inclusion Cysts

As reflected in Table 14-14, there was not a significant difference between the proportion of participants with inclusion cysts in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.303).

TABLE 14-14.

Unadjusted Analysis for Inclusion Cysts by Group

	Inclusion Cysts					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	114	11.2	902	88.8	1,016	Est. RR: 0.87
Comparison	164	12.7	1,128	87.3	1,292	95% C.I.: (0.67,1.12) p-Value: 0.303

Tests of association between the presence of inclusion cysts in both groups and the covariates of age, race, occupation, and presence of pre-SEA acne showed no significant effects due to age (p=0.437), race (p=0.506), or presence of pre-SEA acne (p=0.449). Occupation, however, exhibited a significant effect (p=0.036), with the enlisted flyer category having the highest proportion of participants with inclusion cysts (15.8% versus 11.9% and 10.8% for officers and enlisted groundcrew, respectively.

An adjusted analysis of the proportion of participants with inclusion cysts was performed using logistic regression techniques. Results are presented in Table 14-15.

TABLE 14-15.

Adjusted Analysis for Inclusion Cysts by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,016	1,292	0.86 (0.67,1.12)	0.260	Occupation (p=0.041)

No significant differences for inclusion cysts were found between the Ranch Hand and the Comparison groups (p=0.260). Occupation was the only significant covariate in this analysis (p=0.041).

With reference to the Baseline study, the percentage of participants with inclusion cysts at the followup increased in the Comparison group, and

decreased slightly in the Ranch Hand group. These differences could be due to changes in disease over time, different examiners, or changes in the cohorts examined. Both estimated and adjusted relative risks were less than one in the followup, while the estimated relative risk at the Baseline was slightly greater than one (RR=1.10 for Original Comparisons) but was not statistically significant.

Hyperpigmentation

Table 14-16 shows there was not a significant difference between the proportion of participants with hyperpigmentation in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.762).

TABLE 14-16.

Unadjusted Analysis for Hyperpigmentation by Group

	Hyperpigmentation					
	Present		Absent			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	228	22.4	788	77.6	1,016	Est. RR: 1.03
Comparison	283	21.9	1,009	78.1	1,292	95% C.I.: (0.85,1.26)
						p-Value: 0.762

Tests of association between the presence of hyperpigmentation in both groups and the four covariates revealed there was not a significant effect due to age (p=0.833), but that significant effects were due to race (p<0.001), occupation (p<0.001), and presence of pre-SEA acne (p=0.003). Blacks had a much higher prevalence of hyperpigmentation than nonblacks (53.1% for Blacks, 20.1% for nonblacks), and enlisted personnel had a higher prevalence of hyperpigmentation than officers (enlisted groundcrew, 25.5%; enlisted flyers, 23.5%; officers, 17.4%). The proportion of participants with hyperpigmentation was greater in the absence of pre-SEA acne (23.8%) than in the presence of pre-SEA acne (18.2%).

An adjusted analysis of the proportion of participants with hyperpigmentation was performed using logistic regression techniques. Results are given in Table 14-17.

TABLE 14-17.

Adjusted Analysis for Hyperpigmentation by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,007	1,282	1.04 (0.85,1.27)	0.720	Race ($p<0.001$) Occupation ($p=0.009$) Presence of Pre-SEA Acne ($p=0.009$)

No significant group differences ($p=0.720$) were noted, although significant effects of race ($p<0.001$), occupation ($p=0.009$), and presence of pre-SEA acne ($p=0.009$) were evident.

The proportion of participants with hyperpigmentation has increased since the Baseline study. Almost three times as many abnormalities were found at the followup study (approximately 22% versus 8%). The relative risk estimate was closer to 1 in the followup study, but relative risks from both the Baseline and followup studies were not significantly different from 1. These differences could be due to disease or examination techniques.

Other Abnormalities

The study of other abnormalities encompassed a wide range of dermatological disorders. Included in this variable were the following abnormalities:

(1) Jaundice
(2) Spider Angiomata
(3) Palmar Erythema
(4) Suspected Melanoma
(5) Palmar Keratoses
(6) Actinic Keratoses
(7) Petechiae
(8) Ecchymoses
(9) Conjunctival Abnormality
(10) Oral Mucosal Abnormality
(11) Fingernail Abnormality
(12) Toenail Abnormality
(13) Dermatographia
(14) Cutis Rhomboidalis
(15) Suspected Basal Cell Carcinoma
(16) Suspected Squamous Cell Carcinoma

With respect to the category "Other Abnormalities," a participant was considered normal only if he was negative for all of these conditions. If one or more abnormalities existed, then the participant was considered abnormal.

As reflected in Table 14-18, there was not a significant difference between the proportion of participants with other abnormalities in the Ranch Hand and Comparison groups, unadjusted for any covariates (p=0.349).

TABLE 14-18.

Unadjusted Analysis for Other Abnormalities by Group

	Other Abnormalities					
	Abnormal		Normal			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	608	59.8	408	40.2	1,016	Est. RR: 1.08
Comparison	748	57.9	544	42.1	1,292	95% C.I.: (0.92,1.28)
						p-Value: 0.349

Tests of association between the presence of other abnormalities in both groups and the four covariates found a marginally significant effect due to the presence of pre-SEA acne (p=0.084), and significant effects due to age (p<0.001), occupation (p<0.001), and race (p<0.001). The proportion of participants with other abnormalities in the absence of pre-SEA acne (59.9%) was marginally significantly larger than the proportion of participants with other abnormalities who also had pre-SEA acne (56.1%). The proportion of participants with other abnormalities increased with age (with a low of 43.3% for participants born in or after 1942 to a high of 82.8% for participants born in or before 1922). Nonblacks had a significantly and substantially higher percentage of other abnormalities than Blacks (60.3% and 35.7%, respectively). Enlisted groundcrew had a lower proportion of abnormalities than officers or enlisted flyers (53.3%, 63.2%, and 63.8%, respectively).

An adjusted analysis of the proportion of participants with other abnormalities was performed using logistic regression techniques. Results are presented in Table 14-19.

Again, no significant difference was observed between groups (p=0.432). Age and race were significant covariates in this analysis (p<0.001 for both).

In reference to the Baseline study, the percentage of participants with other abnormalities has increased in both the Comparison and the Ranch Hand groups. In the Baseline study, the estimated relative risk for Ranch Hands versus Original Comparisons was 0.77, significantly less than 1.00. The estimate of the relative risk has increased in the followup study to 1.08. The percentage of other abnormalities has increased from approximately 14 percent in the Baseline study to nearly 59 percent in the followup study.

TABLE 14-19.

Adjusted Analysis for Other Abnormalities by Group

Ranch Hand Total	Comparison Total	Adjusted Relative Risk (95% C.I.)	p-Value	Covariate Remarks
1,016	1,292	1.07 (0.90,1.28)	0.432	Age (p<0.001) Race (p<0.001)

Dermatology Index

Four of the previously analyzed conditions (comedones, acneiform lesions, acneiform scars, and inclusion cysts) were used to construct a dermatology index. All four conditions are indicators of possible chloracne. The index was formulated by counting the number of abnormalities present in a participant for the four conditions. Consequently, the dermatology index ranged from 0 to 4, where 0 indicated that the participant had none of these abnormalities and 4 indicated that the participant had all of these abnormalities.

Table 14-20 presents the number and the percent of participants with each of these five scores by group. A significant difference between the Ranch Hand and Comparison groups was not observed for this dermatology index, unadjusted for any covariates (p=0.576, 4 d.f.).

Covariate main effect analyses found nonsignificant effects due to age (p=0.407) and race (p=0.558), but significant effects for occupation (p=0.010) and the presence of acne pre-SEA (p<0.001). These data are summarized in Table 14-21. By occupation, 55.8 percent of the officers had no abnormalities, whereas 50.8 percent of the enlisted groundcrew and 44.4 percent of the enlisted flyers had no abnormalities. The stratum corresponding to participants with pre-SEA acne present had a larger percentage of participants with at least one abnormality (see Table 14-21).

An adjusted analysis of the five scores of the dermatology index was performed using log-linear modeling techniques. Significant effects were noted for occupation and an interaction between group and presence of pre-SEA acne (p=0.005, p=0.041, respectively). Consequently, an analysis, stratifying by pre-SEA acne status, was performed, and the results are shown in Table 14-22.

The adjusted relative risk for each of the index scores (1 to 4, separately, versus the 0 score), the 95 percent confidence interval, and the p-value for each contrast for each pre-SEA acne class are given in Table 14-23.

TABLE 14-20.

Unadjusted Analysis for the Dermatology Index by Group

	Dermatology Index Score										
	0		1		2		3		4		
Group	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
Ranch Hand	533	52.5	318	31.3	121	11.9	34	3.3	10	1.0	1,016
Comparison	658	50.9	420	32.5	154	11.9	53	4.1	7	0.5	1,292

Overall p-Value (4 d.f.)=0.576

Contrast	Est. Relative Risk (95% C.I.)	p-Value*
1 vs. 0	0.94 (0.78,1.13)	0.480
2 vs. 0	0.97 (0.75,1.26)	0.840
3 vs. 0	0.79 (0.51,1.24)	0.317
4 vs. 0	1.76 (0.67,4.66)	0.327

*Fisher's exact test.

TABLE 14-21.

Association Between the Dermatology Index and Age, Race, Occupation, and Presence of Pre-SEA Acne in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Dermatology Index Score* 0 Number	0 Percent	1 Number	1 Percent	2 Number	2 Percent	3 Number	3 Percent	4 Number	4 Percent	Total[a]	p-Value[b]
Age	Born ≥1942	501	52.2	296	30.8	114	11.9	40	4.2	9	0.9	960	0.407
	Born 1923-1941	647	51.3	408	32.4	156	12.4	42	3.3	8	0.6	1,261	
	Born ≤1922	43	49.4	34	39.1	5	5.7	5	5.7	0	0.0	87	
Race	Black	83	58.0	38	26.6	17	11.9	4	2.8	1	0.7	143	0.558
	Nonblack	1,108	51.2	700	32.3	258	11.9	83	3.8	16	0.8	2165	
Occupation													
	Officer	482	55.8	265	30.7	91	10.5	21	2.4	5	0.6	864	0.010
	Enlisted Flyer	172	44.4	135	34.9	58	15.0	19	4.9	3	0.8	387	
	Enlisted Groundcrew	537	50.8	338	32.0	126	11.9	47	4.4	9	0.9	1,057	
Presence of Pre-Sea Acne**													
	No	842	54.0	514	32.9	153	9.8	44	2.8	7	0.4	1,560	<0.001
	Yes	337	46.2	220	30.1	121	16.6	42	5.8	9	1.2	729	

* Score denotes the number of abnormalities (for comedones, acneiform lesions, acneiform scars, and inclusion cysts) diagnosed.

**Nineteen participants could not be classified.

[a] One participant refused to take the dermatology examination.

[b] Pearson's chi-square test.

TABLE 14-22.

Adjusted Analysis for the Dermatology Index by SEA Acne Class and Group

Pre-SEA Acne Class	Group	Dermatology Index Score*										
		0		1		2		3		4		
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
No pre-SEA acne	Ranch Hand	360	52.6	234	34.2	69	10.1	16	2.3	5	0.7	684
	Comparison	482	55.0	280	32.0	84	9.6	28	3.2	2	0.2	876
Pre-SEA acne	Ranch Hand	167	51.7	82	25.4	51	15.8	18	5.6	5	1.5	323
	Comparison	170	41.9	138	34.0	70	17.2	24	5.9	4	1.0	406

*Score denotes the number of abnormalities (comedones, acneiform lesions, acneiform scars, and inclusion cysts) diagnosed.

TABLE 14-23.

Adjusted Relative Risks for Contrasts of Dermatology Index by Pre-SEA Class

Pre-SEA Acne	Contrast	Adjusted Relative Risk	95% C.I.	p-Value
No	1 abnormality vs. 0 abnormalities	1.12	(0.90,1.39)	0.315
	2 vs. 0	1.10	(0.77,1.55)	0.605
	3 vs. 0	0.77	(0.41,1.44)	0.411
	4 vs. 0	3.09	(0.65,14.62)	0.155
Yes	1 vs. 0	0.60	(0.42,0.85)	0.004
	2 vs. 0	0.73	(0.48,1.12)	0.148
	3 vs. 0	0.75	(0.39,1.43)	0.380
	4 vs. 0	1.19	(0.33,4.38)	0.788

This analysis showed a significant difference between groups only when contrasting the proportion of participants with one abnormality (out of four) to the proportion of participants with no abnormalities for participants with pre-SEA acne (p=0.004). However, Comparisons were more likely to have one abnormality than the Ranch Hands, as is evidenced by the relative risk and confidence interval being less than 1.

In contrast to the Baseline study, the percentage of participants with a score of 1 or more has increased at the followup examination for both the Ranch Hand and Comparison groups (8.1% for Ranch Hands, 12.1% for Comparisons). The estimated relative risks, when the dermatology index is condensed into two categories, were 1.11 for the Baseline examination and 0.94 for the followup examination.

Biopsy Results

Dermatologists were instructed to perform skin biopsies on any lesions they suspected of being malignant. Of the 40 biopsies collected from 35 participants, none was suggestive of chloracne. Histologic descriptions of these biopsies are presented in Table 14-24. With the exception of confirmed basal cell carcinoma, no single diagnostic category predominated.

TABLE 14-24.

Summary of Histologic Descriptions
of Skin Biopsy by Group

Histologic Description	Group		Comments
	Ranch Hand	Comparison	
Basal Cell Carcinoma	7	4	a,b
Suspected Basal Cell Carcinoma	0	3	b
Suspected Unspecified Carcinoma	0	1	
Unspecified Carcinoma	1	0	c
Dermatofibroma	3	0	
Pigmented Nevus	1	2	
Dyschromia	1	0	d
Keratoderma, Acquired	1	1	a
Melanoacanthoma (Papilloma)	0	1	
Intradermal Nevus	1	0	
Junctional Nevus	0	1	
Cavernous Hemangioma	0	1	
Degenerative Skin Disorder	0	1	
Other Specified Disorders of Skin	0	1	
Local Infection of Skin	1	0	c
Other Dermatoses	5	2	c
Total	21	18	

[a]One participant had a basal cell carcinoma at one site and an acquired keratoderma at another site.

[b]One participant had a basal cell carcinoma at one site and a suspected basal cell carcinoma at another site.

[c]One participant had a local infection of the skin, a suspected unspecified carcinoma, and a dermatosis at the same site.

[d]One participant had two cases of dyschromia at two different sites.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). The dermatology index was collapsed into two categories, 0 and greater than 0. All eight dermatological variables were explored, unadjusted for any covariates, using Pearson's chi-square test and Fisher's exact test. Adjusted analyses were performed by logistic regression for these variables, using age, race, presence of pre-SEA acne, and any significant pairwise interactions between the exposure index and these covariates. Overall significance in the proportion of abnormalities among the exposure index levels of low, medium, and high was determined, as well as contrasts in the proportion of abnormalities between the medium and low exposure levels, and between the high and low exposure levels. Age was used as a continuous variable in the adjusted analyses.

Results of the adjusted analyses for these eight variables are presented in Table 14-25, and counterpart results for unadjusted analyses are presented in Table L-1 of Appendix L. Results from further investigation of exposure index by covariate interactions are given in Table L-2 of Appendix L.

Significant or marginally significant results were present for some of these variables based on unadjusted analyses. A borderline significantly higher prevalence of comedones (Est. RR: 1.78, 95% C.I.: [0.95,3.35], p=0.084) for the contrast of medium exposure to low exposure was seen for officers. Marginally significant results for the contrast of high exposure to low exposure were also present for acneiform scars for officers (Est. RR: 2.38, 95% C.I.: [0.94,6.06], p=0.075) and enlisted groundcrew (Est. RR: 1.82, 95% C.I.: [1.00,3.30], p=0.053), as well as for other abnormalities for officers (Est. RR: 1.66, 95% C.I.: [0.98,2.78], p=0.067). The data for these last three variable-occupation combinations supported an increase in the proportion of abnormalities from low to high exposure. Significant or marginally significant results were also observed for medium exposure versus low exposure in officers and enlisted groundcrew for depigmentation, and for high exposure versus low exposure in other abnormalities with enlisted flyers, but prevalence decreased as the exposure level increased in these cases.

The frequency of abnormalities for the different exposure index levels exhibited no consistent pattern across occupations. However, within the officer and enlisted groundcrew occupations, most variables showed the low exposure level to have the lowest prevalence of abnormalities or the high exposure level to have the highest prevalence, whereas very few variables showed this pattern for enlisted flyers.

Adjusted analyses revealed patterns similar to those of the unadjusted analyses. Results of the counterpart adjusted analyses to the situations described above are detailed below.

(1) Comedones in officers, medium versus low: Adj. RR: 1.62, 95% C.I.: (0.83,3.15), p=0.154.

TABLE 14-25.

Adjusted Exposure Index Analysis for Dermatological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Comedones	Officer	126	129	122	Overall		0.334
					M vs. L	1.62 (0.83,3.15)	0.154
					H vs. L	1.44 (0.74,2.83)	0.283
	Enlisted Flyer	55	65	56	Overall		0.413
					M vs. L	0.65 (0.30,1.41)	0.276
					H vs. L	0.61 (0.27,1.37)	0.234
	Enlisted Groundcrew	152	162	140	Overall		0.878
					M vs. L	0.94 (0.55,1.60)	0.808
					H vs. L	1.08 (0.63,1.83)	0.782
Acneiform Lesions	Officer	126	129	122	Overall		0.669
					M vs. L	1.06 (0.52,2.15)	0.880
					H vs. L	1.34 (0.67,2.66)	0.409
	Enlisted Flyer	55	65	56	Overall		0.917
					M vs. L	0.91 (0.32,2.60)	0.856
					H vs. L	1.14 (0.39,3.35)	0.814
	Enlisted Groundcrew	152	162	140	Overall		0.674
					M vs. L	1.01 (0.58,1.75)	0.973
					H vs. L	1.25 (0.71,2.20)	0.431

TABLE 14-25. (continued)

Adjusted Exposure Index Analysis for Dermatological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	126	129	122	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)
Acneiform Scars	Enlisted Flyer	55	65	56	Overall		0.363
					M vs. L	0.82 (0.31,2.13)	0.682
					H vs. L	0.47 (0.16,1.39)	0.174
	Enlisted Groundcrew[a]	152	162	140	Overall		0.068
					M vs. L	1.22 (0.66,2.27)	0.519
					H vs. L	2.00 (1.08,3.67)	0.026
	Officer	126	129	122	Overall		0.006
					M vs. L	0.33 (0.11,0.98)	0.045
					H vs. L	1.50 (0.69,3.25)	0.302
Depigmentation	Enlisted Flyer	55	65	56	Overall		0.493
					M vs. L	0.53 (0.18,1.54)	0.245
					H vs. L	0.67 (0.24,1.90)	0.450
	Enlisted Groundcrew	152	162	140	Overall		****(2)
					M vs. L	****(2)	****(2)
					H vs. L	****(2)	****(2)

TABLE 14-25. (continued)

Adjusted Exposure Index Analysis for Dermatological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer[b]	126	129	122	Overall		0.221
					M vs. L	2.05 (0.91,4.60)	0.082
					H vs. L	1.32 (0.56,3.11)	0.532
Inclusion Cysts	Enlisted Flyer	55	65	56	Overall		0.881
					M vs. L	1.24 (0.41,3.78)	0.707
					H vs. L	1.33 (0.42,4.17)	0.630
	Enlisted Groundcrew	152	162	140	Overall		0.916
					M vs. L	0.91 (0.43,1.93)	0.806
					H vs. L	1.07 (0.51,2.24)	0.856
	Officer	126	129	122	Overall		0.813
					M vs. L	0.92 (0.47,1.79)	0.807
					H vs. L	0.80 (0.41,1.58)	0.525
Hyperpig-mentation	Enlisted Flyer	55	65	56	Overall		0.656
					M vs. L	0.71 (0.29,1.76)	0.465
					H vs. L	1.04 (0.43,2.53)	0.930
	Enlisted Groundcrew	152	162	140	Overall		0.365
					M vs. L	1.20 (0.71,2.01)	0.494
					H vs. L	0.81 (0.46,1.41)	0.450

TABLE 14-25. (continued)

Adjusted Exposure Index Analysis for Dermatological Variables by Occupation

Variable	Occupation	Exposure Index: Low Total	Exposure Index: Medium Total	Exposure Index: High Total	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	126	129	122	Overall		0.309
					M vs. L	1.30 (0.75,2.24)	0.346
					H vs. L	1.53 (0.88,2.65)	0.129
Other Abnormal-ities	Enlisted Flyer	55	65	56	Overall		0.049
					M vs. L	0.66 (0.28,1.56)	0.341
					H vs. L	0.35 (0.14,0.83)	0.018
	Enlisted Groundcrew	152	162	140	Overall		0.764
					M vs. L	0.85 (0.52,1.36)	0.489
					H vs. L	0.87 (0.52,1.43)	0.580
	Officer	126	129	122	Overall		****(1)
					M vs. L	****(1)	****(1)
					H vs. L	****(1)	****(1)
Dermatology Index	Enlisted Flyer	55	65	56	Overall		0.618
					M vs. L	0.74 (0.36,1.54)	0.423
					H vs. L	0.71 (0.33,1.51)	0.368
	Enlisted Groundcrew	152	162	140	Overall		0.469
					M vs. L	1.01 (0.65,1.59)	0.955
					H vs. L	1.30 (0.82,2.06)	0.270

[a]Marginal exposure index-by-presence of pre-SEA acne interaction (p=0.056)--relative risk, confidence interval and p-value presented, and additional information provided in interaction summaries.

****(1): Exposure index-by-presence of pre-SEA acne and exposure index-by-race interaction--relative risk, confidence interval, and p-value not presented.

****(2): Exposure index-by-presence of pre-SEA acne interaction--relative risk, confidence interval and p-value not presented.

(2) Acneiform scars in officers, high versus low: interaction present; direct contrast of adjusted and unadjusted analyses not possible.

(3) Acneiform scars in enlisted groundcrew, high versus low: Adj. RR: 2.00, 95% C.I.: (1.08,3.67), p=0.026; overall p-value=0.068, increase in the proportion of abnormalities with increasing exposure levels supported.

(4) Other abnormalities in officers, high versus low: Adj. RR: 1.53, 95% C.I.: (0.88,2.65), p=0.129.

Other adjusted analyses that showed significance or marginal significance exhibited a decreasing prevalence with increasing exposure level. All other adjusted analyses showed an interaction with covariates (described below) or nonsignificant results.

Interactions were present for three of the eight variables and were observed for officers and enlisted groundcrew. A summary of these interactions is presented below in Table 14-26.

TABLE 14-26.

Summary of Exposure Index by Covariate Interactions Encountered in Adjusted Analysis of Dermatological Variables

Variable	Occupation	Covariate	p-Value
Acneiform Scars	Officer	Race	0.003
Acneiform Scars	Officer	Presence of Pre-SEA acne	0.003
Acneiform Scars	Enlisted Groundcrew	Presence of Pre-SEA acne	(marginal) 0.056
Depigmentation	Enlisted Groundcrew	Presence of Pre-SEA acne	0.035
Dermatology Index*	Officer	Race	0.026
Dermatology Index*	Officer	Presence of Pre-SEA acne	0.029

*Variable was collapsed into two categories, 0 and >0.

As can be seen, all variables and occupations with interactions had a significant exposure index-by-presence of pre-SEA acne interaction or significant exposure index-by-race and exposure index-by-presence of pre-SEA acne interactions. Meaningful interpretation of many of the subsequent stratified analyses was hindered by small sample sizes, but two situations were of particular interest. For acneiform scars on officers, nonblack personnel without pre-SEA acne at low exposure had no participants with scars, whereas nonblack personnel exposed at the medium and high levels had 7.8 percent and 10.5 percent of participants with scars, respectively. Also, with acneiform scars for enlisted groundcrew, an increase in the prevalence of abnormalities for increasing levels of exposure was present for participants with pre-SEA acne, with an adjusted relative risk of 5.38 (95% C.I.: [1.45,19.96], p=0.012) for the contrast of high exposure versus low exposure.

In summary, the results suggested the presence of an increasing dose-response relationship in certain occupations for a few of the dermatological variables or within substrata of these variables, but no consistent pattern was evident throughout the dermatological exposure index evaluation.

LONGITUDINAL ANALYSES

The dermatology index was chosen to assess longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. In testing for this difference, the dermatology index scores were collapsed into two categories: normal (dermatology index score of 0) and abnormal (dermatology index score greater than 0). As shown in Table 14-27, 2x2 tables were constructed for each group. These tables show the number of participants who were abnormal at the Baseline examination and abnormal at the followup, abnormal at Baseline and normal at followup, normal at Baseline and abnormal at followup, and normal at both Baseline and followup. The odds ratios given are the ratios of the number of participants who were normal at the Baseline and abnormal at the followup to the number of participants who were abnormal at the Baseline and normal at the followup (the "off-diagonal" elements).

TABLE 14-27.

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

Group	1982 Baseline Exam	1985 Followup Exam: Abnormal	1985 Followup Exam: Normal	Odds Ratio (OR)*	p-Value (OR_{RH} vs OR_C)
Ranch Hand	Abnormal	241	136	1.68	
	Normal	228	366		
					0.15
Comparison	Abnormal	283	136	2.08	
	Normal	283	437		

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

The changes in normal/abnormal status within each group were compared, and the p-value given was derived from Pearson's chi-square test of the hypothesis that the pattern of change in the two groups was the same. These results showed that the difference in the pattern is not significant (p=0.15).

DISCUSSION

The relative risks for all eight dermatological variables approached unity (none was statistically significant), an observation previously noted at the Baseline examination (except for the category "Other Abnormalities," which predominated in the Comparisons). More dermatological abnormalities were recorded at the followup (for six of the seven variables shared between the examinations) than at the Baseline--the increase in detection was slightly stronger in the Comparison group than in the Ranch Hand group. For example, in the category "Other Abnormalities," the reporting of skin lesions generally increased from about 14 percent to 59 percent. The overall difference between the two examinations probably reflects a combination of factors, e.g., changes in disease, chance, the addition of new participants, and possible differences in clinical practice between the two groups of dermatologists.

The histologic categories of skin cancer (confirmed or suspected, any type), as examined by biopsies, showed a similarity between both groups.

SUMMARY AND CONCLUSIONS

Interval questionnaire data on the occurrence, time, and location of acne were analyzed to assess the possible historical diagnosis of chloracne. No significant difference was observed between groups for reported occurrence of acne, although the Ranch Hand cohort reported slightly more acne. The occurrence of acne relative to 1961 was comparable between groups. A marginally significant difference in the occurrence of post-1961 acne was found, with more Ranch Hands than Comparisons reporting acne strictly post-SEA. The duration of post-1961 acne was not significantly different between the two groups.

For participants with post-SEA acne, the spatial eyeglass distribution of acne (suggesting chloracne) was observed to be similar for the Ranch Hand and Comparison groups, both for individual sites and the combination of acne on the eyelids, ears, and temples. This analysis suggested that the occurrence of skin disease compatible with chloracne was not different in the two groups.

Analyses of the followup physical examination data, as with the Baseline examination, placed primary emphasis on six dermatologic disorders: comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation. Secondary emphasis was given to 16 other minor conditions (generally not associated with chloracne) recorded at the physical examination. No significant findings occurred in any variable, as reflected in Table 14-28.

TABLE 14-28.

Overall Summary Results of Unadjusted and Adjusted Analyses of Questionnaire and Physical Examination Dermatological Variables

Variable	Unadjusted	Adjusted
Questionnaire		
Incidence of Acne		
Occurrence	NS	--
Relative to 1961	NS	--
Relative to SEA (Post-1961 Cases)	NS*	--
Duration of Acne	NS	NS
Location of Acne	NS	--
Physical Examination		
Comedones	NS	NS
Acneiform Lesions	NS	NS
Acneiform Scars	NS	NS
Depigmentation	NS	NS
Inclusion Cysts	NS	NS
Hyperpigmentation	NS	NS
Other Abnormalities	NS	NS
Dermatology Index	NS	****

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

-- Analyses not performed.

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

****Group-by-covariate interaction.

No significant difference was found for any of these variables in the unadjusted analyses. The variable consisting of the 16 secondary conditions, labeled "other abnormalities," had the largest difference in the prevalence of abnormalities for the Ranch Hand cohort over the Comparison group (Est. RR: 1.08, 95% C.I.: [0.92,1.28], p=0.349), but the difference was clearly nonsignificant. The covariate effects of age, race, occupation, and the presence of pre-SEA acne were often profound with respect to the recorded dermatologic conditions.

The adjusted analyses closely mirrored the unadjusted analyses, with no significance noted between groups for any variable. Only one group-by-covariate interaction was observed in the adjusted analysis of the dermatology index, with a group-by-presence of pre-SEA acne interaction noted. However, further analysis of this interaction did not show an adverse effect in the Ranch Hand group.

Exposure index analyses did support dose-response relationships for some of the variables in certain occupational strata, but did not reveal a strong pattern of results suggesting a relationship between skin disease and herbicide exposure.

Overall, the followup examination results paralleled the Baseline findings. Although the followup examination detected more dermatologic abnormalities than those present at Baseline, slightly more abnormalities were found in the Comparisons, and most relative risks approached unity. The longitudinal analysis for the dermatology index showed no statistically significant differences between groups in the change in results from the Baseline to the followup examination.

In conclusion, none of the questionnaire results disclosed an increased likelihood of past chloracne in the Ranch Hands. The physical examination did not diagnose a current case of chloracne. The dermatological data were similar between the Ranch Hand and Comparison groups, and the longitudinal analysis of the dermatology index suggested equivalence between the Baseline and followup examination results.

CHAPTER 14

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CHAPTER 15

CARDIOVASCULAR EVALUATION

INTRODUCTION

Cardiac disease and peripheral vascular disease are not classically recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin.

Most observational and experimental animal studies using 2,4-D, 2,4,5-T, or TCDD have not extensively commented on resulting cardiac abnormalities or dysfunction. The studies described below viewed the cardiac abnormalities as expected consequences of a moribund state, and not as an indicator of primary cardiac toxicity to the putative chemical. Following oral administration of 2,4-D and 2,4,5-T, sheep and cattle developed cardiac hemorrhages.[1] A lethal oral dose of TCDD in young Rhesus monkeys produced increased heart weights in another experiment.[2] Horses and cats showed generalized vascular degeneration following exposure to soil contaminated with TCDD,[3] and mice and guinea pigs fed high amounts of TCDD manifested low heart weights.[4] A teratogenic experiment using 2,4,5-T in developing fish eggs showed graduated lethality and cardiovascular anomalies, which included enlarged veins and heart chambers.[5] Another study using ventricular muscle strips from chick embryos exposed to PCB's (including TCDD) showed a marked decrease in contractility.[6] This primary cardiotoxic response was presumably mediated by the Ah receptor, and was associated with increased prostaglandin synthesis.

Human case reports, case series of individuals with chloracne, and epidemiological studies also confirmed that cardiac function is not a sensitive indicator of exposure to herbicides or TCDD. In three case reports of acute 2,4-D poisoning, cardiac dilation and cardiac arrest were observed in the one fatal case,[7] while only transient nodal tachycardia was observed in one of the two nonfatal cases.[8,9] Three laboratory technicians with chloracne, neurological symptoms, and hypercholesterolemia following significant direct exposure to TCDD did not manifest any cardiac dysfunction,[10] however, of 10 industrial workers with chloracne, 4 complained of heart palpitations and shortness of breath.[11] In another two studies totaling 128 industrial workers, no excesses of cardiac complaints or findings were noted.[12-14]

Furthermore, in two contemporary epidemiological studies using similar cohorts from the Nitro, West Virginia, plant, no significant cardiac impairments were detected in exposed workers.[15,16] However, one study found significantly lower levels of high density lipoprotein (HDL) cholesterol in individuals with chloracne as contrasted to individuals without chloracne.[16] Two recent clinical-epidemiological pilot studies of residential areas in Missouri contaminated by TCDD did not disclose any significant cardiac disease in exposed residents,[17,18] although the Times Beach study noted a borderline association of diminished peripheral pulses in the exposed group (as did the AFHS Baseline study).

Because the herbicide literature has not identified consistent cardiovascular findings that merited a specific clinical focus, this study has collected generalized data on past cardiac events by questionnaire and medical record reviews. Current cardiac and peripheral vascular status were measured by physical examination and laboratory procedures. Coronary heart disease (CHD) has been of general concern in this study because both male cohorts are largely within the high risk ages of 40 to 65.

Since TCDD probably does not directly and permanently affect cardiovascular function, a theoretical question that arises is whether TCDD might have altered a cardiovascular disease risk factor that will exert a future adverse impact. There may be indirect evidence for such a possibility.

Risk factors for CHD include age, sex, race, family history, past personal history, diabetes (all types), smoking, cholesterol (and cholesterol-HDL ratio), diet, blood pressure, body weight, exercise pattern, stress (personality type), and alcohol.[19-22] Of these risk factors, hypertension and cholesterol have received consistent attention in clinical and epidemiological evaluations. Hypertension, either at routine examination or via specific study,[23] has not been related to phenoxy herbicide or TCDD exposure. However, hypercholesterolemia has been repeatedly associated with acute exposure to chlorophenols and dioxin.[10,12,13,16,24,25]

Baseline Summary Results

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

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

Over 80 percent of reported cardiac conditions obtained from the study questionnaire were verified by a detailed review of medical records. There was also strong correlation between the past medical history of cardiac disease and the Baseline cardiovascular examination findings. However, the differences in peripheral pulse abnormalities primarily occurred in older individuals without a history of cardiovascular disease. These abnormalities, therefore, may be a precursor to more serious arterial disease or central dysfunction.

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

Parameters of the 1985 Cardiovascular Examination

The 1985 cardiovascular examination was very similar to the 1982 Baseline examination. Data collection was divided into three major categories: heart disease history, central cardiac function, and peripheral vascular function.

Historical data were collected by a questionnaire administered at the examination site, covering the interval from 1982 through 1985. In addition, the review-of-systems portion of the physical examination recorded the overall history of heart trouble and other serious illnesses. Medical records were sought on all individuals to verify the reported conditions and to determine the time of occurrence of major cardiac events. Each participant was classified as to whether or not he developed essential hypertension, and whether he developed heart disease or had an acute myocardial infarction since his tour of duty in Southeast Asia (SEA). These endpoints were analyzed along with all other dependent variables to assess the degree of correlation between the history of cardiovascular disease and present medical findings. In addition, mortality findings were combined with the cardiovascular disease histories to form additional endpoints.

Central cardiac function was assessed by the measurements of systolic blood pressure, heart sounds (by auscultation), and an ECG. Blood pressure was determined in a standardized manner (see section on Physical Examination Data), and all examiners and diagnosticians were retrained on the detection of fourth heart sounds and the notation of innocent murmurs without recording them as abnormal heart sounds. ECG's were obtained after adherence to a 4-hour fast and abstinence from tobacco. Twelve-lead ECG's were recorded with a rhythm strip, and the following items were considered to be abnormal: right bundle branch block (RBBB), left bundle branch block (LBBB), nonspecific T-wave changes, bradycardia, tachycardia, arrhythmia, and other diagnoses (e.g., A-V block, evidence of a prior myocardial infarction).

Evaluation of the peripheral vascular system was based on diastolic blood pressure, funduscopic examination, auscultation of the carotid arteries, and determination of the quality of five peripheral pulses. The presence of carotid bruits was recorded in both carotid arteries. The femoral, popliteal, dorsalis pedis, posterior tibial, and radial pulses were assessed both by manual palpation and Doppler techniques because of the significant group differences discovered at the Baseline examination. Doppler results were considered the "gold standard" for the pulse measurements, although sensitivity correlations were established with palpation results. Rate changes of abnormal pulses occurring since the Baseline examination were also examined.

In addition to the above dependent variables, considerable analytical attention was directed to the cardiovascular risk factors of age, race, occupation (OCC), and updated values for smoking history (pack-years [PACKYR], and current smoking level [CSMOK]), alcohol history (drink-years [DRKYR], and current drinking level [ALC]), cholesterol (CHOL), HDL, cholesterol-HDL ratio (CHOL/HDL), percent body fat (%BFAT), personality score (PS), and differential cortisol response (DIFCORT).

Individuals with a verified history of diabetes (or those with an elevated 2-hour postprandial glucose level) were excluded from all analyses except the morbidity-mortality analysis. In addition, individuals with peripheral edema were excluded from analyses of the manual peripheral pulses because of the difficulty of measuring the pulse in the presence of edema.

Logistic regression models were used for dichotomous variables, and general linear models for continuous variables. All covariates except race and occupation were treated as continuous variables. Due to the large number of covariates, analyses were carried out as follows. Models adjusting only for age, race, and occupation were examined first, followed by models incorporating group (GRP)-by-age, group-by-race, and group-by-occupation interactions. Analyses were then performed, adjusting for (1) all covariates and (2) all covariates, but with only one variable selected from among each of the sets: pack-years of smoking, current smoking; cholesterol, HDL, cholesterol-HDL ratio; and drink-years of alcohol, current alcohol intensity. Selection of the covariate from each set was based on examination of the pairwise covariate-by-dependent variable associations and the coefficient from the fully adjusted model.

Stepwise modeling was then conducted using all covariates, but with only one variable selected from each of the sets described above. Only group-by-covariate interactions were examined, as were the three-factor interactions of group-by-age-by-race, group-by-age-by-occupation, and group-by-race-by-occupation. "Best models" refer to the models including only the statistically significant covariate and interaction terms. Minor numeric disparities in the tables that follow reflect missing dependent variable or covariate data. Parallel analyses using Original Comparisons can be found in Tables M-12 through M-20 of Appendix M.

Morbidity and mortality data on the full Ranch Hand cohort and an appropriate Comparison cohort were tabulated for four endpoints: (1) death (any cause) or verified nonfatal heart disease, (2) death (any cause) or verified nonfatal myocardial infarction, (3) fatal or nonfatal verified heart disease, and (4) fatal or nonfatal verified myocardial infarction or fatal heart disease. This analysis involved a number of assumptions, particularly with respect to missing histories in the noncompliant study subjects.

RESULTS AND DISCUSSION

Questionnaire Data: Reported and Verified Heart Disease

For each participant, a cardiovascular disease history was obtained from both the questionnaire and physical examination review of systems history. The baseline and third-year followup data were merged to determine, for each participant completing the third-year followup examination, whether there was ever a reported history of cardiovascular disease following service in Vietnam. Reported conditions were verified by medical record reviews and classified according to the ICD-9-CM. The following three variables were analyzed in terms of both reported and verified events:

Variables	ICD-9CM Codes
Essential Hypertension	401
Heart Disease (Excluding Essential Hypertension)	391, 393-398, 402, 404 410-414, 415-417, 420-429
Acute Myocardial Infarction	410

Table 15-1 gives the unadjusted analysis of reported and verified cardiovascular disease in the Ranch Hand and Comparison groups and the results of unadjusted group contrasts. Essential hypertension was reported in slightly over 25 percent of the participants, with rates not significantly different in the two groups (p=0.596). About 80 percent of these cases were verified, leaving similar rates of 20.7 and 20.2 percent in the Ranch Hand and Comparison groups, respectively, for verified essential hypertension. Reported heart disease was a little higher in the Ranch Hand group (28.1% vs. 26.1%) but the difference in the percentage of verified heart disease was of borderline significance (23.8% vs. 20.3%, p=0.054). The rates of reported and verified myocardial infarctions were about 2 percent and 1 percent, respectively, and not significantly different in the two groups.

The associations between each of the covariates and the three verified cardiovascular endpoints are presented in Tables 15-2, 15-3, and 15-4. The tables containing the covariate associations with the reported cardiovascular diseases are included in Tables M-1 through M-3 of Appendix M. All reported cardiac illnesses (verified and unverified) are included in these tables. Many of the classic risk factors were identified. Age, smoking, cholesterol and/or cholesterol-HDL ratio, percent body fat, differential cortisol, and alcohol use were significantly associated with reported and verified essential hypertension, although the smoking effect was in the opposite direction of that expected. Age, occupation, and the cholesterol-HDL ratio were significantly associated with reported and verified heart disease, with more disease found in officers than in enlisted personnel. Age, pack-years of smoking, cholesterol-HDL ratio, and drink-years of alcohol were significantly associated with reported and/or verified myocardial infarction (the smoking effect being in the expected direction).

The results of logistic regression analyses adjusting for these variables are presented in Table 15-5. The results were similar to the unadjusted results, but the adjusted relative risk for verified heart disease reached statistical significance (p=0.036). No significant group-by-covariate interactions were noted. Nearly identical results were obtained in the analysis of the Ranch Hands and Original Comparisons (see Tables M-12 and M-13 of Appendix M).

Morbidity-Mortality Analysis

Differential mortality in the two groups could introduce bias in the analysis of morbidity data. For the cardiovascular evaluation, morbidity and mortality data on all Ranch Hands (diabetics included) and the first Comparison of the randomly ordered set matched to the Ranch Hands were combined to estimate the frequency of four hierarchical cardiovascular endpoints. Because of competing mortality and possible misclassification of the cause of death, the endpoints of death (any cause) or verified nonfatal heart disease, and death (any cause) or verified nonfatal myocardial infarction were examined to assess group differences in the most extreme case (i.e., all deaths being associated with cardiovascular disease). The other two endpoints were limited to fatal or nonfatal verified heart disease, and fatal or nonfatal verified myocardial infarction or fatal heart disease.

The analysis was based on 1,257 Ranch Hands and 1,253 Comparisons. The history of each individual from the end of his tour of duty in SEA to the present was reviewed. Histories of verified heart disease and myocardial

TABLE 15-1.

Unadjusted Analyses for Reported and Verified Heart Disease by Group

		Group					
		Ranch Hand		Comparison			
Variable	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Reported Essential Hypertension	n	942		1,206			
	Yes	247	26.2	304	25.2	1.05 (0.87,1.28)	0.596
	No	695	73.8	902	74.8		
Verified Essential Hypertension	n	942		1,206			
	Yes	195	20.7	244	20.2	1.03 (0.83,1.27)	0.787
	No	747	79.3	962	79.8		
Reported Heart Disease (Excluding Hypertension)	n	942		1,206			
	Yes	265	28.1	315	26.1	1.11 (0.91,1.34)	0.298
	No	677	71.9	891	73.9		
Verified Heart Disease (Excluding Hypertension)	n	942		1,206			
	Yes	224	23.8	245	20.3	1.22 (1.00,1.50)	0.054
	No	718	76.2	961	79.7		
Reported Myocardial Infarction	n	942		1,206			
	Yes	20	2.1	22	1.8	1.17 (0.63,2.15)	0.617
	No	922	97.9	1,184	98.2		
Verified Myocardial Infarction	n	942		1,206			
	Yes	9	1.0	13	1.1	0.88 (0.38,2.08)	0.779
	No	933	99.0	1,193	98.9		

TABLE 15-2.

Association Between Verified Essential Hypertension and the Covariates in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal	p-Value
Age	Born ≥1942	934	17.2	0.001
	Born <1942	1,214	22.9	
Race	Black	126	25.4	0.191
	Nonblack	2,022	20.1	
Occupation	Officer	807	21.2	
	Enlisted Flyer	354	20.1	0.798
	Enlisted Groundcrew	987	20.0	
Current Smoking	0	1,262	22.8	
	>0 - 20	463	16.6	0.005
	>20	422	17.5	
Pack-Years Smoking	0	512	24.8	
	>0 - 10	760	17.9	0.010
	>10	869	20.0	
Cholesterol	≤200	766	15.5	
	>200 - 230	650	21.1	<0.001
	>230	732	25.0	
HDL	≤40	719	21.6	
	>40 - 50	754	20.6	0.524
	>50	675	19.1	
Cholesterol-HDL Ratio	≤4.2	717	16.2	
	>4.2 - <5.5	743	21.3	0.001
	≥5.5	688	24.0	
Percent Body Fat	<10	10	0.0	
	10 - 25	1,758	16.7	<0.001
	>25	379	38.5	
Personality Score	<-5	829	22.3	
	-5 - 5	731	20.5	0.113
	>5	580	17.8	
Differential Cortisol	≤0.6	704	23.6	
	>0.6 - 4.0	745	19.1	0.033
	>4.0	683	18.4	
Current Alcohol Use (Drinks/Day)	0	592	21.4	
	>0 - 1	809	17.2	0.011
	>1	738	23.2	
Drink-Years Alcohol	≤1.25	691	21.1	
	>1.25 - 25	719	18.4	0.116
	>25	666	22.8	

TABLE 15-3.

Association Between Verified Heart Disease and the Covariates in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal	p-Value
Age	Born ≥1942	934	17.9	<0.001
	Born <1942	1,214	24.9	
Race	Black	126	23.0	0.826
	Nonblack	2,022	21.8	
Occupation	Officer	807	24.8	
	Enlisted Flyer	354	20.9	0.034
	Enlisted Groundcrew	987	19.8	
Current Smoking	0	1,262	22.7	
	>0 - 20	463	21.2	0.461
	>20	422	19.9	
Pack-Years Smoking	0	512	23.2	
	>0 - 10	760	20.9	0.617
	>10	869	21.9	
Cholesterol	≤200	766	21.2	
	>200 - 230	650	21.1	0.533
	>230	732	23.2	
HDL	≤40	719	21.7	
	>40 - 50	754	20.4	0.357
	>50	675	23.6	
Cholesterol-HDL Ratio	≤4.2	717	24.1	
	>4.2 - <5.5	743	18.8	0.041
	≥5.5	688	22.7	
Percent Body Fat	<10	10	30.0	
	10 - 25	1,758	22.1	0.619
	>25	379	20.3	
Personality Score	<-5	829	21.4	
	-5 - 5	731	20.9	0.369
	>5	580	24.0	
Differential Cortisol	≤0.6	704	19.2	
	>0.6 - 4.0	745	22.4	0.084
	>4.0	683	24.0	
Current Alcohol Use Drinks/Day	0	592	23.0	
	≤1	809	22.5	0.441
	>0 - 1	738	20.3	
Drink-Years Alcohol	≤1.25	691	21.4	
	>1.25 - 25	719	22.0	0.968
	>25	666	21.8	

TABLE 15-4.

Association Between Verified Myocardial Infarction and the Covariates in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal	p-Value
Age	Born ≥1942	934	0.2	0.002
	Born <1942	1,214	1.6	
Race	Black	126	0.0	0.471
	Nonblack	2,022	1.1	
Occupation	Officer	807	0.9	
	Enlisted Flyer	354	1.4	0.697
	Enlisted Groundcrew	987	1.0	
Current Smoking	0	1,262	0.8	
	>0 - 20	463	1.7	0.228
	>20	422	1.0	
Pack-years Smoking	0	512	0.2	
	>0 - 10	760	0.8	0.018
	>10	869	1.7	
Cholesterol	≤200	766	0.5	
	>200 - 230	650	0.9	0.095
	>230	732	1.6	
HDL	≤40	719	1.5	
	>40 - 50	754	0.9	0.210
	>50	675	0.6	
Cholesterol-HDL Ratio	≤4.2	717	0.4	
	>4.2 - <5.5	743	0.9	0.046
	≥5.5	688	1.7	
Percent Body Fat	<10	10	0.0	
	10 - 25	1,758	1.0	0.872
	>25	379	0.8	
Personality Score	<-5	829	0.8	
	-5 - 5	731	1.5	0.278
	>5	580	0.7	
Differential Cortisol	≤0.6	704	1.0	
	>0.6 - 4.0	745	1.1	0.989
	>4.0	683	1.0	
Current Alcohol Use (Drinks/Day)	0	592	1.5	
	>0 - 1	809	0.9	0.376
	>1	738	0.8	
Drink-Years Alcohol	≤1.25	691	1.3	
	>1.25 - 25	719	0.4	0.143
	>25	666	1.4	

TABLE 15-5.

Adjusted Analyses for Reported and Verified Heart Disease

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Reported Essential Hypertension	1.14 (0.93,1.41)	0.211	AGE ($p<0.001$), CSMOK ($p=0.001$),CHOL ($p<0.001$), %BFAT ($p<0.001$), ALC ($p<0.001$)
Verified Essential Hypertension	1.11 (0.89,1.39)	0.347	AGE ($p=0.021$), CSMOK ($p=0.021$), CHOL ($p<0.001$), %BFAT ($p<0.001$), PS ($p=0.039$)
Reported Heart Disease	1.12 (0.92,1.36)	0.258	AGE ($p<0.001$)
Verified Heart Disease	1.25 (1.02,1.54)	0.036	AGE ($p<0.001$)
Reported Myocardial Infarction	1.16 (0.60,2.23)	0.667	AGE ($p<0.001$),OCC ($p=0.014$), CHOL/HDL ($p=0.016$)
Verified Myocardial Infarction	0.93 (0.38,2.23)	0.865	AGE ($p<0.001$), CHOL/HDL ($p=0.025$)

*Abbreviations:

CSMOK: Current smoking
CHOL: Cholesterol
%BFAT: Percent body fat
ALC: Current alcohol use (drinks/day)
PS: Personality score
OCC: Occupation
CHOL/HDL: Cholesterol-HDL ratio

infarction for living individuals who were noncompliant at Baseline and at the followup were missing. For the living noncompliant individuals, the observed rate in the compliant individuals was used to estimate the number of nonfatal events among the noncompliant individuals for each cohort. It was assumed that there were no nonfatal cardiovascular events in the noncompliant individuals who died due to a cause other than cardiovascular system failure. The results are shown in Table M-4 of Appendix M.

There was a total of 66 deaths in the Ranch Hand group and 77 in the group of Comparisons. The estimated percentage of Ranch Hands who died (any cause) or had a verified nonfatal history of heart disease was 27.4 as contrasted to 24.5 in the Comparisons.

The rate of verified nonfatal myocardial infarctions was approximately 1 percent in each group. The estimated percentage of deaths (any cause) or verified nonfatal myocardial infarction was 6.4 percent in the Ranch Hands and 7.0 percent in the Comparisons.

Only 5 of the 66 deaths in the Ranch Hands and 3 of the 77 deaths in the Comparisons either were from heart disease, or were individuals who had verified heart disease histories. The estimated percentage of fatal and nonfatal verified heart disease was 22.5 percent in the Ranch Hands and 18.6 percent in the Comparisons.

Of the 66 deaths in the Ranch Hands only 1 individual died from cardiovascular disease or had a verified history of myocardial infarction as compared to 2 of the 77 deaths in the Comparisons. The estimated percentage of fatal or nonfatal verified myocardial infarction or fatal heart disease was 1.2 percent in the Ranch Hands and 1.0 percent in the Comparisons.

These contrasts must be interpreted guardedly since they involve some unverifiable assumptions. Nevertheless, they are consistent with the morbidity findings presented in the chapter, and tend to show that the clinical cardiovascular disease spectrum is approximately equal in both groups.

Physical Examination Data

Central Cardiac Function

Central cardiac function was assessed by the measurement of systolic blood pressure, heart sounds, and an ECG. Systolic blood pressure was determined by a standardized sphygmometer, at the appearance of the first sound with the nondominant arm placed at heart level; the lowest value of three readings was recorded. Detection of abnormal heart sounds was conducted by standard auscultation with the participant placed in sitting, supine, and left lateral supine positions. Fourth heart sounds were assessed; murmurs were graded in intensity and location and were judged to be functional (normal) or organic (abnormal) in nature. Fourth heart sounds were scored as abnormal. ECG data were collected by a standardized 12-lead machine; approximately 95 percent of the clinical interpretations were performed by one cardiologist. All participants were asked to abstain from smoking for at least 4 hours prior to their ECG.

Systolic Blood Pressure

Systolic blood pressure was analyzed both as continuous and dichotomized variables (normal, 140 or less mm Hg; abnormal, more than 140 mm Hg). Combined distributional data from both groups revealed significant digit preference for values ending in zero ($p<0.0001$ for both systolic and diastolic readings), but standard statistical analyses were performed since the zero-digit peaks (e.g., 130, 140, 150 mm Hg) were relatively uniform and did not visually differ between the Ranch Hand and Comparison groups. Zero digit readings were recorded for 59.4 percent of the systolic blood pressures and 55.0 percent of the diastolic blood pressures.

Table 15-6 gives the percentage of participants with abnormally high systolic values. The percent of abnormals was not significantly different from each other ($p=0.529$). Systolic blood pressure, analyzed as a continuous variable, had a mean of 118.96 mm Hg (95% C.I.: [118.06,119.86]) for the Ranch Hand group and a mean of 119.55 mm Hg (95% C.I.: [118.71,120.39]) for the Comparison group. These means were not significantly different ($p=0.349$). The means were also not significantly different when Original Comparisons were used ($p=0.182$).

The association between each of the covariates (categorized into either two or three levels) and dichotomized systolic blood pressure in the combined Ranch Hand and Comparison groups is shown in Table 15-7. Age, cholesterol, percent body fat, personality score, and alcohol use (both current use and drink-years) were significantly associated with increased systolic pressure. These covariate effects were in the direction typically found in other studies,[26,27] except for personality score where those participants with low scores (in the Type B direction) had the highest percentage of abnormal values.

Adjustment of the categorical systolic blood pressure by the above covariates was performed by logistic regression analysis, and these results are presented in Table 15-8. As shown, there were no significant differences between the Ranch Hand and Comparison groups ($p=0.920$). Age, cholesterol, percent body fat, personality score, and current alcohol use all had statistically significant effects. An adjusted analysis of systolic blood pressure in the continuous form revealed a significant group (GRP)-by-age-by-race interaction ($p=0.012$) along with the significant main effects of current smoking ($p<0.001$), cholesterol ($p<0.001$), percent body fat ($p<0.001$), personality score ($p<0.001$), and current alcohol use ($p=0.002$). Exploration of the interaction revealed that among Blacks there was a group-by-age interaction ($p=0.007$), with a mean systolic pressure greater in the Ranch Hand group than in the Comparison group at the younger age levels, but lower at the older age levels. The estimated Ranch Hand-Comparison difference was 4.56 ($\pm$ 3.30) mm Hg at the Baseline age of 35 and -16.01 ($\pm$ 5.87) mm Hg at the Baseline age of 53 (see Table M-5 of Appendix M). In the nonblack cohort the group-by-age interaction was not significant ($p=0.338$), nor was there evidence of any overall group effect ($p=0.356$). In the analysis of the Ranch Hands and Original Comparisons, there were no statistically significant group differences, either unadjusted or adjusted for covariate effects (see Tables M-14 and M-15 of Appendix M).

TABLE 15-6.

Unadjusted Analyses for Central Cardiac Function By Group (Diabetics Excluded)

		Group					
		Ranch Hand		Comparison			
Variable	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Systolic Blood Pressure	n	942		1,205			
	Abnormal	60	6.4	85	7.1	0.90 (0.64, 1.26)	0.529
	Normal	882	93.6	1,120	92.9		
Heart Sounds	n	941		1,206			
	Abnormal	31	3.3	32	2.7	1.25 (0.76,2.06)	0.384
	Normal	910	96.7	1174	97.3		
ECG (Overall)	n	947		1,206			
	Abnormal	121	12.8	169	14.0	0.90 (0.70,1.16)	0.430
	Normal	821	87.2	1,037	86.0		
ECG: RBBB	n	942		1,206			
	Abnormal	5	0.5	9	0.7	0.71 (0.24,2.13)	0.542
	Normal	937	99.5	1,197	99.3		
ECG: LBBB	n	942		1,206			
	Abnormal	0	0.0	0	0.0	--	--
	Normal	942	100.0	1,206	100.0		
ECG: Nonspecific T-Wave Changes	n	942		1,206			
	Abnormal	85	9.0	107	8.9	1.02 (0.76,1.37)	0.904
	Normal	857	91.0	1,099	91.1		

TABLE 15-6. (continued)

Unadjusted Analyses for Central Cardiac Function By Group
(Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Group: Ranch Hand Percent	Group: Comparison Number	Group: Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
ECG: Bradycardia	n	942		1,206			
	Abnormal	45	4.8	56	4.6	1.03 (0.69,1.54)	0.889
	Normal	897	95.2	1,150	95.4		
ECG: Tachycardia	n	942		1,206			
	Abnormal	0	0.0	0	0.0	--	--
	Normal	942	100.0	1,206	100.0		
ECG: Arrhythmia	n	942		1,206			
	Abnormal	31	3.3	41	3.4	0.97 (0.60,1.55)	0.889
	Normal	911	96.7	1,165	96.6		
ECG: Other Diagnoses	n	942		1,206			
	Abnormal	97	10.3	132	11.0	0.93 (0.71,1.23)	0.631
	Normal	845	89.7	1,074	89.0		

--No relative risk given, since no abnormals are present.

TABLE 15-7.

Association Between Central Cardiac Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Systolic Blood Pressure	<0.001	NS	NS	NS	NS	<0.001	NS	NS	0.001	0.002	NS	0.018	<0.001
Heart Sounds	0.005	NS	NS*	NS	NS	NS	NS*	0.003	NS	NS	NS	NS	NS
ECG (Overall)	<0.001	NS	NS*	NS	0.010	NS*	NS*	0.016	<0.001	NS	NS	NS	NS
ECG: RBBB	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ECG: Nonspecific T-Wave Changes	<0.001	NS	NS	NS	0.038	0.002	NS	<0.001	<0.001	NS	NS	NS	0.006
ECG: Bradycardia	NS*	NS	0.010	NS	0.007	NS*	0.002	<0.001	NS	NS	NS	NS	NS
ECG: Arrhythmia	NS	NS	0.023	NS	0.028	NS	NS	NS	NS	NS	NS	NS	NS
ECG: Other Diagnoses	<0.001	NS	0.011	NS*	0.023	NS	NS	NS	NS	NS	NS	0.019	NS

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

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

TABLE 15-8.

Adjusted Analyses for Central Cardiac Function (Diabetics Excluded)*

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Systolic Blood Pressure (Discrete)	0.98 (0.69,1.40)	0.920	AGE (p<0.001) CHOL (p=0.004) %BFAT (p<0.001) PS (p=0.002) ALC (p=0.020)
Systolic Blood Pressure (Continuous)	****	****	GRP*RACE*AGE (p=0.012) CSMOK (p<0.001) CHOL (p<0.001) %BFAT (p<0.001) PS (p<0.001) ALC (p=0.002)
Heart Sounds	1.33 (0.80,2.24)	0.276	AGE (p<0.001) RACE (p=0.003) CHOL/HDL (p=0.002)
ECG (Overall)	****	****	AGE (p<0.001) RACE (p=0.005) %BFAT (p<0.001) GRP*PACKYR (p=0.008)
ECG: RBBB	0.72 (0.24,2.15)	0.555	AGE (p=0.008)
ECG: Nonspecific ST-T-Wave Changes	1.12 (0.81,1.53)	0.497	AGE (p<0.001) RACE (p=0.005) CHOL (p=0.007) %BFAT (p<0.001)

TABLE 15-8. (continued)

Adjusted Analyses for Central Cardiac Function
(Diabetics Excluded)*

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
ECG: Bradycardia	1.08 (0.72,1.62)	0.726	OCC (p=0.047) CHOL/HDL (p<0.001)
ECG: Arrhythmia	****	****	AGE (p=0.001) OCC (p<0.001) GRP*PACKYR (p=0.018) GRP*%BFAT (p=0.038)
ECG: Other Diagnoses	0.92 (0.69,1.23)	0.575	AGE (p<0.001) RACE (p=0.015) CSMOK (p=0.039)

*Some adjusted analyses did not explore effects of all covariates due to sparse number of abnormalities (see text).

**Additional Abbreviations:

GRP: group
PACKYR: pack-years smoking

****Group-by-covariate interaction, relative risk/difference in group means, 95% confidence interval, and p-value not presented (see Table M-5 of Appendix M).

Heart Sounds

As shown in Table 15-6, the unadjusted frequency of abnormal heart sounds in the two groups was not significantly different (p=0.384).

The covariate tests of association (Table 15-7) showed significant effects for age (p=0.005), cholesterol-HDL ratio (p=0.003), and a borderline association with occupation (p=0.069). Increased age (born before 1942) had a frequency of 3.9 percent heart sound abnormalities as contrasted to 1.6 percent abnormalities in the younger age group (born in or after 1942). The cholesterol-HDL ratio (less than or equal to 4.2, between 4.2 and 5.5, and greater than or equal to 5.5) was positively associated with increasing frequencies of abnormal heart sounds (1.7, 2.6, and 4.7 percent, respectively). The observed frequencies of abnormal heart sounds were 3.8, 1.4, and 2.7 percent in the officers, enlisted flyers, and the enlisted groundcrew, respectively.

The adjusted analysis (Table 15-8) did not detect any significant group differences (p=0.276). Age, race, and the cholesterol-HDL ratio were significant covariates (p<0.001, p=0.003, and p=0.002, respectively). No two- or three-way group interactions were noted. Similarly, nonsignificant results were found in the analyses of the Original Comparisons versus the Ranch Hands (see Table M-15 of Appendix M).

Electrocardiograph Findings

All ECG tracings were scored as normal or abnormal; specific abnormalities included RBBB, LBBB, nonspecific T-wave changes, bradycardia, tachycardia, arrhythmia, and other diagnoses.

The unadjusted analysis of these variables (Table 15-6) showed no statistically significant differences in the overall ECG results, or any of the specific subcategories, between the Ranch Hand and Comparison groups. Two additional findings in the analysis were of interest: (1) the Ranch Hands had a uniformly lower number of ECG abnormalities than the Comparisons (though not statistically significant), and (2) the sum of the specific ECG findings exceeds the proportion of abnormalities scored on the overall ECG because some individuals accounted for two or more abnormalities.

The associations between the covariates and the various ECG findings are presented in Table 15-7. Age was significantly associated with the overall ECG findings (p<0.001), nonspecific T-wave changes (p<0.001), and other ECG diagnoses (p<0.001), with more abnormalities found in the older age group. Occupation was significantly associated with bradycardia (p=0.010), arrhythmia (p=0.023), and other ECG findings (p=0.011). A higher percentage of officers than enlisted flyers or groundcrew had bradycardia, whereas enlisted flyers had the lowest proportion of arrhythmias, and enlisted groundcrew had the highest percentage. Officers and enlisted flyers had a higher percentage than the enlisted groundcrew cohort of other ECG findings.

Pack-years of smoking was significantly associated with the overall ECG findings (p=0.010), T-wave changes (p=0.038), bradycardia (p=0.007), arrhythmia (p=0.028), and other ECG diagnoses (p=0.023). For the overall ECG findings, nonspecific T-wave changes, and arrhythmias, the moderate smoking group (greater than 0 to 10 pack-years) had the fewest abnormalities.

Bradycardia was negatively associated with pack-years of smoking, with the highest frequency of abnormalities (7.2%) found in the 0 pack-years category versus the lowest proportion (3.6%) of abnormalities in the greater than 10 pack-years category. Cholesterol levels and/or the cholesterol-HDL ratio were positively associated with abnormalities in the overall ECG ($p=0.016$) and T-wave findings ($p<0.001$), but were negatively associated with bradycardia ($p<0.001$).

Increased percent body fat was significantly associated with overall ECG abnormalities ($p<0.001$) and nonspecific T-wave changes ($p<0.001$). Drink-years of alcohol was only associated with T-wave changes ($p=0.006$), with more abnormalities in the greater than 25 drink-years category than in the less than or equal to 1.25 drink-years category, but relatively fewer abnormalities in the more than 1.25 to 25 drink-years category. The covariate of current alcohol use was associated only with the category of other ECG diagnoses ($p=0.019$), but not in a consistent manner (individuals averaging less than one drink per day had more abnormalities than nondrinkers, but those averaging more than one drink per day had the lowest percentage of abnormalities). The covariates of race, current smoking, personality score, and differential cortisol level, however, did not significantly affect the variables of central cardiac function.

Results from the adjusted logistic regression analyses are shown in Table 15-8. No significant group differences were detected for categorical RBBB, T-wave changes, bradycardia, and other ECG diagnoses. The covariates of age, race, percent body fat, pack-years of smoking, current smoking, cholesterol, and cholesterol-HDL ratio were significantly associated with one or more of the ECG variables. RBBB was adjusted only for age due to the small number of abnormalities.

The adjusted analysis of the overall ECG findings revealed a significant group-by-pack-year interaction ($p=0.008$), and the analysis of the arrhythmia variable disclosed two significant interactions: a group-by-pack-year association ($p=0.018$) and a group-by-percent body fat association ($p=0.038$). All of these interactions are displayed in Table M-5 of Appendix M. In the case of the overall ECG findings, the adjusted relative risk among nonsmokers was significantly less than one ($p=0.038$), i.e., a lower risk for Ranch Hands than Comparisons. For heavy smokers (30 pack-years), the adjusted relative risk was 1.25 (95% C.I.: [0.89,1.76], $p=0.197$). For cardiac arrhythmias, exploration of the group-by-pack-year interaction at the approximate mean percent body fat of 21 percent showed a borderline significant relationship favoring the nonsmoking Ranch Hands (Adj. RR: 0.58, 95% C.I.: [0.30,1.10], $p=0.093$); heavy smoking Ranch Hands had a higher proportion of arrhythmias than heavy smoking Comparisons, but this association was not statistically significant ($p=0.162$). For the group-by-percent body fat interaction, 10 percent and 30 percent body fat levels were analyzed at the approximate median of 7 pack-years of smoking. The adjusted relative risk of 0.23 (95% C.I.: [0.07,0.78]) was statistically significant for the 10 percent body fat category ($p=0.018$), indicating a lower adjusted frequency of cardiac arrhythmias for nonobese Ranch Hands than for nonobese Comparisons. This situation was reversed for obese Ranch Hands, but the association was not statistically significant (RR: 1.88, 95% C.I.: [0.66,5.34], $p=0.234$).

The adjusted analyses using the Original Comparisons were nearly identical to the analyses of the total Comparison group, including the three

group interactions for overall ECG findings and cardiac arrhythmias described above. The analyses of the Original Comparison group are found in Tables M-15 and M-16 of Appendix M.

Peripheral Vascular Function

Peripheral vascular function was assessed by the diastolic blood pressure, funduscopic examination of small vessels, the presence or absence of carotid bruits, and both manual palpation and Doppler bilateral measurements of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Individual peripheral pulses were combined to form overall indices of peripheral vascular status. Diastolic blood pressure was measured by the standard auscultatory technique, and was recorded at the pressure level corresponding to the disappearance of sound. The funduscopic examination was conducted with undilated pupils in a standard manner, with emphasis placed upon the detection of arterio-venous nicking, hemorrhages, exudate, and papilledema. Carotid bruits were assessed by standard bilateral auscultation; confirmation of bruits was not attempted by the Doppler technique. Manual pulse determinations were performed by the examining physician, independent of the Doppler measurements performed by qualified technicians. Tobacco abstinence for at least four hours was required for the Doppler examination, but not for the manual palpation. Only the physician diagnostician had access to both sets of pulse data.

Diastolic Blood Pressure

Diastolic blood pressure was analyzed as a continuous variable and as a dichotomized variable (normal value less than or equal to 90 mm Hg; abnormal value greater than 90 mm Hg). As with the systolic readings, a significant zero digit preference was noted for the diastolic blood pressure values.

Table 15-9 arrays the results of the unadjusted categorical analyses. As shown, there are no statistically significant group differences for the proportions of diastolic abnormalities ($p=0.999$). Diastolic blood pressure, analyzed as a continuous variable, had a mean of 79.76 mm Hg (95% C.I.: [71.97, 80.35]) for the Ranch Hand group and a mean of 79.77 mm Hg (95% C.I.: [79.24, 80.30]) for the Comparison Group. These means were not significantly different ($p=0.986$). The means were also not significantly different when Original Comparisons were used ($p=0.555$).

The tests of covariate association with diastolic blood pressure are given in Table 15-10. Cholesterol, cholesterol-HDL ratio, percent body fat, differential cortisol, and current alcohol use were significantly related to diastolic blood pressure ($p<0.001$, $p=0.006$, $p<0.001$, $p=0.041$, and $p=0.014$, respectively). For increasing cholesterol, cholesterol-HDL ratio, and percent body fat, increases in proportions of abnormal diastolic blood pressure were obtained, whereas for increasing differential cortisol values, a decline in blood pressure abnormalities was found. Current alcohol use (drinks per day) revealed an inconsistent association with diastolic blood pressure abnormalities, with nondrinkers having a higher proportion of abnormalities than low-level drinkers, but a lower proportion of abnormalities than moderate drinkers (8.3, 6.4, and 10.6 percent abnormalities, respectively). The covariates of age, race, occupation, current smoking, pack-years of smoking, HDL, personality score, and drink-years of alcohol were not associated with diastolic blood pressure abnormalities.

TABLE 15-9.

Unadjusted Analyses for Peripheral Vascular Function by Group
(Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Diastolic Blood Pressure	n	942		1,204			
	Abnormal	79	8.4	101	8.4	1.00 (0.74,1.36)	0.999
	Normal	863	91.6	1,103	91.6		
Funduscopic Examination	n	941		1,206			
	Abnormal	7	0.7	6	0.5	1.50 (0.50,4.47)	0.472
	Normal	934	99.3	1,200	99.5		
Carotid Bruits	n	941		1,205			
	Abnormal	7	0.7	7	0.6	1.28 (0.45,3.66)	0.646
	Normal	934	99.3	1,198	99.4		
Radial Pulses (Manual)	n	929		1,191			
	Abnormal	4	0.4	8	0.7	0.64 (0.19,2.13)	0.465
	Normal	925	99.6	1,183	99.3		
Radial Pulses (Doppler)	n	942		1,203			
	Abnormal	3	0.3	4	0.3	0.96 (0.21,4.30)	0.952
	Normal	939	99.7	1,199	99.7		
Femoral Pulses (Manual)	n	929		1,191			
	Abnormal	20	2.2	25	2.1	1.03 (0.57,1.86)	0.932
	Normal	909	97.8	1,166	97.9		

TABLE 15-9. (continued)

Unadjusted Analyses for Peripheral Vascular Function by Group
(Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Femoral Pulses (Doppler)	n	942		1,205			
	Abnormal	6	0.6	4	0.3	1.92 (0.54,6.82)	0.312
	Normal	936	99.4	1,201	99.7		
Popliteal Pulses (Manual)	n	929		1,191			
	Abnormal	16	1.7	28	2.4	0.73 (0.39,1.35)	0.317
	Normal	913	98.3	1,163	97.6		
Popliteal Pulses (Doppler)	n	942		1,204			
	Abnormal	10	1.1	8	0.7	1.60 (0.63,4.08)	0.322
	Normal	932	98.9	1,196	99.3		
Dorsalis Pedis Pulses (Manual)	n	929		1,191			
	Abnormal	102	11.0	127	10.7	1.03 (0.78,1.36)	0.818
	Normal	827	89.0	1,064	89.3		
Dorsalis Pedis Pulses (Doppler)	n	938		1,202			
	Abnormal	228	24.3	274	22.8	1.09 (0.89,1.33)	0.412
	Normal	710	75.7	928	77.2		
Posterior Tibial Pulses (Manual)	n	929		1,191			
	Abnormal	27	2.9	31	2.6	1.12 (0.66,1.89)	0.674
	Normal	902	97.1	1,160	97.4		
Posterior Tibial Pulses (Doppler)	n	939		1,202			
	Abnormal	19	2.0	25	2.1	0.97 (0.53,1.78)	0.928
	Normal	920	98.0	1,177	97.9		

TABLE 15-9. (continued)

Unadjusted Analyses for Peripheral Vascular Function by Group,
(Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Group: Ranch Hand Percent	Group: Comparison Number	Group: Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Leg Pulses (Manual)	n	929		1,191			
	Abnormal	131	14.1	177	14.9	0.94 (0.74,1.20)	0.624
	Normal	798	85.9	1,014	85.1		
Leg Pulses (Doppler)	n	938		1,202			
	Abnormal	237	25.3	288	24.0	1.07 (0.88,1.31)	0.490
	Normal	701	74.7	914	76.0		
Peripheral Pulses (Manual)	n	929		1,191			
	Abnormal	133	14.3	181	15.2	0.93 (0.73,1.18)	0.575
	Normal	796	85.7	1,010	84.8		
Peripheral Pulses (Doppler)	n	938		1,202			
	Abnormal	239	25.5	290	24.1	1.08 (0.88,1.31)	0.472
	Normal	699	74.5	912	75.9		
All Pulses (Manual)	n	929		1,191			
	Abnormal	133	14.3	182	15.3	0.93 (0.73,1.18)	0.535
	Normal	796	85.7	1,009	84.7		
All Pulses (Doppler)	n	938		1,201			
	Abnormal	239	25.5	291	24.2	1.07 (0.88,1.30)	0.509
	Normal	699	74.5	910	75.8		

TABLE 15-10.

Association Between Peripheral Vascular Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Diastolic Blood Pressure	NS	NS	NS	NS	NS	<0.001	NS	0.006	<0.001	NS	0.041	0.014	NS
Funduscopic Examination	0.004	0.040	NS	NS	NS	NS	NS	0.016	0.026	NS	NS	0.004	NS
Carotid Bruits	NS*	NS	NS	NS*	NS	NS*	NS	NS	NS	NS	NS	NS	0.021
Radial Pulses (Manual)	NS	NS	NS	NS	NS	NS	NS	0.033	NS	NS	NS	NS	NS
Radial Pulses (Doppler)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Femoral Pulses (Manual)	<0.001	NS	NS	NS	NS	NS*	0.002	<0.001	0.001	NS	NS	NS	<0.001
Femoral Pulses (Doppler)	NS*	NS	NS	0.001	0.006	NS*	NS	0.019	NS	NS	NS	NS	0.013
Popliteal Pulses (Manual)	NS*	NS	NS	NS	0.001	NS	NS	0.002	NS	NS	NS	NS	NS*
Popliteal Pulses (Doppler)	0.002	NS	NS	<0.001	0.010	NS	NS	NS*	NS	NS	NS	NS	NS

TABLE 15-10. (continued)

Association Between Peripheral Vascular Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Dorsalis Pedis Pulses (Manual)	0.018	NS	NS*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Dorsalis Pedis Pulses (Doppler)	NS*	0.001	0.007	NS	NS	NS	NS	NS	NS	NS	NS	NS
Posterior Tibial Pulses (Manual)	0.034	<0.001	NS	<0.001	<0.001	NS*	NS	NS	NS	NS	NS	NS
Posterior Tibial Pulses (Doppler)	0.003	NS*	NS	0.021	NS	NS	NS	0.035	NS	0.028	NS*	NS	NS*
Leg Pulses (Manual)	0.001	NS	NS	NS	0.031	NS	0.013	0.013	NS	NS	NS	NS	NS
Leg Pulses (Doppler)	0.020	0.009	0.012	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Peripheral Pulses (Manual)	<0.001	NS	NS	NS	0.028	NS	0.013	0.010	NS	NS	NS	NS	NS

TABLE 15-10. (continued)

Association Between Peripheral Vascular Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Peripheral Pulses (Doppler)	0.037	0.015	0.019	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
All Pulses (Manual)	<0.001	NS	NS	NS	0.023	NS	0.013	0.012	NS	NS	NS	NS	NS
All Pulses (Doppler)	0.032	0.014	0.023	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

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

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

The adjusted categorical and continuous analyses are shown in Table 15-11. No significant group differences were found in the proportions of diastolic abnormalities (p=0.653), or in the difference of group mean values (p=0.299). The covariates of current smoking, cholesterol, percent body fat, and current alcohol use were statistically significant in both the categorical and continuous analyses; age was significant only in the analysis of group mean differences (p=0.005). No significant group-by-covariate interactions were found in either the logistic regression or general linear models. The adjusted analyses for the Original Comparisons were very similar to those described on the total Comparison group (see Table M-18 of Appendix M).

Funduscopic Examination

The funduscopic examination detected only 13 individuals with arteriovenous nicking (a sign of chronic blood pressure elevation) or vessel hemorrhages, 7 from the Ranch Hands and 6 from the Comparisons (p=0.472, Table 15-9).

The covariate tests of association are given in Table 15-10. Age, race, cholesterol/HDL ratio, percent body fat, and current drinking were statistically significant (p=0.004, 0.040, 0.016, 0.026, and 0.004, respectively). All funduscopic abnormalities were found in the older age group (born in or before 1942). Blacks had a higher proportion of abnormalities than nonblacks (2.4 percent versus 0.5 percent, respectively). The highest cholesterol-HDL category contained the highest proportion of funduscopic abnormalities; and increasing levels of percent body fat were associated with increases in proportions of abnormalities. Current alcohol consumption showed that nondrinkers had the highest proportion of abnormalities. The covariates of occupation, current smoking, pack-years of smoking, cholesterol, HDL, personality score, differential cortisol and drink-years of alcohol did not show significant effects.

In the adjusted analysis by logistic regression (Table 15-11), there were no significant differences in funduscopic abnormalities between the Ranch Hand and Comparison groups (Adj. RR: 1.78; 95% C.I.: [0.56,5.62], p=0.322). Due to sparse data the model was adjusted only for the covariates of age, race, cholesterol-HDL ratio, percent body fat, and current alcohol consumption; and all were significant in the model. No group interactions were detected, and the results of the contrast of the Ranch Hand with the Original Comparison group were also nonsignificant (Table M-18 of Appendix M).

Carotid Bruits

The unadjusted group contrast of carotid bruits is displayed in Table 15-9. The proportions of bruits in both groups were similar (Est. RR: 1.28, 95% C.I.: [0.45,3.66], p=0.646). Overall, only 14 bruits were detected, 7 from each group, limiting the scope of the adjusted analyses.

The covariate effects are given in Table 15-10. Age, current smoking, and cholesterol were of borderline statistical significance, whereas drink-years of alcohol was significantly correlated with carotid bruits (p=0.021), with the greater than 25 drink-years category having the highest proportion.

TABLE 15-11.

Adjusted Analysis for Peripheral Vascular Function by Group (Diabetics Excluded)*

Variable	Statistical/ Clinical Analysis	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
Diastolic Blood Pressure	Discrete	1.08 (0.78,1.48)	0.653	CSMOK (p=0.040) CHOL (p<0.001) %BFAT (p<0.001) ALC (p=0.008)
	Continuous	0.38 (-0.34, 1.11)[a]	0.299[a]	AGE (p=0.005) CSMOK (p<0.001) CHOL (p<0.001) %BFAT (p<0.001) ALC (p=0.002)
Funduscopic Examination		1.78 (0.56,5.62)	0.322	AGE (p<0.001) RACE (p<0.001) CHOL/HDL (p=0.017) %BFAT (p=0.037) ALC (p=0.038)
Carotid Bruits		1.05 (0.35,3.16)	0.928	AGE (p=0.024) DRKYR (p<0.001)
Radial Pulses	Manual	0.64 (0.19,2.14)	0.472	AGE (p=0.040)
	Doppler	0.96 (0.21,4.30)[b]	0.952[b]	--
Femoral Pulses	Manual	1.21 (0.63,2.31)	0.562	AGE (p<0.001) CHOL/HDL (p=0.010) %BFAT (p<0.001) DIFCORT (p=0.002)
	Doppler	1.74 (0.48,6.31)	0.401	AGE (p=0.001) CSMOK (p=0.001) CHOL/HDL (p=0.042)
Popliteal Pulses	Manual	****	****	AGE (p=0.003) PACKYR (p=0.005) CHOL/HDL (p=0.011) GRP*RACE (p=0.038)
	Doppler	1.50 (0.58,3.91)	0.401	AGE (p<0.001) RACE (p=0.023) CSMOK (p<0.001)
Dorsalis Pedis Pulses	Manual	****	****	AGE (p=0.004) DRKYR (p=0.038) GRP*OCC (p=0.046)
	Doppler	1.07 (0.87,1.31)	0.535	AGE (p=0.004) RACE (p=0.006) %BFAT (p=0.003)

TABLE 15-11. (continued)

Adjusted Analysis for Peripheral Vascular Function by Group (Diabetics Excluded)*

Variable	Statistical/ Clinical Analysis	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
Posterior Tibial Pulses	Manual	****	****	AGE (p<0.001) RACE (p<0.001) PACKYR (p=0.007) GRP*OCC (p=0.017)
	Doppler	0.94 (0.50,1.77)	0.849	AGE (p<0.001) RACE (p=0.002) CSMOK (p=0.007) CHOL/HDL (p=0.015)
Leg Pulses	Manual	****	****	AGE (p<0.001) GRP*OCC (p=0.016) GRP*%BFAT (p=0.034)
	Doppler	1.06 (0.87,1.30)	0.549	AGE (p=0.001) RACE (p=0.029) %BFAT (p=0.006)
Peripheral Pulses	Manual	****	****	AGE (p<0.001) %BFAT (p=0.018) GRP*OCC (p=0.033)
	Doppler	1.06 (0.87,1.30)	0.562	AGE (p=0.001) %BFAT (p=0.006)
All Pulses	Manual	****	****	AGE (p<0.001) %BFAT (p=0.022) GRP*OCC (p=0.036)
	Doppler	1.06 (0.86,1.29)	0.603	AGE (p=0.001) %BFAT (p=0.006)

*Some adjusted analyses did not explore effects of all covariates due to sparse number of abnormalities (see text).

**Additional Abbreviations:
DRKYR: drink-years of alcohol
DIFCORT: differential cortisol.

[a]Difference in group means (Ranch Hand-Comparison) and associated p-value given, rather than relative risk, for continuous analysis of dependent variables.

[b]Unadjusted for any covariates--same results as for unadjusted analysis.

****Group-by-covariate interaction--relative risk, confidence interval, and p-value not presented (see Table M-6 of Appendix M).

The adjusted analysis was performed with only the covariates of age and drink-years of alcohol due to the small number of detected bruits. The results (Table 15-11) demonstrate a lack of significant group differences (Adj. RR: 1.05, 95% C.I.: 0.35, 3.16], p=0.928). Both age and drink-years of alcohol were significant adjusting variables, but no significant group interactions were noted. The results of the Ranch Hand, Original Comparison group contrast was also nonsignificant (see Table M-18 of Appendix M).

Peripheral Pulses

Five peripheral pulses (radial, femoral, popliteal, dorsalis pedis, and posterior tibial) were analyzed using data assessments from both manual palpation and Doppler recordings. Palpation data from the examining physician were judged abnormal if the pulse was diminished or absent on either side. Assessment of the Doppler data was more complex and involved visual examination of the waveform morphology (pulsatility, systolic forward flow, and diastolic reverse flow) on analog strips and Polaroid® photographs, with careful comparison of the laterality of results. Confirmatory functional data (e.g., treadmill, segmental pressure readings) of abnormal pulses were not performed. The interpretation of each pulse was scored as normal, mild impairment, moderate impairment, severe impairment, or total occlusion (for the purpose of this analysis, all interpretations other than normal were considered abnormal). All Doppler measurements were conducted with a minimum of a 4-hour abstinence from smoking; compliance to the nonsmoking requirement was recorded by the Doppler technician.

Besides analysis of each pulse as a distinct dependent variable, three pulse aggregates were prescribed for analysis in order to maintain continuity with the Baseline analysis. The rationale of the pulse aggregates was to localize pulse abnormalities in broad anatomic categories. The aggregates were: leg pulses (femoral, popliteal, dorsalis pedis, and posterior tibial); peripheral pulses (radial, femoral, popliteal, dorsalis pedis, and posterio tibial); and all pulses (peripheral pulses plus carotid pulses, the latter assessed by only manual techniques). Any one abnormal pulse in an aggregate constituted an abnormality for the overall category.

The agreement of manual and Doppler assessments was tested by McNemar's chi-square test using paired data when an individual was compliant to both examination procedures. The paired analyses for the radial, femoral, popliteal, dorsalis pedis, posterior tibial, leg, peripheral, and all pulses are displayed in Table 15-12. As shown, the two methods of pulse assessment differed profoundly ($p<0.001$) for the femoral, popliteal, dorsalis pedis, leg pulses, peripheral pulses, and all pulses, but only mildly ($p=0.044$) for the posterior tibial pulse; the methodology differences for the radial pulse were not significantly discordant ($p=0.149$). Further, as shown by the off-diagonal elements in the specific pulse tables, the manual palpation method classified more cases as abnormal for the femoral, popliteal, and posterior tibial pulses, whereas the Doppler technique detected more abnormalities for the dorsalis pedis pulse, and consequently, the three pulse aggregates. Overall, more credence is given to the Doppler results due to the more "objective" means of determining a pulse abnormality.

The unadjusted analyses of all the pulses and pulse aggregates by manual and Doppler techniques (Table 15-9) showed that no statistically significant

TABLE 15-12.

Agreement Between Manual and Doppler Pulse Assessments
(McNemar's χ^2 Test)

Radial

MANUAL \ DOPPLER	Normal	Abnormal
Normal	2,102	3
Abnormal	9	3

$\chi^2 = 2.08$ p=0.149

Femoral

MANUAL \ DOPPLER	Normal	Abnormal
Normal	2,072	3
Abnormal	38	6

$\chi^2 = 28.2$ p<0.001

Popliteal

MANUAL \ DOPPLER	Normal	Abnormal
Normal	2,067	8
Abnormal	35	8

$\chi^2 = 15.7$ p<0.001

Dorsalis Pedis

MANUAL \ DOPPLER	Normal	Abnormal
Normal	1,546	341
Abnormal	71	155

$\chi^2 = 175.6$ p<0.001

Posterior Tibial

MANUAL \ DOPPLER	Normal	Abnormal
Normal	2,035	23
Abnormal	40	16

$\chi^2 = 4.1$ p=0.044

Leg

MANUAL \ DOPPLER	Normal	Abnormal
Normal	1,462	346
Abnormal	135	170

$\chi^2 = 91.7$ p<0.001

Peripheral

MANUAL \ DOPPLER	Normal	Abnormal
Normal	1,455	347
Abnormal	139	172

$\chi^2 = 88.2$ p<0.001

All

MANUAL \ DOPPLER	Normal	Abnormal
Normal	1,454	347
Abnormal	138	173

$\chi^2 = 89.2$ p<0.001

group differences were detected for any pulse or pulse combination by either technique.

The covariate tests of association for each pulse and pulse combination by technique are listed in Table 15-10. The following paragraphs describe the results shown in this table.

Increased age (born before 1942) was significantly associated with a higher proportion of pulse abnormalities for the femoral pulses (manual; $p<0.001$), popliteal pulses (Doppler; $p=0.002$), dorsalis pedis pulses (manual; $p=0.018$), posterior tibial pulses (manual, $p=0.034$; Doppler, $p=0.003$), leg pulses (manual, $p=0.001$; Doppler, $p=0.020$), peripheral pulses (manual, $p<0.001$; Doppler, $p=0.037$), and all pulses (manual, $p<0.001$, Doppler, $p=0.032$). Age was of borderline significance ($0.050<p\leq0.100$) for femoral pulses (Doppler), and for popliteal pulses (manual) and dorsalis pedis pulses (Doppler).

Race was associated with dorsalis pedis pulses (Doppler, $p=0.001$), posterior tibial pulses (manual, $p<0.001$), leg pulses (Doppler, $p=0.009$), peripheral pulses (Doppler, $p=0.015$), and all pulses (Doppler, $p=0.014$), with Blacks having a lower proportion of abnormalities for the dorsalis pedis, leg, peripheral, and all pulses than nonblacks, but a higher proportion of abnormalities for the posterior tibial pulse. Race was of borderline significance for the Doppler-determined posterior tibial pulses. Occupation was significantly associated with abnormalities of the dorsalis pedis pulses (Doppler, $p=0.007$), leg pulses (Doppler, $p=0.012$), peripheral pulses (Doppler, $p=0.019$), and all pulses (Doppler, $p=0.023$), with officers uniformly having more abnormalities than enlisted flyers, who had more abnormalities than enlisted groundcrew.

Current smoking (cigarettes per day) was significantly associated with increased abnormalities for the posterior tibial pulses (manual, $p<0.001$; Doppler, $p=0.021$), femoral pulses (Doppler, $p=0.001$), and the popliteal pulses (Doppler, $p<0.001$), despite the 4-hour abstinence prior to the Doppler examination. A relationship of increased smoking and increased abnormalities was only observed for the Doppler determination of the femoral and popliteal pulses. Pack-years of smoking was significantly related to increased abnormalities with popliteal pulses (manual, $p=0.001$; Doppler, $p=0.010$), posterior tibial pulses (manual, $p<0.001$), femoral pulses (Doppler, $p=0.006$), leg pulses (manual, $p=0.031$), peripheral pulses (manual, $p=0.028$), and all pulses (manual, $p=0.023$). Classical increasing associations were noted for the popliteal pulses (manual and Doppler), the posterior tibial pulses (manual), and the femoral pulses (Doppler).

For the related variables involving cholesterol, the cholesterol-HDL ratio showed the most numerous and strongest associations with pulse abnormalities. The cholesterol-HDL ratio was significantly and positively associated with increases in manually determined radial, femoral, and popliteal pulse abnormalities ($p=0.033$, $p<0.001$, and $p=0.002$, respectively); however, other significant associations with all pulses and the leg and peripheral pulse indices revealed an inconsistent pattern ($p=0.012$, $p=0.013$, and $p=0.010$, respectively). In addition, the ratio was significantly related to femoral and posterior tibial pulse abnormalities, as detected by the Doppler technique ($p=0.019$, $p=0.035$, respectively), but the relationships were not uniform from low to high values of the ratio. HDL was significantly associated with manually determined pulse abnormalities for femoral, leg,

peripheral, and all pulses (p=0.002, p=0.013, p=0.013, p=0.013, respectively), but in all four cases, the mid-level category of HDL (greater than 40 to 50) was associated with the lowest proportion of abnormalities. Cholesterol showed only marginally significant associations with increased abnormalities of femoral pulse (manual and Doppler) and posterior tibial pulses (manual).

Percent body fat was significantly associated with increases of femoral pulse abnormalities (manual, p=0.001); personality score was associated with posterior tibial deficits (Doppler; p=0.028; nonlinear pattern); and drink-years of alcohol was related to femoral pulse abnormalities detected by both methods (manual, p<0.001; Doppler, p=0.013). Finally, in addition to numerous other marginally significant associations (e.g., drink-years and posterior tibial abnormalities, Doppler, p=0.083; drink-years and popliteal abnormalities, manual, p=0.085), differential cortisol showed a nonlinear association with posterior tibial pulse abnormalities (Doppler, p=0.074).

The distribution of each of the covariates in the Ranch Hand and Comparison groups is presented in Table 15-13. As noted, the distributions of the three matching variables, age, race, and occupation, are nearly identical (p=0.987, p=0.745, and p=0.661, respectively). For current smoking, however, Ranch Hands smoke significantly more cigarettes per day (higher mean level) than the Comparisons (p=0.043) a finding also observed at Baseline. Additionally, the difference in mean percent body fat was of borderline significance (p=0.074), with a slightly higher average level in the Comparison group.

The results of the adjusted analyses for the manual and Doppler pulse determinations are presented in Table 15-11. Due to the small number of abnormalities, manual radial pulses were adjusted only for age and the cholesterol-HDL ratio, and Doppler radial pulses were not adjusted for any covariates. Similarly, femoral Doppler pulses were adjusted only for age, current smoking, and the cholesterol-HDL ratio. Doppler popliteal pulses were adjusted only for main covariate effects, i.e., interactions were not examined.

The adjusted analyses of all Doppler-determined pulse and pulse aggregate abnormalities did not disclose any significant differences between the Ranch Hand and Comparison groups. Age showed a consistent and profound effect in all of the adjusted Doppler analyses, whereas race, percent body fat, and smoking were significantly influential in about half of the analyses, and the cholesterol-HDL ratio was significant for only two of the pulse variables. The effects of these four covariates were all in the expected (classical) direction.

For the manual pulse readings, the adjusted results (Table 15-11) were decidedly different from the Doppler analyses, with all but the radial and femoral pulses involved in significant group-by-covariate interactions. There were no significant group differences for the radial and femoral pulses (p=0.472, p=0.562, respectively). For manually determined popliteal pulses, there was a significant group-by-race interaction (p=0.038), with Blacks having an adjusted relative risk of 6.74 (95% C.I.: [0.72,63.40], p=0.095) in contrast to nonblacks, who had an adjusted relative risk of 0.55 (95% C.I.: 0.28,1.12] p=0.099]). All significant group-by-covariate interactions are shown in Table M-6 of Appendix M.

TABLE 15-13.

Summary Statistics for Cardiovascular Covariates by Group

Covariate	Covariate Category	Group: Ranch Hand	Group: Comparison	p-Value
		Percent	Percent	
Race	Black	5.6	6.0	
	Nonblack	94.4	94.0	0.745
Occupation	Officer	37.2	37.9	
	Enlisted Flyer	17.3	15.8	
	Enlisted Groundcrew	45.5	46.3	0.661
		Mean ± SE	Mean ± SE	
Age (At Baseline)	--	43.57±0.25	43.57±0.22	0.987
Current Smoking[a]	--	10.50±0.50	9.19±0.42	0.043
Pack-years Smoking	--	12.62±0.52	12.51±0.48	0.883
Cholesterol	--	216.8±1.3	218.1±1.2	0.463
HDL	--	46.32±0.42	46.90±0.35	0.288
Cholesterol-HDL Ratio	--	4.99±0.05	4.92±0.04	0.303
Percent Body Fat	--	20.85±0.16	21.23±0.14	0.074
Personality Score	--	-1.11±0.30	-1.50±0.26	0.322
Differential Cortisol	--	2.31±0.13	2.46±0.12	0.398
Current Alcohol Use (Drinks per Day)	--	1.23±0.07	1.28±0.07	0.611
Drink-years Alcohol	--	25.62±1.44	22.91±0.96	0.117

[a]Equivalent cigarettes/day.

--Covariate not categorized for these results.

For the dorsalis pedis, posterior tibial, leg, peripheral, and all pulses, significant group interactions with occupation were detected ($p=0.046$, $p=0.017$, $p=0.016$, $p=0.033$, and $p=0.036$, respectively). In all cases, the adjusted relative risk was less than one for the officers and greater than one for the enlisted flyers and groundcrew. In addition, the adjusted relative risk for enlisted flyers was consistently greater than the risk for the enlisted groundcrew. Statistically significant associations by pulse, by occupational category, were as follows: Posterior tibial pulses in enlisted flyer, $p=0.032$; leg pulses in officers (21% body fat level), $p=0.026$; peripheral pulses in officers, $p=0.030$; all pulses in officers, $p=0.030$. All other pulse-occupational strata contrasts were not statistically significant. As there was also a significant group by percent body fat interaction for leg pulses ($p=0.034$), each occupational category was analyzed by level of obesity (obese, percent body fat greater than 25 percent; nonobese, percent body fat equal to or less than 25 percent). For officers, the adjusted relative risks were less than one for both the obese (Adj. RR: 0.44, 95% C.I.: [0.17, 1.12], $p=0.084$) and the nonobese (Adj. RR: 0.66, 95% C.I.: [0.42,1.04], $p=0.072$). For enlisted flyer personnel, the adjusted relative risks were greater than one for both body fat categories, but were not statistically significant. The enlisted groundcrew manifested an adjusted relative risk of less than 1 for obese individuals (Adj. RR: 0.91, 95% C.I.: [0.39,2.10], $p=0.818$), and greater than 1 for nonobese individuals (Adj. RR: 1.20, 95% C.I.: [0.79,1.83], $p=0.390$), but also not statistically significant.

The unadjusted analyses of the manual and Doppler pulse assessments (shown in Table M-17 of Appendix M), using the Original Comparisons, did not disclose any significant group differences. For the Doppler adjusted analyses, the results for the Ranch Hand versus Original Comparison contrasts were similar to those found in the Ranch Hand versus total Comparison group, i.e., no statistically significant group differences or group-by-covariate interactions.

For the adjusted manual pulse determinations, however, the results differed somewhat from the contrast of the Ranch Hand versus total Comparison group in terms of the significant group-by-covariate interactions detected (see Tables M-18 and M-19 of Appendix M). As before, there were no statistically significant group differences for radial and femoral pulses. For popliteal pulses, however, there was a significant ($p=0.048$) group-by-occupation interaction, with an adjusted relative risk of less than one for the officers ($p=0.219$) and greater than one for the enlisted flyers, although not significantly so ($p=0.165$). For dorsalis pedis pulses, there were no significant group effects or interactions, but for posterior tibial pulses the results were similar to those found in the contrast of the Ranch Hands versus the total Comparison group analysis, i.e., a significant group-by-occupation interaction. For the three pulse aggregates, there were significant group-by-occupation and group-by-percent body fat interactions for the leg pulses (officers having a risk less than one; enlisted flyers and enlisted groundcrew having risks greater than one) and significant group-by-percent body fat interactions for peripheral pulses and all pulses (individuals with low percent body fat having adjusted relative risks greater than one, and obese individuals having an adjusted risk less than one).

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted for the Ranch Hand officer, enlisted flyer, and enlisted groundcrew cohorts separately to determine if any dose-response relationships could be identified. In many cases, the data were too sparse to permit statistical comparisons. Adjusted analyses included the exposure level and only the main effects of age, race, pack-years of smoking, cholesterol-HDL ratio, percent body fat, personality score, differential cortisol, and current drinks per day, whenever appropriate. (In several instances, the stepwise logistic modeling did not detect any statistically significant covariate effects. However, adjusted best model results may differ slightly from the unadjusted results due to the omission of individuals with missing covariate information from the adjusted analysis.)

Reported and Verified Heart Disease

Tabular results of adjusted exposure index analyses for reported and verified heart disease are presented in Table 15-14 (unadjusted exposure index analyses are in Table M-7 of Appendix M). There were no statistically significant differences for reported or verified essential hypertension or reported or verified myocardial infarction by exposure level. (The data on myocardial infarctions were quite sparse.) Results were also negative for reported and verified heart disease, except for the enlisted groundcrew cohort, where the percentage of individuals with reported or verified disease was lowest in the medium exposure category.

Central Cardiac Function

Table 15-15 gives the adjusted exposure results for systolic blood pressure (dichotomized), heart sounds, and ECG findings. The unadjusted exposure analyses are given in Table M-8 of Appendix M. The only exposure level effect reaching statistical significance was the medium versus low contrast for bradycardia in the enlisted groundcrew ($p=0.048$), where the adjusted relative risk was significantly less than one.

There were borderline significant effects, with adjusted relative risks greater than one for systolic blood pressure (enlisted groundcrew, medium versus low exposure) and T-wave findings (enlisted flyers, medium versus low contrast). There were borderline significant effects, with relative risks less than one for T-wave findings in the enlisted groundcrew cohort, medium versus low exposure (unadjusted only), and high versus low contrast (adjusted only).

The results for systolic blood pressure analyzed as a continuous variable showed no statistically significant exposure level effects, either unadjusted or adjusted for covariates. The adjusted medium versus low exposure level contrast was of borderline significance in the enlisted groundcrew ($p=0.069$). Age, percent body fat, and personality score were significant covariates in one or more occupational strata.

TABLE 15-14.

Adjusted Exposure Index Analyses for Reported and Verified Heart Disease by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Reported Essential Hypertension	Officer	Medium vs. Low	0.92 (0.50,1.70)	0.795	AGE (p=0.016)
		High vs. Low	1.08 (0.58, 2.01)	0.810	%BFAT (p<0.001)
	Enlisted Flyer	Medium vs. Low	0.84 (0.34,2.05)	0.704	%BFAT (p=0.002)
		High vs. Low	1.34 (0.57,3.16)	0.509	
	Enlisted Groundcrew	Medium vs. Low	1.37 (0.79,2.43)	0.289	%BFAT (p<0.001)
		High vs. Low	1.26 (0.68,2.33)	0.459	
Verified Essential Hypertension	Officer	Medium vs. Low	0.94 (0.48,1.84)	0.849	%BFAT (p<0.001)
		High vs. Low	1.36 (0.70,2.65)	0.363	
	Enlisted Flyer	Medium vs. Low	0.45 (0.15,1.33)	0.150	DIFCORT (p=0.026)
		High vs. Low	0.92 (0.35,2.40)	0.865	
	Enlisted Groundcrew	Medium vs. Low	1.47 (0.82,2.66)	0.201	%BFAT (p<0.001)
		High vs. Low	1.33 (0.71,2.49)	0.379	
Reported Heart Disease	Officer	Medium vs. Low	0.79 (0.45,1.38)	0.407	AGE (p=0.011)
		High vs. Low	0.69 (0.39,1.23)	0.204	
	Enlisted Flyer	Medium vs. Low	1.30 (0.58,2.94)	0.529	NONE
		High vs. Low	0.66 (0.27,1.62)	0.368	
	Enlisted Groundcrew	Medium vs. Low	0.51 (0.29,0.90)	0.020	AGE (p=0.046)
		High vs. Low	1.10 (0.65,1.86)	0.711	

TABLE 15-14. (continued)

Adjusted Exposure Index Analyses for Reported and Verified Heart Disease by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Verified Heart Disease	Officer	Medium vs. Low	0.75 (0.42,1.34)	0.332	AGE (p=0.007)
		High vs. Low	0.73 (0.40,1.32)	0.298	
	Enlisted Flyer	Medium vs. Low	1.11 (0.48,2.59)	0.803	NONE
		High vs. Low	0.57 (0.22,1.46)	0.242	
	Enlisted Groundcrew	Medium vs. Low	0.38 (0.20,0.73)	0.004	AGE (p=0.024)
		High vs. Low	0.95 (0.55,1.66)	0.865	
Reported Myocardial Infarction	Officer	Medium vs. Low	4.01 (0.43,37.2)	0.222	ALC (p=0.044)
		High vs. Low	1.20 (0.07, 19.9)	0.897	
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low			
	Enlisted Groundcrew	Medium vs. Low	0.86 (0.13,5.47)	0.873	AGE (p<0.001)
		High vs. Low	0.79 (0.14,4.35)	0.787	
Verified Myocardial Infarction	Officer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low	--	--	--
		High vs. Low	--	--	--

--Analysis not performed due to sparse cells.

TABLE 15-15.

Adjusted Exposure Index Analyses for Central Cardiac Function Variables by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Systolic Blood Pressure	Officer	Medium vs. Low	0.78 (0.27,2.26)	0.638	AGE (p=0.004)
		High vs. Low	1.03 (0.35,3.08)	0.952	PS (p=0.010)
	Enlisted Flyer	Medium vs. Low	0.94 (0.22,3.98)	0.936	NONE
		High vs. Low	0.74 (0.16,3.46)	0.697	
	Enlisted Groundcrew	Medium vs. Low	2.76 (0.93,8.24)	0.069	AGE (p=0.041)
		High vs. Low	1.97 (0.61,6.32)	0.254	%BFAT (p=0.006)
Heart Sounds	Officer	Medium vs. Low	0.71 (0.16,3.16)	0.660	AGE (p=0.004)
		High vs. Low	1.33 (0.33,5.40)	0.689	DIFCORT (p=0.009)
	Enlisted Flyer	--	--		--
	Enlisted Groundcrew	Medium vs. Low	0.25 (0.05,1.41)	0.116	CHOL/HDL (p<0.001)
		High vs. Low	1.26 (0.40,4.00)	0.689	
ECG	Officer	Medium vs. Low	1.36 (0.63,2.97)	0.435	AGE (p=0.007)
		High vs. Low	1.15 (0.50,2.62)	0.741	%BFAT (p=0.009)
	Enlisted Flyer	Medium vs. Low	1.54 (0.53,4.32)	0.412	AGE (p=0.007)
		High vs. Low	0.86 (0.29,2.49)	0.779	%BFAT (p<0.001)
	Enlisted Groundcrew	Medium vs. Low	0.66 (0.29,1.54)	0.342	AGE (p=0.001)
		High vs. Low	0.76 (0.34,1.71)	0.516	PACKYR (p=0.036) DIFCORT (p=0.038)

TABLE 15-15. (continued)

Adjusted Exposure Index Analyses for
Central Cardiac Function Variables by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Nonspecific T-Wave Changes	Officer	Medium vs. Low	1.65 (0.65,4.20)	0.289	AGE (p=0.027)
		High vs. Low	1.47 (0.55,3.92)	0.441	RACE (p=0.027)
					%BFAT (p=0.002)
	Enlisted Flyer	Medium vs. Low	3.10 (0.85,11.28)	0.085	AGE (p=0.032)
		High vs. Low	1.64 (0.43,6.28)	0.472	%BFAT (p<0.001)
	Enlisted Groundcrew	Medium vs. Low	0.50 (0.19,1.28)	0.150	AGE (p=0.003)
		High vs. Low	0.37 (0.14,1.02)	0.055	
Bradycardia	Officer	Medium vs. Low	1.06 (0.37,3.06)	0.912	RACE (p=0.035)
		High vs. Low	1.10 (0.37,3.27)	0.865	
	Enlisted Flyer	Medium vs. Low	5.09 (0.57,45.1)	0.144	NONE
		High vs. Low	2.04 (0.18,23.1)	0.569	
	Enlisted Groundcrew	Medium vs. Low	0.21 (0.04,0.98)	0.048	NONE
		High vs. Low	0.50 (0.15,1.65)	0.254	
Arrhythmia	Officer	Medium vs. Low	0.21 (0.04,1.14)	0.070	AGE (p=0.011)
		High vs. Low	0.17 (0.02,1.44)	0.105	
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low			
	Enlisted Groundcrew	Medium vs. Low	0.63 (0.18,2.26)	0.484	PACKYR (p<0.001)
		High vs. Low	0.99 (0.32,3.02)	0.984	

TABLE 15-15. (continued)

Adjusted Exposure Index Analyses for
Central Cardiac Function Variables by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
	Officer	Medium vs. Low	1.29 (0.61,2.72)	0.704	AGE (p=0.003)
		High vs. Low	0.86 (0.37,1.96)	0.711	
Other Diagnoses	Enlisted Flyer	Medium vs. Low	0.54 (0.17,1.78)	0.312	AGE (p=0.034)
		High vs. Low	0.37 (0.11,1.32)	0.522	
	Enlisted Groundcrew	Medium vs. Low	0.91 (0.36,2.29)	0.841	AGE (p<0.001)
		High vs. Low	0.76 (0.30,1.92)	0.562	RACE (p=0.030)

--Analysis not performed due to sparse cells.

Peripheral Vascular System

There were no significant dose-response effects for diastolic blood pressure (dichotomized), funduscopic abnormalities, or carotid bruits (Table 15-16). Analysis of diastolic blood pressure as a continuous variable also did not reveal any statistically significant exposure level effects. Significant covariates were percent body fat, personality type, cholesterol-HDL ratio, and current alcohol use.

Exposure index analyses of the peripheral pulses did not detect any statistically significant exposure effects, either unadjusted (Tables M-9 and M-10 of Appendix M for the manual and Doppler pulse readings) or adjusted (Tables 15-17 and 15-18).

Main-effect exposure analyses of 6 historical and verified heart disease variables, 10 central cardiac function variables, and 11 peripheral cardiac function variables (with both manual and Doppler results), showed no evidence of a dose-response relationship at the followup examination. Two statistically significant and several borderline significant exposure associations lacked a pattern of dose-response consistency, and appeared to be random in nature.

Association of Cardiovascular Examination Findings With Verified Heart Disease

The central and peripheral cardiovascular examination findings were analyzed together with the verified cardiovascular disease endpoints to determine the degree of correlation between the third-year followup examination and the past medical history. The results are shown in Table M-11 of Appendix M. There were highly significant associations between verified essential hypertension and systolic and diastolic blood pressures, ECG abnormalities, and abnormal fundi ($p<0.001$, <0.001, <0.001, 0.008, respectively). There was also a significant association between essential hypertension and abnormal heart sounds ($p=0.036$), as well as a borderline significant association between hypertension and carotid bruits ($p=0.080$). The frequency of verified essential hypertension, however, was not significantly different in those with and without peripheral pulse abnormalities (as determined by either the manual or Doppler technique).

For verified heart disease, there was a negative association with diastolic blood pressure ($p=0.043$) and positive associations with ECG abnormalities, heart sounds, abnormal fundi, and abnormal peripheral pulses as determined by the Doppler technique ($p<0.001$, $p=0.017$, $p=0.014$, and $p=0.007$, respectively). Finally, there were significant positive associations between ECG and heart sound abnormalities ($p<0.001$ for both) and the occurrence of a verified myocardial infarction. The consistency between the examination findings and the past medical history provides support for the overall validity of the cardiovascular measurement systems, whether by self-report, medical records, physician assessments, or objective determinations (e.g., ECG).

TABLE 15-16.

Adjusted Exposure Index Analyses for
Diastolic Blood Pressure Funduscopic Abnormalities
and Carotid Bruits by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Diastolic Blood Pressure	Officer	Medium vs. Low	0.79 (0.27,2.30)	0.667	%BFAT (p=0.002)
		High vs. Low	1.44 (0.54,3.86)	0.465	
	Enlisted Flyer	Medium vs. Low	0.76 (0.19,2.98)	0.697	%BFAT (p=0.006)
		High vs. Low	1.06 (0.29,3.84)	0.928	
	Enlisted Groundcrew	Medium vs. Low	1.50 (0.63,3.59)	0.363	CHOL/HDL (p=0.037)
		High vs. Low	1.24 (0.53,2.86)	0.667	%BFAT (p<0.001)
Funduscopic Abnormalities	Officer	--	--	0.337[a]	--
	Enlisted Flyer	--	--	--	--
			--	--	--
	Enlisted Groundcrew	--	--	--	--
Carotid Bruits	Officer	--	--	0.388[a]	--
	Enlisted Flyer	--	--	--	--
	Enlisted Groundcrew	--	--	--	--

[a]Overall analysis; sparse cells, chi-square test may not be valid.

--Analysis not performed due to sparse cells.

TABLE 15-17.

Adjusted Exposure Index Analyses for Peripheral Vascular System Manual Pulse Readings by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
	Officer	Medium vs. Low	--	--	--
		High vs. Low			
Radial Pulses	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low			
	Enlisted Groundcrew	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Officer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
Femoral Pulses	Enlisted Flyer	Medium vs. Low	0.36 (0.02,7.42)	0.509	RACE (p=0.006)
		High vs. Low	3.20 (0.31,32.6)	0.238	%BFAT (p=0.032)
					PS (p=0.041)
	Enlisted Groundcrew	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Officer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
Popliteal Pulses	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low	0.91 (0.14,5.90)	0.928	AGE (p=0.030)
		High vs. Low	1.05 (0.20,5.52)	0.952	RACE (p=0.048)
					DIFCORT (p=0.048)

TABLE 15-17. (continued)

Adjusted Exposure Index Analyses for Peripheral Vascular System Manual Pulse Readings by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
	Officer	Medium vs. Low	0.88 (0.40,1.97)	0.764	NONE
		High vs. Low	0.52 (0.20,1.33)	0.171	
Dorsalis Pedis Pulses	Enlisted Flyer	Medium vs. Low	1.53 (0.51,4.65)	0.447	NONE
		High vs. Low	1.39 (0.45,4.33)	0.569	
	Enlisted Groundcrew	Medium vs. Low	0.61 (0.27,1.35)	0.222	NONE
		High vs. Low	0.95 (0.45,2.02)	0.897	
	Officer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
Posterior Tibial Pulses	Enlisted Flyer	Medium vs. Low	0.75 (0.13,4.20)	0.741	RACE (p=0.027)
		High vs. Low	1.26 (0.26,6.10)	0.772	
	Enlisted Groundcrew	Medium vs. Low	2.00 (0.48,8.33)	0.337	AGE (p=0.003)
		High vs. Low	1.51 (0.37,6.17)	0.569	RACE (p<0.001)
	Officer	Medium vs. Low	0.96 (0.44,2.12)	0.920	NONE
		High vs. Low	0.84 (0.37,1.95)	0.697	
Leg Pulses	Enlisted Flyer	Medium vs. Low	1.01 (0.37,2.75)	0.984	PS (p=0.034)
		High vs. Low	1.21 (0.45,3.27)	0.711	
	Enlisted Groundcrew	Medium vs. Low	0.69 (0.35,1.36)	0.285	NONE
		High vs. Low	0.89 (0.46,1.75)	0.741	

TABLE 15-17. (continued)

Adjusted Exposure Index Analyses for Peripheral Vascular System Manual Pulse Readings by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Peripheral Pulses	Officer	Medium vs. Low	0.89 (0.41,1.94)	0.764	NONE
		High vs. Low	0.86 (0.42,1.75)	0.719	
	Enlisted Flyer	Medium vs. Low	1.01 (0.37,2.75)	0.984	PS (p=0.034)
		High vs. Low	1.21 (0.45,3.27)	0.711	
	Enlisted Groundcrew	Medium vs. Low	0.69 (0.35,1.36)	0.285	NONE
		High vs. Low	0.89 (0.46,1.75)	0.741	
All Pulses	Officer	Medium vs. Low	0.89 (0.41,1.94)	0.764	NONE
		High vs. Low	0.86 (0.42,1.75)	0.719	
	Enlisted Flyer	Medium vs. Low	1.01 (0.37,2.75)	0.984	PS (p=0.034)
		High vs. Low	1.21 (0.45,3.27)	0.711	
	Enlisted Groundcrew	Medium vs. Low	0.69 (0.35,1.36)	0.285	NONE
		High vs. Low	0.89 (0.46,1.75)	0.741	

--Analysis not performed due to sparse cells.

TABLE 15-18.

Adjusted Exposure Index Analyses for Peripheral Vascular System Doppler Pulse Reading by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Dorsalis Pedis Pulses	Officer	Medium vs. Low	1.12 (0.63,1.97)	0.704	NONE
		High vs. Low	1.08 (0.60,1.96)	0.787	
	Enlisted Flyer	Medium vs. Low	1.30 (0.51,3.28)	0.575	NONE
		High vs. Low	1.43 (0.56,3.64)	0.447	
	Enlisted Groundcrew	Medium vs. Low	0.94 (0.53,1.65)	0.772	RACE (p=0.034)
		High vs. Low	1.04 (0.58,1.87)	0.764	
Posterior Tibial Pulses	Officer	Medium vs. Low	2.09 (0.38,11.6)	0.401	AGE (p=0.025)
		High vs. Low	1.01 (0.13,7.58)	0.992	DIFCORT (p=0.026)
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
Leg Pulses	Officer	Medium vs. Low	1.26 (0.71,2.21)	0.430	NONE
		High vs. Low	1.19 (0.66,2.13)	0.562	
	Enlisted Flyer	Medium vs. Low	1.57 (0.63,3.90)	0.327	NONE
		High vs. Low	1.58 (0.63,3.98)	0.327	
	Enlisted Groundcrew	Medium vs. Low	0.94 (0.54,1.87)	0.818	NONE
		High vs. Low	1.01 (0.57,1.80)	0.772	

TABLE 15-18. (continued)

Adjusted Exposure Index Analyses for Peripheral Vascular System Doppler Pulse Reading by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Peripheral Pulses	Officer	Medium vs. Low	1.26 (0.71,2.21)	0.430	NONE
		High vs. Low	1.19 (0.66,2.13)	0.562	
	Enlisted Flyer	Medium vs. Low	1.57 (0.63,3.90)	0.327	NONE
		High vs. Low	1.58 (0.63,3.98)	0.327	
	Enlisted Groundcrew	Medium vs. Low	0.90 (0.52,1.57)	0.704	NONE
		High vs. Low	1.02 (0.58,1.79)	0.960	
All Pulses	Officer	Medium vs. Low	1.26 (0.71,2.21)	0.430	NONE
		High vs. Low	1.19 (0.66,2.13)	0.562	
	Enlisted Flyer	Medium vs. Low	1.57 (0.63,3.90)	0.327	NONE
		High vs. Low	1.58 (0.63,3.98)	0.327	
	Enlisted Groundcrew	Medium vs. Low	0.90 (0.52,1.57)	0.704	NONE
		High vs. Low	1.02 (0.58,1.79)	0.960	

--Analysis not performed due to sparse cells.

LONGITUDINAL ANALYSES

Two cardiovascular variables, the index of all pulses (by palpation) and the overall ECG interpretation, were investigated to assess the longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables are classified as abnormal or normal. As shown in Table 15-19, 2x2 tables were constructed for each group for each variable. These tables show the number of participants who were abnormal at Baseline and abnormal at followup, abnormal at Baseline and normal at followup, normal at Baseline and abnormal at followup, and normal at both Baseline and followup examinations. The odds ratio given is the ratio of the number of participants who were normal at the Baseline and abnormal at the followup to the number of participants who were abnormal at the Baseline and normal at the followup (the "off-diagonal" elements). The changes in normal/abnormal status within each group are contrasted between the Ranch Hand and Comparison groups, and the p-value is derived from Pearson's chi-square test of the hypothesis that the pattern of change in the two groups is the same.

TABLE 15-19.

Longitudinal Analyses of All Pulses Index and Overall ECG's: A Contrast of Baseline and First Followup Examination Abnormalities

Variable	Group	1982 Baseline Exam	1985 Followup Exam		Odds* Ratio (OR)	p-Value (OR_{RH} vs. OR_C)
			Abnormal	Normal		
All Pulses (Manual)	Ranch Hand	Abnormal	50	72	1.44	
		Normal	104	743		0.01
	Comparison	Abnormal	40	63	2.43	
		Normal	153	880		
ECG (Overall)	Ranch Hand	Abnormal	86	192	0.22	
		Normal	43	650		0.42
	Comparison	Abnormal	112	208	0.27	
		Normal	56	763		

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

The data showed a significant difference (p=0.01) in the pulse index in the two groups between examinations. The percentage of Ranch Hands and Comparisons with abnormalities for the pulse index increased from the Baseline examination to the followup examination; however, the Comparison group showed a larger increase in the proportion of pulse index abnormalities. The greater relative increase in the Comparisons caused the significant result. No significant group differences were detected between examinations for overall ECG abnormalities (p=0.42).

DISCUSSION

In general, the foregoing analyses on a wide range of cardiovascular variables, have shown a lack of significant differences between the Ranch Hands and the Comparisons. The sole exception was the finding of increased verified heart disease in the Ranch Hands versus the Comparisons (24% and 20%, respectively, p=0.054, unadjusted; p=0.036, adjusted). These results were not noted in the Baseline examination (p=0.982, unadjusted). A review of the relative risk patterns, whether or not statistically significant, for all of the other cardiovascular variables showed general equality, with about half of the risks below unity and half above. This rough equivalence suggests that, although the Ranch Hands have slightly more reported heart disease, the finding is not mirrored by substantial and consistent clinical cardiovascular defects at this time. This observation should not be lightly dismissed, and is cause for continued close surveillance.

The most notable cardiovascular finding at the followup examination was the lack of significant peripheral pulse abnormalities, which were unexpectedly found at the 1982 Baseline examination (p=0.05). The primary contributory cause of the change in pulse significance from Baseline to followup was probably the rigid 4-hour tobacco abstinence required prior to Doppler testing (due to the known vasoconstriction effects of nicotine). Tobacco abstinence, however, was not a requirement for the Baseline manual pulse readings. Although tobacco abstinence was not a requirement prior to manual readings at the followup examination, there was general compliance to the smoking prohibition, particularly if a participant's general physical examination preceded the Doppler testing. Therefore it might be expected that the manual readings would show more pulse abnormalities than Doppler testing; in fact, this was the case (see section on Peripheral Pulses).

Whatever the true cause(s), the prevailing fact is that there are no longer significant group differences in pulse abnormalities, as noted by both manual and Doppler techniques, regardless of the poor agreement between the two methods.

The close approximation of the estimated relative risks to unity for practically all of the cardiovascular variables is clearly indicative of equivalent cardiovascular health between the two groups. Furthermore, the general similarity of the unadjusted and adjusted results was suggestive of near equivalence of the important cardiovascular risk factors in the Ranch Hands and Comparisons (see Table 15-13), as well as a balance for unanalyzed or hidden covariates of importance.

These health assessments of the two groups are considerably strengthened by the almost consistent, classical effects of the covariates in this chapter. In particular, the age effect was uniformly profound, affecting

almost all of the dependent variables in the functional categories of reported-verified heart diseases, and central and peripheral vascular function. The covariates of race, percent body fat, and cholesterol (particularly the cholesterol-HDL ratio), and smoking were also generally strong and consistent in their effects. Statistically significant, positive associations were seen between the current level of smoking and posterior tibial, popliteal, and femoral pulses, as well as borderline significant associations between current smoking and other ECG diagnoses, carotid bruits, and reported myocardial infarctions. However, significant negative associations were observed between current smoking and reported and verified essential hypertension. Pack-years of smoking was significantly positively associated with several ECG variables and pulse assessments, although not always in a consistently increasing manner. There was a statistically significant and consistently increasing effect of pack-years of smoking on reported and verified myocardial infarctions, but there was a negative association between pack-years of smoking and verified essential hypertension, with the greatest number of abnormalities in the zero pack-year category. Alcohol was infrequently interactive with the dependent variables, but covariate tests of association generally revealed the classical pattern of more cardiovascular abnormalities in the nondrinking category than in the low drinking category.

Personality score, however, usually failed to demonstrate the "expected" aggregation of cardiovascular abnormalities in the Type A direction. In fact, most associations were in the Type B direction. Generally, only cardiovascular studies ascertaining personality type by the Structured Interview technique have shown an association of Type A personality (Type A-1, in particular) to heart disease endpoints, and conversely, studies using questionnaire techniques to measure personality type have not demonstrated the association. Lastly, the strong association between historical-verified cardiovascular events and the specific dependent variables provides assurance that the overall cardiovascular measurements have been accurate and valid.

SUMMARY AND CONCLUSIONS

The cardiovascular health of both cohorts was assessed by collection of reported and record-verified heart disease events; measurement of central cardiac function by systolic blood pressure, abnormal heart sounds, and electrocardiograph (ECG) findings; and evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Table 15-20 presents the overall summary of the unadjusted and adjusted results. Where possible, the analyses used the covariates of age, race, occupation, percent body fat, cholesterol, high density lipoprotein (HDL) cholesterol, cholesterol-HDL ratio, smoking history (pack-years and current smoking level), alcohol history (drink-years and current drinking level), personality score, and differential cortisol.

The cardiovascular variables did not reveal significant group differences, with the exception of verified heart disease, for which the proportions of recorded cardiac events were 24 and 20 percent in the Ranch Hand and Comparison groups, respectively, ($p=0.054$ unadjusted, $p=0.036$ adjusted). This finding was not reinforced by results of individual questionnaire or examination variables showing impairment in the Ranch Hands. There was a remarkable balance in relative risks above and below unity between the groups.

TABLE 15-20.

Overall Summary Results of Unadjusted and Adjusted Analyses
Cardiovascular Variables

Variable	Statistical/ Clinical Analysis	Unadjusted	Adjusted
Historical and Verified Heart Disease			
Reported Hypertension		NS	NS
Verified Hypertension		NS	NS
Reported Heart Disease[a]		NS	NS
Verified Heart Disease[a]		NS*	S[b]
Reported Heart Attack		NS	NS
Verified Heart Attack		NS	NS
Central Cardiac Function			
Systolic Blood Pressure	Discrete	NS	NS
	Continuous	NS	****
Heart Sounds		NS	NS
Electrocardiogram (Overall)		NS	****
ECG: RBBB		NS	NS
ECG: LBBB		---	N/A
ECG: Nonspecific T-Wave Changes		NS	NS
ECG: Bradycardia		NS	NS
ECG: Tachycardia		---	N/A
ECG: Arrhythmia		NS	****
ECG: Other Diagnoses		NS	NS

TABLE 15-20. (continued)

Overall Summary Results of Unadjusted and Adjusted Analyses
Cardiovascular Variables

Variable	Statistical/ Clinical Analysis	Unadjusted	Adjusted
Peripheral Vascular Function			
Diastolic Blood Pressure	Discrete	NS	NS
	Continuous	NS	NS
Funduscopic Examination		NS	NS
Carotid Bruits		NS	NS
Radial Pulses	Manual	NS	NS
	Doppler	NS	NS
Femoral Pulses	Manual	NS	NS
	Doppler	NS	NS
Popliteal Pulses	Manual	NS	****
	Doppler	NS	NS
Dorsalis Pedis Pulses	Manual	NS	****
	Doppler	NS	NS
Posterior Tibial Pulses	Manual	NS	****
	Doppler	NS	NS
Leg Pulses	Manual	NS	****
	Doppler	NS	NS
Peripheral Pulses	Manual	NS	****
	Doppler	NS	NS
All Pulses	Manual	NS	****
	Doppler	NS	NS

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

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

****Group-by-covariate interaction.

[a]Excluding hypertension.

[b]RH>C (Adj. RR: 1.25; 95% C.I.: [1.02, 1.54], p=0.036).

Other related analyses showed an absence of significant group differences in reported or verified hypertension, reported or verified heart attacks, and reported heart disease. There was good correlation between the verified cardiovascular history and the central and peripheral cardiovascular abnormalities detected at the physical examination, supporting accuracy and validity of the cardiovascular measurements.

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

In the analysis of peripheral vascular function, no significant group differences were observed for abnormalities involving radial, femoral, popliteal, posterior tibial, dorsalis pedis, or three anatomic aggregates of these pulses, either by manual palpation or Doppler techniques. This overall finding was in distinct contrast to the 1982 Baseline examination, which by the manual palpation method, showed significant peripheral pulse deficits in the Ranch Hands. This favorable pulse reversal over the two examinations is primarily attributed to the rigid 4-hour tobacco abstinence applied prior to Doppler testing, although other factors may be related. The lack of group differences for pulse abnormalities was noted even though the manual and Doppler techniques differed significantly ($p<0.05$, $p<0.001$ for most) in the detection of abnormalities for all but one of the pulses or pulse combinations.

For manually-determined pulse abnormalities, there was a significant group-by-race interaction for the popliteal pulses, a significant group-by-percent body fat interaction for the leg pulses, and significant group-by-occupation interactions for the posterior tibial, dosalis pedis, and the three pulse aggregates (leg, peripheral, and all pulses). No interactions were encountered in the adjusted analyses of the Doppler results, and none showed significant group differences.

Statistical analyses involving the Original Comparisons also showed no significant differences in the cardiovascular measurements between groups, although slightly different interactions were detected in some of the adjusted analyses.

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

The longitudinal analysis of the pulse index confirmed the significant difference in the change in the pattern of results from the Baseline examination to the followup examination, largely due to a relatively greater

increase of pulse abnormalities in the Comparison group than in the Ranch Hand group. There was no significant change in pattern between the two groups in overall ECG findings between examinations.

There was a similar distribution of the covariates between groups, except for a slightly higher level of current Ranch Hand smoking (also observed at Baseline), and a corresponding slightly lower mean percent body fat. The general covariate effects were strong and showed expected, classical associations with the cardiovascular measurements. However, unexpected effects were consistently noted for personality score, with higher proportions of various cardiovascular abnormalities associated with scores in the Type B direction, a finding possibly attributable to the method of personality determination. Nonetheless, the repeated demonstration of classical covariate associations with cardiovascular pathology lends considerable credence to the quality of the data. Although smoking was positively associated with many of the cardiovascular measurements, negative associations were seen between current smoking and reported and verified essential hypertension and between pack-years of smoking and verified hypertension.

In conclusion, of 27 cardiovascular variables, only one, verified heart disease, showed a significant excess in the Ranch Hands, but this finding was largely unsupported by other cardiac measurements. Both manual palpation and Doppler recordings of five peripheral pulses were similar in both groups, in marked contrast to the 1982 Baseline examination which found significant pulse deficits in the Ranch Hand group. This change at the followup examination was most likely due to required tobacco abstinence prior to the pulse measurements. Exposure index analyses did not support a consistent dose-response relationship for any variable. Overall, there was remarkable similarity in the cardiovascular health between the Ranch Hand and Comparison groups.

CHAPTER 15

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CHAPTER 16

HEMATOLOGICAL EVALUATION

INTRODUCTION

Although direct impairment of the hematopoietic system may result from exposure to chlorophenols or dioxin, marked abnormalities in many of the circulating hematological elements may also be due to the severe and often endstage toxicity observed in other organs or organ systems. Animal experiments have confirmed both direct and indirect hematopoietic effects of TCDD. In a chronic low-dose feeding study of TCDD in eight monkeys, decreased hemoglobin and hematocrit values were noted at the 6-month mark in all animals.[1] Four of these monkeys expired in 7 to 11 months and all had anemia, leukopenia, and thrombocytopenia. Necropsy of three sacrificed animals at 1 year showed multi-organ pathology including bone marrow degeneration, atrophy of lymphopoietic tissue, and numerous hemorrhages in a variety of organs. In another monkey experiment, using single low and high doses of TCDD, early hematological effects included increased neutrophil counts in the low-dose group and lymphopenia and thrombocytopenia in the high-dose group.[2] At the end of the experiment, half the sternal bone-marrow samples revealed a decrease in overall cellularity and an increase in the myeloid-erythroid cell ratio.

Rat experiments with TCDD demonstrated relatively consistent results. One study revealed elevated erythrocyte, reticulocyte, and neutrophil counts with depressed values for the mean corpuscular volume, mean corpuscular hemoglobin, platelet counts, and clot retraction times.[3] The authors attributed most of these effects to terminal dehydration and nonspecific toxicity. Another rat study using gavage doses of TCDD varying from 0.001 to 1.0 µg/kg demonstrated depressed red blood cell counts and packed cell volumes in the high-dose group.[4] In a mixed-dose regimen using rats, mice, and guinea pigs, dose-related decreases in lymphocyte and leukocyte numbers were observed in mice and guinea pigs within 1 week following TCDD administration.[5] Thrombocytopenia and hemoconcentration were found in rats. Because of the lymphopenia in mice and guinea pigs, TCDD was judged to be immunosuppressive.

In general, human observational studies showed fewer and less consistent hematological findings than the structured animal experiments. A case report of 2,4-D intoxication with marked neurological findings described transient bone marrow depression with peripheral leukopenia and granulocytopenia.[6] In two industrial accidents involving significant contamination with TCDD and resulting cases of chloracne, only temporary depression of peripheral leukocyte and lymphocyte formation was observed.[7,8]

Two contemporary indepth morbidity studies[9,10] of the Nitro, West Virginia, accident included routine clinical complete blood counts and differential counts, and hemoglobin and hematocrit determinations. Though these studies shared overlapping study cohorts, they did not report any of the

hematological results in their publications; presumably, there were no significant differences in any of the parameters between the exposed and the unexposed cohorts.

The two pilot studies of TCDD-contaminated residential areas in Missouri also included routine hematological assays of peripheral blood.[11,12] One study paradoxically noted a significantly increased mean platelet count in the high-risk group, although the data were not adjusted for smoking.[11] The Quail Run study, predominantly emphasizing cell-mediated immunity, found significant group differences in the mean leukocyte count, mean absolute granulocyte count, and the mean percentage of monocytes in the differential count.[12] Unfortunately, the authors neglected to identify the group (exposed or unexposed) that had the abnormal hematological findings. However, the finding of a significantly higher proportion of individuals with white blood cell counts exceeding 10,000/mm^3 was in the exposed group.

Baseline Summary Results

A number of statistically significant group differences and interactions emerged in the analysis of the 1982 Baseline examination. The Ranch Hand group had a significantly higher adjusted mean red blood cell corpuscular volume and corpuscular hemoglobin value than the Comparison group ($p=0.05$, $p=0.04$, respectively), although the magnitude of the difference was small in each case. The Ranch Hand adjusted mean values for six other parameters, i.e., red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin concentration, and platelet count, were nearly identical to the adjusted means of the Comparison group, and all were well within normal range. Similarly, the percent of abnormal values for these eight variables, as established by the upper and lower limits of normal, did not vary by group.

Linear models demonstrated the profound effect of smoking, as measured in pack-years. With increased smoking, white blood cell, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and platelet values increased, whereas the mean corpuscular hemoglobin concentration showed a significant negative association with smoking. The red blood cell count revealed a borderline significant negative relationship to smoking. No statistically significant group-by-smoking interactions were detected.

The exposure index analyses conducted within the Ranch Hand group disclosed two statistically significant exposure-level effects as well as seven significant or borderline-significant exposure-level-by-smoking interactions. In the officer cohort, the percentage of mean corpuscular hemoglobin abnormalities increased with increasing exposure level. The high-exposure group also had the highest percentage of mean corpuscular hemoglobin concentration abnormalities. No significant associations were found, however, in the enlisted flyer or enlisted groundcrew cohort. Five interactions involved a decreasing association (gradient of slopes) between the hematological measure and pack-years of smoking with increasing exposure level, one showed an increasing association with increasing exposure level, and one was uninterpretable. The report concluded that the overall statistical findings were somewhat consistent among themselves, and that medical morbidity was not significant.

Parameters of the 1985 Hematological Evaluation

The 1985 hematological assessment was identical to the 1982 Baseline evaluation. The eight hematological variables were red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (PLT); these variables were determined by routine hematological procedures. The normal ranges of the SCRF-determined values differed somewhat from those employed in 1982 by the Kelsey-Seybold Clinic.

As before, the analysis of the hematological data included the covariates of age, race, occupation, and smoking. Updated and more comprehensive smoking data, in terms of pack-years and current smoking (including cigar- and pipe-smoking), were used in most analyses.

Excluded were three individuals with fever at the time of examination (two Ranch Hands and one Comparison). Hematological variables in the continuous form were analyzed by general linear models adjusting for age, race, occupation, and smoking. The hematological data, trichotomized as abnormally low, normal, or abnormally high, were subjected to log-linear (logit) analysis, adjusted for the same covariates. Minor differences in the table totals within this chapter reflect rare missing data for either the dependent variables or the covariates. Parallel analyses using Original Comparisons can be found in Tables N-4 through N-9 of Appendix N.

RESULTS AND DISCUSSION

General

Eight hematological assays were performed on peripheral blood specimens obtained from all participants on the first day of the physical examination. Table 16-1 lists the assays, the abbreviations used in this chapter, the SCRF laboratory normal range for each assay, and the required laboratory coefficient of variation for each assay. The SCRF laboratory norms varied to some extent from the values used at the Baseline examination (see pages XVI-3-1, Baseline Report). The SCRF laboratory coefficients of variation met or exceeded contract requirements and were uniformly achieved due to the precision of the Coulter 5-Plus automated instrument, in conjunction with rigorous FIR CUSUM quality control techniques (see Chapter 6).

The overall precision in the laboratory aspects of the hematological assays is reflected in the analytic ability to discern minute mean shifts between groups. Representative statistical power statements are as follows. Sample sizes were sufficiently large to detect a 0.87 percent mean shift in RBC and a 2.5 percent mean shift in PLT values using an α-level of 0.05 (two-sided) and a power of 0.80. Further, the sample sizes were sufficient to detect a 1.66-fold increase in the frequency of abnormal values for RBC, and a 1.96-fold increase in the frequency of abnormal values for PLT, with 80 percent certainty.

TABLE 16-1.

Laboratory Parameters for
Hematological Test Variables

Hematological Test	Abbreviation	SCRF Laboratory Normal Range	Contract Required Coefficient of Variation (in percent)
Red Blood Cell Count	RBC	4.3-5.9 million/cubic mm	2.0
White Blood Cell Count	WBC	4.5-11.0 thousand/cubic mm	2.5
Hemoglobin	HGB	13.9-16.3 grams/100 ml	1.1
Hematocrit	HCT	39.0-55.0 ml/100 ml	3.0
Mean Corpuscular Volume	MCV	80.0-97.0 cubic micra	2.0
Mean Corpuscular Hemoglobin	MCH	26.0-34.0 micromicrogram	2.0
Mean Corpuscular Hemoglobin Concentration	MCHC	31.0-37.0 percent	2.0
Platelet Count	PLT	130-400 thousand/cubic mm	3.5

The statistical analyses in this chapter are presented in the following order: unadjusted tests, covariate tests of association, adjusted analyses, exposure analyses, and longitudinal contrasts. A variable-by-variable discussion summarizes all of the analyses, and representative exposure analyses are also presented. Group-by-covariate interactions are narratively presented, and illustrated by calculating Ranch Hand-Comparison differences at selected covariate levels. The interaction data tables are found in Tables N-2 and N-3 of Appendix N.

Unadjusted Categorical Analyses

Data from the eight hematological variables were categorized as abnormally low, normal, or abnormally high according to the SCRF laboratory norms cited in Table 16-1. The frequency distribution of these discretized data is presented by group in Table 16-2. As shown, there were no statistically significant, or even marginally significant, differences between the groups. Only one abnormal MCHC value was found among all study participants.

TABLE 16-2.

Unadjusted Categorical Analyses for Hematological Variables by Group

Variable	Group	Abnormally Low Number	Abnormally Low Percent	Normal Number	Normal Percent	Abnormally High Number	Abnormally High Percent	Total	p-Value*
RBC	Ranch Hand	30	3.0	976	96.2	8	0.8	1,014	0.910
	Comparison	42	3.2	1,239	95.9	11	0.8	1,292	
WBC	Ranch Hand	45	4.4	906	89.4	62	6.1	1,013	0.883
	Comparison	63	4.9	1,149	88.9	80	6.2	1,292	
HGB	Ranch Hand	39	3.8	752	74.2	223	22.0	1,014	0.848
	Comparison	44	3.4	960	74.3	288	22.3	1,292	
HCT	Ranch Hand	11	1.1	1,001	98.7	2	0.2	1,014	0.999
	Comparison	15	1.2	1,274	98.6	3	0.2	1,292	
MCV	Ranch Hand	10	1.0	857	84.5	147	14.5	1,014	0.992
	Comparison	13	1.0	1,094	84.7	185	14.3	1,292	
MCH	Ranch Hand	7	0.7	943	93.0	64	6.3	1,014	0.755
	Comparison	7	0.5	1,211	93.7	74	5.7	1,292	
MCHC	Ranch Hand	1	0.1	1,013	99.9	0	0.0	1,014	--
	Comparison	0	0.0	1,292	100.0	0	0.0	1,292	
PLT	Ranch Hand	5	0.5	987	97.4	21	2.1	1,013	0.828
	Comparison	3	0.2	1,264	97.9	24	1.9	1,291	

*Chi-square test, 2 d.f., except for HCT and PLT which were obtained from continuity adjusted chi-square tests on 1 d.f. (Abnormally high category pooled with normal, and abnormally low category pooled with normal for HCT and PLT, respectively.)

--Only one abnormal MCHC value; p-value not given.

Unadjusted Analyses of Continuous Data

The unadjusted tests of group means from the continuous data for the eight variables are displayed in Table 16-3. The variables WBC and PLT were analyzed in logarithmic units because of their right-skewed original distributions. Antilog values of the means are given for ease of interpretation but their standard error or variance terms are consequently omitted since the relevance of these terms pertains only to the logarithmic scale. The sample sizes were 1,014 for the Ranch Hand group and 1,292 for the Comparisons, except for WBC (Ranch Hands, 1,013; Comparisons, 1,292) and PLT (Ranch Hands, 1,013; Comparisons, 1,291). As shown in Table 16-3, there were no statistically significant group differences between the unadjusted means of each variable.

TABLE 16-3.

Unadjusted Continuous Analyses for Hematological Variables (Contrast of Group Means)

Variable	Group Mean±SE		Difference ±SE	t-Statistic	p-Value
	Ranch Hand	Comparison			
RBC	4.964±0.012	4.982±0.010	-0.019±0.016	-1.19	0.233
WBC[a]	7.003	6.891	--	1.34	0.182
HGB	15.624±0.033	15.626±0.029	-0.002±0.044	-0.05	0.958
HCT	45.904±0.097	45.952±0.083	-0.048±0.127	-0.38	0.703
MCV	92.596±0.150	92.346±0.132	0.250±0.200	1.25	0.210
MCH	31.544±0.055	31.431±0.049	0.113±0.074	1.53	0.125
MCHC	34.040±0.021	34.009±0.017	0.031±0.027	1.17	0.243
PLT[a]	265.2	263.0	--	0.96	0.337

[a]Means transformed from log scale.

--Difference and standard errors (SE) not presented, since variables were analyzed on logarithmic scale.

Dependent Variable and Covariate Relationships

The data from the Ranch Hand and Comparison groups were pooled for each of the eight hematological variables and analyzed independently with the covariates of age (born in or after 1942, born before 1942), race (Black, nonblack), occupation (officer, enlisted flyer, enlisted groundcrew), and smoking history (0 pack-years; greater than 0 to 10 pack-years; and greater than 10 pack-years). These analyses are summarized in terms of statistical significance (p-values) in Table 16-4. As noted, each of the dependent variables was substantially affected by one or more of the covariates. The exact nature of the covariate influence, e.g., directionality, significance, consistency across related variables, is presented in the variable-by-variable discussion section. Covariate effects were also analyzed in continuous form with the use of linear regression models (see Table 16-6 and discussion following). In addition, covariate distributions were examined between groups (see Table N-1 of Appendix N).

TABLE 16-4.

Association Between Hematological Variables and Age, Race, Occupation, and Smoking History in the Combined Ranch Hand and Comparison Groups

Variable	Age	Race	Occupation	Smoking History
RBC	0.010	<0.001	NS	NS
WBC	NS*	<0.001	0.001	<0.001
HGB	NS	0.002	<0.001	0.003
HCT	NS	<0.001	NS	NS
MCV	<0.001	<0.001	0.004	<0.001
MCH	<0.001	<0.001	0.003	<0.001
MCHC	--	--	--	--
PLT	NS	NS	NS	0.004

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

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

--Not analyzed due to sparse data.

Adjusted Categorical Analyses

Log-linear (logit) models for each of the hematological variables were fit to adjust for age, race, occupation, and smoking history. In addition, all significant group-by-covariate interactions were examined. The covariate of current level of smoking (used in the adjusted continuous analyses described below) was not included in the categorical analyses to avoid problems with sparse cells. Adjusted relative risks for Ranch Hand-Comparison contrasts were calculated for the categories of abnormally low values versus normal values and for abnormally high values versus normal values. Adjusted relative risks were not computed for the abnormally high versus normal categories for HCT, or for the abnormally low versus normal categories for PLT, due to sparse data. The results of these analyses are given in Table 16-5 and were quite similar to the unadjusted results, with no statistically significant or borderline significant associations found.

TABLE 16-5.

Adjusted Categorical Analyses for Hematological Variables (Abnormal Versus Normal), Adjusted for Age, Race, Occupation, and Smoking

	Abnormally Low vs. Normal		Abnormally High vs. Normal	
Variable	Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value
RBC	0.93 (0.59,1.47)	0.762	1.04 (0.48,2.28)	0.920
WBC	0.96 (0.66,1.42)	0.854	0.97 (0.69,1.36)	0.852
HGB	1.12 (0.74,1.80)	0.522	0.98 (0.80,1.19)	0.824
HCT	1.02 (0.51,2.06)[a]	0.954[a]	--	--
MCV	1.08 (0.52,2.26)	0.787	0.99 (0.78,1.26)	0.960
MCH	1.33 (0.56,3.17)	0.525	1.10 (0.79,1.54)	0.574
PLT	--	--	1.14 (0.66,1.98)[b]	0.638[b]

[a]Abnormally low versus normal/abnormally high.

--Not analyzed due to sparse data.

[b]Abnormally high versus normal/abnormally low.

Adjusted Analyses of Continuous Data

General linear regression models were performed, adjusting for age (at the Baseline examination), race, occupation (OCC), smoking history (pack-years [PACKYR]), and current level of smoking (cigarettes per day [CSMOK]). The linear models were fit to examine the main effects of group (GRP) membership, the covariates, and two- and three-factor interactions among these variables (only three-factor interactions involving group were considered). The hierarchical modeling approach as described in Chapter 7, Statistical Methods, was performed to arrive at a "best model" containing the group effect and all statistically significant covariate main effects and interactions.

The results of the adjusted analyses for the hematological variables, along with the significance of the adjusting covariates and covariate interactions are summarized in Table 16-6.

These results indicated a lack of significant group differences for RBC, HGB, HCT, MCV, MCH, and MCHC after adjustment for five covariates. Two analyses, WBC and PLT, showed significant group-by-covariate interactions; the statistics of these interactions (along with borderline interactions for RBC) are given in Table N-2 of Appendix N, and the narrative descriptions of these interactions are included in the following variable-by-variable summary presentations.

Discussion

The following variable-by-variable discussion presents the findings for the unadjusted and adjusted results, main covariate effects, group-associated interactions, and when appropriate, Ranch Hand versus Original Comparison contrasts, and comparisons to Baseline results. The results of the covariate effects and covariate interactions (not involving group) for the adjusted analyses are found in Table 16-6; group-by-covariate interactions are given in Table N-2 of Appendix N.

Red Blood Cell Count (RBC)

Both the categorical and continuous unadjusted analyses found no statistically significant differences in RBC values between groups.

The covariate associations for both groups combined showed a significant effect of age (RBC abnormally low in 4.0% of the older cohort versus 1.9% of the younger; $p=0.010$) and race (Blacks having 6.3% and 4.2% in the abnormally low and high categories versus 2.9% and 0.6% in nonblacks, respectively; $p<0.001$).

Continuous regression analyses also detected significant effects of current smoking ($p=0.004$) and an age-by-occupation interaction ($p=0.013$). The adjusted categorical analysis showed no significant group difference, but the adjusted continuous analysis revealed a borderline significant ($p=0.086$) three-factor interaction of group-by-occupation-by-smoking history. Estimated Ranch Hand-Comparison contrasts revealed a significant difference ($p=0.010$) for enlisted groundcrew, 30 pack-years with Ranch Hands exhibiting a slightly lower RBC count than the Comparisons (see Table N-2 of Appendix N).

TABLE 16-6.

Adjusted Continuous Analyses for Hematological Variables,
(Ranch Hand-Comparison Group Differences)

Variable	Ranch Hand-Comparison Group Difference ± SE	p-Value	Covariate Remarks*
RBC	-0.021±0.015[a]	0.172	AGE*OCC (p=0.013) CSMOK (p=0.004)
WBC	****	****	GRP*RACE*AGE (p=0.005) GRP*AGE*PACKYR (p=0.004) GRP*RACE*OCC (p=0.004)
HGB	-0.034±0.042	0.410	AGE*OCC (p=0.002) RACE*OCC (p=0.013) CSMOK (p<0.001)
HCT	-0.151±0.121	0.210	AGE*OCC (p=0.004) RACE*OCC (p=0.003) OCC*PACKYR (p=0.035) CSMOK (p<0.001)
MCV	0.108±0.188	0.565	RACE*AGE (p<0.001) RACE*OCC (p=0.015) RACE*CSMOK (p=0.025)
MCH	0.062±0.070	0.378	RACE*AGE (p=0.015) CSMOK (p<0.001) OCC (p<0.001)
MCHC	0.032±0.026	0.226	RACE (p=0.001) CSMOK (p=0.042)
PLT	****	****	GRP*RACE*PACKYR (p<0.001) GRP*RACE*CSMOK (p=0.024) OCC (p=0.039) AGE (p=0.006)

*Abbreviations
OCC: Occupation
CSMOK: Current level of smoking (cigarettes per day)
GRP: Group
PACKYR: Smoking history (pack-years)

[a]Also, borderline significant three-factor interaction (see text).

****Group-by-covariate interaction; group difference, standard error (SE) and p-value not presented.

A similar, but slightly weaker interaction was observed in the analysis of the Original Comparisons versus the Ranch Hands. The general finding of insignificant group differences supported the Baseline observations (despite the use of different statistical procedures), but the followup results differed by the mild three-factor interaction.

White Blood Cell Count (WBC)

The categorical and unadjusted continuous analyses did not disclose any significant differences in WBC levels between the Ranch Hand and Comparison groups.

Covariate tests showed a borderline effect of age (with the older cohort having a slightly lower proportion of abnormally low WBC levels--4.2% versus 5.4% in the younger cohort), and the highly significant effects of race ($p<0.001$), occupation ($p=0.001$), and smoking history ($p<0.001$). Blacks had a much higher proportion of abnormally low WBC counts (15.4%) versus nonblacks (4.0%); higher proportions of enlisted flyers and enlisted groundcrew personnel (9.1% and 7.2%, respectively) had abnormally high WBC counts versus officers (3.6%). Increasing frequencies of leukocytosis were associated with increasing levels of smoking.

The adjusted categorical analysis was nonrevealing with respect to group differences, but the adjusted continuous analysis disclosed three significant three-factor interactions involving group membership: group-by-race-by-age ($p=0.005$), group-by-age-by-smoking history (pack-years; $p=0.004$), and group-by-race-by-occupation ($p=0.004$).

Further analyses were conducted stratifying by race (see Table N-2 of Appendix N). Among Blacks, the best model revealed significant group-by-occupation and group-by-age interactions ($p=0.045$, $p=0.024$, respectively). Group differences for covariate levels corresponding to young officers and young enlisted flyers were statistically significant, with the adjusted mean WBC value considerably lower in the Ranch Hand group than in the Comparison group. Conversely, the adjusted difference for the older enlisted groundcrew was in the opposite direction. The results for nonblacks were more precise: The group-by-age-by-smoking history interaction was highly significant ($p=0.002$), with young heavy smokers having a WBC level approximately 12 percent greater in the Ranch Hands than the Comparisons.

Other differences were small in magnitude and not statistically significant. Ranch Hand and Original Comparison contrasts were similar for nonblacks, but for Blacks, the group-by-occupation and group-by-age interactions did not reach statistical significance ($p=0.077$, $p=0.134$, respectively). The nonsignificance of the unadjusted and categorical adjusted analyses was equivalent to the findings at the Baseline examination. However, possibly due to different model selections, no interactions were noted at Baseline. Race and occupation were not used as covariates at Baseline.

Hemoglobin (HGB)

None of the four analyses, unadjusted and adjusted categorical tests and unadjusted and adjusted tests of mean differences, detected a significant difference between groups.

Covariate tests of association revealed the profound effects of race (8.4% abnormally low in Blacks versus 3.3% in nonblacks; p=0.002), occupation (25.1% and 25.6% abnormally high in enlisted flyers and groundcrew, respectively, versus 16.7% in officers; p<0.001), and smoking history (with proportions of abnormally high HGB levels associated with increases in pack-years of smoking; p=0.003). Continuous analyses detected significant effects of current smoking (p<0.001), occupation-by-age (p=0.002), and occupation-by-race (p=0.013) interactions. No significant group-by-covariate interactions were noted. Analysis of the Ranch Hands and Original Comparisons, however, found significant three-factor interactions of group-by-race-by-age (p=0.030) and group-by-race-by-occupation (p=0.020) (see Tables N-7 and N-8 of Appendix N). For equivalent analyses, the followup results were quite analogous to the Baseline study results.

Hematocrit (HCT)

All of the unadjusted and adjusted categorical tests and analyses of mean differences failed to detect any group differences. Since there were only five abnormally high values, this category was combined with the normal category in the categorical analyses.

The association of race to HCT was highly significant, with 4.9 percent abnormally low values noted in Blacks versus 0.9 percent in nonblacks (p<0.001). Regression analyses also detected significant effects of current smoking (p<0.001) as well as age-by-occupation (p=0.004), race-by-occupation (p=0.003), and occupation-by-smoking history (p=0.035) interactions. In both categorical and continuous adjusted analyses, no significant group-by-covariate interactions were detected. Analyses of data from the Ranch Hands and Original Comparisons, however, detected significant three-factor interactions of group-by-race-by-age (p=0.026) and group-by-race-by-occupation (p=0.011) (see Tables N-7 and N-8 of Appendix N).

Mean Corpuscular Volume (MCV)

No significant group differences were detected for MCV abnormalities or mean values by any of the unadjusted or adjusted analyses.

Main covariate effects were profound for age (p<0.001), race (p<0.001), occupation (p=0.004), and smoking history (p<0.001). The older cohort had a greater frequency of abnormally high MCV values than did the younger age group (18.0% vs. 9.4%, respectively), and Blacks had a far greater frequency of abnormally low MCV values than nonblacks (7.7% vs. 0.6%, respectively). Enlisted groundcrew personnel had a lower percentage of abnormally high values than officers or enlisted flyers (12.5%, 15.5%, and 17.0%, respectively), and increases in pack-years of smoking were associated with increasing percentages of abnormally high levels (0 pack-years: 4.7%; greater than 0 to 10 pack-years: 13.1%; and greater than 10 pack-years: 21.0%).

Continuous analyses detected significant interactions of race-by-age (p<0.001), race-by-occupation (p=0.015), and race-by-current smoking (p=0.025). The analysis of the Ranch Hand and Original Comparisons revealed a significant group-by-race interaction (p=0.031) for the categorical analyses and significant group-by-age-by-smoking history (p=0.041) and group-by-age-by-current smoking (p=0.012) interactions in the continuous

analyses. Various contrasts are given in Table N-8 of Appendix N. No explanations are apparent for these interactions except chance. The followup examination results of MCV (i.e., significant interactions) differed from the Baseline results, which showed a significantly larger adjusted mean MCV value in the Ranch Hands.

Mean Corpuscular Hemoglobin (MCH)

MCH abnormalities and mean values did not differ significantly by group in any of the unadjusted or adjusted analyses.

Main effects were very significant for all of the covariates. The older cohort had a greater frequency of abnormally high MCH values than the younger group (7.9% vs. 3.2%, respectively; $p<0.001$), while Blacks had a greater frequency of low abnormalities than nonblacks (4.9% vs. 0.3%, respectively; $p<0.001$). Enlisted groundcrew had a higher proportion of abnormalities in the lower range than enlisted flyers and officers (1.0%, 0.3%, 0.2%, respectively), but they had a lower proportion of high-range abnormalities compared to the other occupations (4.3%, 7.8%, and 7.3%, respectively). The overall p-value was 0.003. Increasing pack-years of smoking was associated with increasing frequencies of high abnormal MCH results (0 pack-years: 2.1%; greater than 0 to 10 pack-years: 6.0%; and greater than 10 pack-years: 8.3%; $p<0.001$).

Continuous analyses detected a significant race-by-age interaction ($p=0.015$), as well as significant effects of current smoking ($p<0.001$) and occupation ($p<0.001$). The followup findings did not support the Baseline observation of significantly increased MCH in the Ranch Hands, although the mean was still higher (both unadjusted and adjusted) in the Ranch Hand group.

In the analysis of the Ranch Hands and the Original Comparisons, a significant three-factor interaction of group-by-age-by-current smoking emerged ($p=0.026$). Table N-8 of Appendix N presents Ranch Hand-Comparison differences for selected covariate levels corresponding to 35- and 53-year-old nonsmokers, one-pack-per-day current smokers, and two-packs-per-day current smokers. The differences were positive for all contrasts except the 53-year-old smokers, when the differences became increasingly more negative with increasing levels of smoking.

Mean Corpuscular Hemoglobin Concentration (MCHC)

In both groups, only one abnormal MCHC count was recorded for either the abnormally low or abnormally high categories, precluding unadjusted or adjusted categorical tests, and exploration of main covariate effects. No significant group differences were detected by the unadjusted or adjusted tests of MCHC means, although race ($p=0.001$) and current smoking ($p=0.042$) were significantly associated with MCHC (higher MCHC in nonblacks and decreasing MCHC associated with increasing current levels of smoking). Similar findings were noted in the analysis of Ranch Hand and Original Comparisons, and overall, the followup findings were comparable to the 1982 Baseline MCHC results.

Platelet Count (PLT)

Neither the unadjusted nor the adjusted categorical analysis showed statistically significant group differences. Analysis of continuous data disclosed significant effects due to occupation ($p=0.039$), age ($p=0.006$), group-by-race-by-smoking history ($p<0.001$), and group-by-race-by-current smoking ($p=0.024$) interactions, with higher PLT values in the heavily smoking Ranch Hands but similar values for nonsmokers (see Table N-2 of Appendix N).

The significant interactions of group-by-race-by-smoking history ($p=0.011$) and group-by-age ($p=0.040$) were also noted for the analyses involving the Original Comparisons (see Table N-8 of Appendix N). The percentages of abnormally high PLT counts increased with increasing pack-years of smoking (0 pack-years: 0.8%; greater than 0 to 10 pack-years: 2.0%; and greater than 10 pack-years: 2.6%). Other than the interactions encountered in the adjusted analyses, the overall findings at the followup were comparable to the Baseline PLT results.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). Log-linear models were fit to the categorical data to examine the effects of exposure and pack-years of smoking, as well as the interaction between these variables. The normal and abnormally high categories were pooled for the RBC count, and the abnormally low and normal response categories were pooled for MCV, MCH, and PLT due to empty cells in some strata. Because of the small numbers of abnormal values, analyses were not conducted for HCT or MCHC. The results of the unadjusted categorical analyses are presented in Table 16-7, and the counterpart adjusted analyses are given in Table 16-8.

The unadjusted analyses showed only a statistically significant result for the WBC count in the enlisted flyer category, due primarily to an excess of abnormally low values in the high exposure category. The very sparse data support a trend from low to high exposure, and the finding of abnormally low WBC counts associated with exposure is in the direction expected for an herbicide effect. However, the exposure association with abnormally low WBC counts converted to borderline significance ($p=0.082$) in the adjusted analysis. There were no statistically significant exposure level-by-smoking history interactions. Similar analyses in the other occupational strata (with much larger sample sizes) did not produce this pattern.

The unadjusted analysis of means for all eight hematological variables was carried out by a one-way analysis of variance. The results are arrayed in Table 16-9.

These analyses revealed only one statistically significant result ($p=0.038$), the RBC count in the enlisted groundcrew stratum where individuals in the medium exposure category had a higher mean RBC level than those in the low or high exposure categories. Thus, these significant RBC findings did not demonstrate a dose-response relationship. The results for HCT in the enlisted groundcrew stratum were of borderline significance ($p=0.052$) with the highest mean HCT level in the medium exposure category. In contrast to the categorical analyses, mean WBC levels in the enlisted flyers were not significantly different among the three exposure levels.

TABLE 16-7.

Unadjusted Categorical Exposure Index Analyses
for Hematological Variables by Occupation

Variable	Occupation	Exposure Index	Abnormally Low Number	Abnormally Low Percent	Normal Number	Normal Percent	Abnormally High Number	Abnormally High Percent	Total	p-Value
RBC	Officer	Low	3	2.4	123	96.8	1	0.8	127	0.522[a]
		Medium	4	3.1	125	96.2	1	0.8	130	
		High	6	4.9	114	93.4	2	1.6	122	
	Enlisted Flyer	Low	1	1.8	54	98.2	0	0.0	55	0.401[a]
		Medium	1	1.5	64	98.5	0	0.0	65	
		High	3	5.3	54	94.7	0	0.0	57	
	Enlisted Groundcrew	Low	6	3.9	148	96.1	0	0.0	154	0.329[a]
		Medium	2	1.2	158	97.5	2	1.2	162	
		High	4	2.8	136	95.8	2	1.4	142	
WBC	Officer	Low	7	5.5	115	90.6	5	3.9	127	0.919
		Medium	7	5.4	118	90.8	5	3.8	130	
		High	5	4.1	110	90.2	7	5.7	122	
	Enlisted Flyer	Low	0	0.0	51	92.7	4	7.3	55	0.045
		Medium	1	1.6	59	92.2	4	6.2	64	
		High	6	10.5	47	82.5	4	7.0	57	
	Enlisted Groundcrew	Low	4	2.6	139	90.3	11	7.1	154	0.839
		Medium	8	4.9	142	87.6	12	7.4	162	
		High	7	4.9	125	88.0	10	7.0	142	
HGB	Officer	Low	7	5.5	100	78.7	20	15.8	127	0.425
		Medium	2	1.5	106	81.5	22	16.9	130	
		High	6	4.9	92	75.4	24	19.7	122	
	Enlisted Flyer	Low	3	5.4	36	65.4	16	29.1	55	0.350
		Medium	3	4.6	51	78.5	11	16.9	65	
		High	5	8.8	36	63.2	16	28.1	57	
	Enlisted Groundcrew	Low	5	3.2	119	77.3	30	19.5	154	0.352
		Medium	4	2.5	110	67.9	48	29.6	162	
		High	4	2.8	102	71.8	36	25.4	142	

TABLE 16-7. (continued)

Unadjusted Categorical Exposure Index Analyses
for Hematological Variables by Occupation

Variable	Occupation	Exposure Index	Abnormally Low		Normal		Abnormally High		Total	p-Value
			Number	Percent	Number	Percent	Number	Percent		
MCV	Officer	Low	1	0.8	111	87.4	15	11.8	127	0.580[b]
		Medium	1	0.8	111	85.4	18	13.8	130	
		High	0	0.0	102	83.6	20	16.4	122	
	Enlisted Flyer	Low	0	0.0	43	78.2	12	21.8	55	0.764[b]
		Medium	0	0.0	54	83.1	11	16.9	65	
		High	0	0.0	47	82.5	10	17.5	57	
	Enlisted Groundcrew	Low	2	1.3	139	90.3	13	8.4	154	0.091[b]
		Medium	3	1.8	133	82.1	26	16.0	162	
		High	3	2.1	117	82.4	22	15.5	142	
MCH	Officer	Low	1	0.8	117	92.1	9	7.1	127	0.916[b]
		Medium	0	0.0	121	93.1	9	6.9	130	
		High	0	0.0	112	91.8	10	8.2	122	
	Enlisted Flyer	Low	0	0.0	51	92.7	4	7.3	55	0.855[b]
		Medium	0	0.0	60	92.3	5	7.7	65	
		High	0	0.0	54	94.7	3	5.3	57	
	Enlisted Groundcrew	Low	1	0.6	147	95.4	6	3.9	154	0.626[b]
		Medium	2	1.2	151	93.2	9	5.6	162	
		High	3	2.1	130	91.6	9	6.3	142	
PLT	Officer	Low	2	1.6	120	94.5	5	3.9	127	0.487[b]
		Medium	1	0.8	126	97.7	2	1.6	129	
		High	0	0.0	119	97.5	3	2.5	122	
	Enlisted Flyer	Low	1	1.8	51	92.7	3	5.4	55	0.135[b]
		Medium	0	0.0	64	98.5	1	1.5	65	
		High	0	0.0	57	100.0	0	0.0	57	
	Enlisted Groundcrew	Low	0	0.0	152	98.7	2	1.3	154	0.914[b]
		Medium	1	0.6	158	97.5	3	1.8	162	
		High	0	0.0	140	98.6	2	1.4	142	

[a]Normal pooled with abnormally high.

[b]Abnormally low pooled with normal.

TABLE 16-8.

Adjusted Categorical Exposure Index Analyses (Log-Linear Models) for Hematological Variables by Occupation (p-Values)

Variable	Occupation	Exposure Index Effect*	Smoking History Effect**	Exposure Index-by-Smoking History
RBC	Officer	0.593	0.246	0.472
	Enlisted Flyer	0.552	0.364	0.981
	Enlisted Groundcrew	0.310	0.515	0.717
WBC	Officer	0.928	0.001	0.616
	Enlisted Flyer	0.082	0.121	0.971
	Enlisted Groundcrew	0.761	0.009	0.104
HGB	Officer	0.444	0.393	0.424
	Enlisted Flyer	0.413	0.647	0.980
	Enlisted Groundcrew	0.299	0.104	0.143
MCV	Officer	0.718	<0.001	0.334
	Enlisted Flyer	0.619	0.020	0.490
	Enlisted Groundcrew	0.101	0.028	0.574
MCH	Officer	0.852	0.002	0.777
	Enlisted Flyer	0.800	0.168	0.514
	Enlisted Groundcrew	0.681	0.288	0.530
PLT	Officer	0.410	0.099	0.708
	Enlisted Flyer	0.178	0.816	0.976
	Enlisted Groundcrew	0.910	0.363	0.996

*Adjusted for smoking history (no interaction).

**Adjusted for exposure index (no interaction).

TABLE 16-9.

Unadjusted Continuous Exposure Index Analyses for Hematological Variables by Occupation (Analysis of Variance)

Occupation	Variable	Exposure Index Mean ± SE Low	Medium	High	p-Value
		(n=127)	(n=130)	(n=122)	
Officer	RBC	4.904±0.030	4.861±0.029	4.899±0.034	0.560
	WBC[a]	6.488	6.553	6.753	0.512
	HGB	15.468±0.084	15.463±0.087	15.593±0.094	0.507
	HCT	45.379±0.243	45.313±0.255	45.791±0.284	0.380
	MCV	92.648±0.430	93.260±0.365	93.548±0.367	0.252
	MCH	31.606±0.161	31.851±0.134	31.884±0.123	0.314
	MCHC	34.090±0.060	34.123±0.060	34.067±0.059	0.801
	PLT[a]	253.66	255.70[b]	256.72	0.799
		(n=55)	(n=65)	(n=57)	
Enlisted Flyer	RBC	4.972±0.048	4.942±0.037	4.957±0.053	0.894
	WBC[a]	7.531	7.236	6.966	0.378
	HGB	15.785±0.149	15.629±0.110	15.721±0.180	0.744
	HCT	46.345±0.425	45.908±0.315	46.300±0.535	0.717
	MCV	93.269±0.618	92.923±0.501	93.400±0.572	0.817
	MCH	31.782±0.222	31.675±0.187	31.735±0.208	0.933
	MCHC	34.065±0.075	34.058±0.072	33.956±0.072	0.508
	PLT[a]	272.87	275.34[c]	261.13	0.382
		(n=154)	(n=162)	(n=142)	
Enlisted Groundcrew	RBC	4.990±0.032	5.094±0.031	4.999±0.033	0.038
	WBC[a]	7.185	7.236	7.389	0.686
	HGB	15.566±0.099	15.807±0.075	15.685±0.090	0.147
	HCT	45.740±0.284	46.580±0.210	46.086±0.252	0.052
	MCV	91.737±0.399	91.672±0.404	92.376±0.458	0.436
	MCH	31.251±0.154	31.138±0.151	31.468±0.166	0.325
	MCHC	34.032±0.059	33.941±0.051	34.031±0.057	0.409
	PLT[a]	270.97	273.42	268.27	0.748

[a]Standard errors (SE) not presented, since variables were analyzed on logarithmic scale.

[b]n=129.

[c]n=64.

SUMMARY AND CONCLUSIONS

The functional integrity of the hematopoietic system was assessed by the measurement of eight peripheral blood variables: red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (PLT). These variables were analyzed in the discrete form to detect differences in the percentages of values outside the designated laboratory range, as well as in the continuous form to detect shifts in mean values between the two groups. A summary of all of these analyses, unadjusted and adjusted for the covariates of age, race, occupation, and smoking, is presented in Table 16-12.

The unadjusted discrete analysis of the percent abnormal values, both low and high, showed no statistically significant differences between the Ranch Hand and Comparison groups for any of the hematological variables. Similarly, the adjusted categorical analysis disclosed that none of the adjusted relative risks was significant for either group, and that no significant group-by-covariate interactions were present.

The unadjusted continuous analysis did not detect any significant differences in group means for any of the eight variables. The adjusted continuous analysis found no significant group differences for HGB, HCT, MCV, MCH, and MCHC, but encountered significant three-factor interactions for WBC (group-by-race-by-age, group-by-age-by-smoking history, and group-by-race-by-occupation), for PLT (group-by-race-by-smoking history and group-by-race-by-current level of smoking), and a borderline interaction for RBC (group-by-occupation-by-smoking history). Ranch Hand versus Original Comparison analyses revealed further significant interactions for HGB, HCT, MCV, and MCH. As no group strata demonstrated consistent patterns of hematologic impairment, biologic relevance was not assigned to the interactions. The covariate effects of age, race, occupation, and smoking history were highly significant for many of the hematological variables.

The effect of race was particularly profound for all variables except PLT. There was fair consistency in the covariate effects upon the RBC-related variables. Generally, decreasing hematologic values were associated with increasing age and the Black race, and increasing hematologic values were associated with increasing smoking. The detection of these classical covariate effects lends credence to the overall finding of nonsignificant group differences for all of the hematological variables. Significant group differences found for MCV and MCH at the Baseline examination were not significant at the first followup. Other differences (e.g., covariate effects, interactions) between the Baseline and followup examinations may be due to small numeric shifts in the cohorts under study (see Chapter 2) and the selection of alternate statistical models, or due to chance.

Unadjusted continuous exposure analyses in the Ranch Hand group revealed only one significant effect (RBC in enlisted groundcrew) and one borderline effect (HCT in enlisted groundcrew), but neither was consistent with a plausible dose-response relationship. The adjusted continuous exposure analyses found only one significant contrast (HCT, medium exposure versus low exposure, enlisted groundcrew). However, seven exposure level-by-covariate interactions were noted for four of the hematological variables. Discrete outcome analyses of the exposure level index revealed a significant result only for WBC in the enlisted flyers.

TABLE 16-12.

Overall Summary Results of Unadjusted and Adjusted Analyses of Hematological Variables

	Unadjusted		Adjusted	
	Mean	Categorical	Mean	Categorical
RBC	NS	NS	NS*	NS
WBC	NS	NS	****	NS
HGB	NS	NS	NS	NS
HCT	NS	NS	NS	NS
MCV	NS	NS	NS	NS
MCH	NS	NS	NS	NS
MCHC	NS	--	NS	--
PLT	NS	NS	****	NS

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

NS*: Borderline significant group-by-covariate interaction ($0.05 \leq p < 0.10$).

--Analysis not performed due to sparse data.

****Group-by-covariate interaction.

Note: Significant group-by-covariate interaction, Ranch Hands versus Original Comparisons only, for HGB, HCT, MCV, and MCH.

The longitudinal analyses of MCV, MCH, and PLT found significant differences only for PLT values between the Baseline and followup examinations, with the Baseline group difference in mean values closing to near equivalence at the followup examination.

In conclusion, none of the eight hematological variables were found to differ significantly between the Ranch Hand and Comparison groups. In fact, group equivalence was more apparent at the followup examination than at the Baseline examination. The classical effects of age, race, and smoking were demonstrated with most of the hematological variables. The longitudinal analyses also suggested that neither group manifested an impairment of the hematopoietic system. Exposure index analyses did not support a plausible dose-response relationship for any of the hematological variables.

CHAPTER 16

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CHAPTER 17

RENAL ASSESSMENT

INTRODUCTION

Renal dysfunction and overt renal disease are not considered to be important clinical sequelae of exposure to phenoxy acids, chlorophenols, or TCDD.

In man and animals, 2,4-D, 2,4,5-T, and TCDD are excreted by the kidney, largely in the unmetabolized state via a first-order kinetic process.[1-5] Excretion of these compounds appears to be a function of the proximal convoluted tubules.[6-8] In experimental animals, renal damage is generally noted only when very high or lethal doses of TCDD have been administered, an observation that reflects the severe systemic toxicity of TCDD as contrasted to a doubtful role of primary nephrotoxicity.[9-12]

A variety of experimental pharmacokinetic studies have been conducted in man using both ingested 2,4-D and 2,4,5-T.[3-5,13,14] Most of these studies suggested an unconjugated excretion of these compounds by first-order kinetics. No acute deleterious effects, as detected by urinalysis or blood chemistries, were either noted or recorded for the volunteer subjects.

In contrast, following significant exposure to a horse arena filled with TCDD-contaminated waste products, a 6-year-old girl developed hemorrhagic cystitis, pyelonephritis, and proteinuria.[15] Horses exposed to this arena and other contaminated arenas also frequently manifested hematuria. A thorough 5-year followup examination of the young girl was essentially normal and did not reveal any renal sequalae.[16]

Most dioxin morbidity studies have only briefly mentioned renal disease and function, and then in the context of routine data collected at physical examination rather than as a specific clinical focus. Some studies of significant occupational exposure have been almost devoid of commentary on renal dysfunction.[17-19] A contemporary study of a residentially exposed cohort showed negative renal findings.[20]

The Times Beach, Missouri, pilot study demonstrated historical "trends" of increased urinary tract disease by questionnaire, along with a compatible pattern of leukocyturia and hematuria manifest at physical examination, but none of the observations was statistically significant.[21] The Monsanto industrial morbidity studies reported essentially negative urinalysis findings, although data were not presented.[22,23]

Baseline Summary Results

The 1982 Baseline examination assessed renal disease and function by questionnaire and basic urinalysis testing.

Based on questionnaire information, the Ranch Hand group reported significantly more kidney disease than the Comparisons ($p=0.039$), but this finding was not substantiated by laboratory test results, even when all abnormalities were summed over the five tests of BUN, creatinine clearance, presence of occult blood, five or more urine WBC's per high-power field (HPF), and the presence of urine protein. The Comparison group manifested a twofold increase in proteinuria ($p=0.055$). The distributions of creatinine clearance levels were similar in both groups, as were the means of the BUN, urine specific gravity, and WBC's/HPF. Difficulty in assessing the degree and significance of hidden noncompliance to the full 24-hour urine collection made the interpretation of the creatinine clearance test results somewhat problematic. Of some interest, known noncompliance to urine collection was observed much more frequently ($p<0.001$) in the elderly participants. Of 18 herbicide exposure analyses, only 1 (enlisted flyer category) was statistically significant vis-a-vis a history of kidney disease, and it did not demonstrate a linear increase from low to high exposure.

The validity of the renal assessment was reinforced by the demonstrated effects of the covariates of age (born in or after 1942, born before 1942) and 2-hour status after postprandial glucose levels (less than 120 mg/dl, greater than or equal to 120 mg/dl). Blood urea nitrogen increased with age and specific gravity decreased ($p<0.001$ for both), while an abnormally high postprandial glucose level indicative of diabetes was associated only with an increasing urine specific gravity, as expected.

Overall, the Baseline renal assessment suggested an excess of historical kidney disease in the Ranch Hand group that was not corroborated by laboratory urinalysis testing.

Parameters of the 1985 Renal Assessment

Because of the essentially negative Baseline results, the fact that kidney disease is not a prime clinical endpoint, and the manifest compliance problems with a 24-hour urine collection, the 1985 examination process did not emphasize further inquiry into renal disease and function.

The onsite NORC questionnaire did not specifically probe for a 1982-1985 interval history of kidney disease, although severe cases may be captured by the generic question, "any other major condition?" or by a detailed extraction of review-of-systems data obtained at the physical examination. Laboratory testing parameters included all the Baseline dependent variables except the creatinine clearance level (omitted because the plasma creatinine assay was deleted from the test battery). Also, the analysis of composite renal abnormalities was deleted. In addition, the 24-hour urine collection was reduced to a 12-hour collection (5:30 a.m. to 5:30 p.m.) to ease participant burden while still maintaining validity for the porphyrin analyses (see Chapter 13). The accuracy of the 12-hour urine collection was not assessed during the 1985 examination.

Renal data analyses paralleled the Baseline analysis except for deleting one of the dependent variables and a composite analysis, adding the covariate of race, and defining the covariate of diabetic class as diabetic, impaired, or normal. No clinical exclusion categories applied to the renal analysis. Minor numerical differences in the tables are due to rare missing dependent

variable or covariate data. Adjusted statistical analyses using the above covariates were based on 1,016 Ranch Hands and 1,293 Comparisons and used logistic regression and analysis of covariance methods. When age was used as a covariate in the logistic regression models, the continuous form was used mathematically, but for summary table purposes, age is displayed as a dichotomy. Parallel analyses using the Original Comparisons can be found in Appendix O (see Tables O-3 through O-5). Tests of association between dependent variables and covariates emphasized Fisher's exact test and Pearson's chi-square test for discrete dependent variables and t-tests and analysis of variance techniques for continuous dependent variables.

RESULTS AND DISCUSSION

Questionnaire Data

History of renal disease was assessed by a self-administered review-of-systems question list at the physical examination. Specific structured questions on renal disease were not incorporated in the NORC questionnaire. The review-of-systems questions, i.e., "kidney trouble?" "kidney stones?" were open-ended with respect to time, and reflected conditions that arose at any time in the past.

These questionnaire data did not show a significant difference between the Ranch Hand and Comparison groups, as reflected by the analysis in Table 17-1.

Tests of association between the historical presence of kidney disease in both groups and the covariates of race, occupation, diabetes, and age are given in Table 17-2.

TABLE 17-1.

Unadjusted Analysis of History of Kidney Disease/Kidney Stones by Group

	History of Kidney Disease/Stones						
	Yes		No				
Group	Number	Percent	Number	Percent	Total	Est. Relative Risk (95% C.I.)	p-Value
Ranch Hand	94	9.3	920	90.7	1,014	0.93 (0.70,1.23)	0.619
Comparison	128	9.9	1,163	90.1	1,291		

TABLE 17-2.

Association Between Kidney Disease/Kidney Stones and Age, Race, Occupation, and Diabetic Class in the Combined Ranch Hand and Comparison Groups

		History of Kidney Disease/Stones					
		Yes		No			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	66	6.9	894	93.1	960	<0.001[a]
	Born <1942	156	11.6	1,189	88.4	1,345	
Race	Nonblack	214	9.9	1,949	90.1	2,163	0.106[a]
	Black	8	5.6	134	94.4	142	
Occupation	Officer	83	9.6	781	90.4	864	
	Enlisted Flyer	36	9.3	350	90.7	386	0.969[b]
	Enlisted Groundcrew	103	9.8	952	90.2	1,055	
Diabetic* Class	Diabetic	14	8.0	161	92.0	175	
	Impaired	41	14.5	242	85.5	283	0.011[b]
	Normal	166	9.0	1,677	91.0	1,843	

[a]Fisher's exact test.

[b]Pearson's chi-square test.

*Unable to classify four participants, due to missing 2-hour postprandial glucose level and no historical evidence of diabetes.

These results showed that there was no significant effect due to race or occupation. In contrast, there was a significant effect due to diabetic class ($p=0.011$), with participants in the impaired diabetic class having a significantly higher proportion of past kidney disease than those in the normal or diabetic classes. Older participants also had a significantly higher history of past renal events than younger participants ($p<0.001$).

A logistic regression analysis of the history of kidney disease and kidney stones using the above four covariates gave a result very similar to the unadjusted analysis (Adj. RR: 0.95, 95% C.I.: [0.71,1.25], $p=0.693$). Race and occupation were not significant covariates. However, diabetic class and age were significant covariates ($p=0.041$ and $p<0.001$, respectively).

These analyses showed that there was no difference in the history of renal disease between the Ranch Hand and Comparison groups, and that the

proportions of past kidney disease and kidney stones were significantly influenced by age and diabetic class. While these findings are consistent with traditional expectations in renal disease, they were in direct contrast to the findings of the 1982 Baseline examination, which revealed a significant excess of historical kidney disease in the Ranch Hand group, and group data that were not influenced by age or glucose levels.

It is concluded that there were no significant group differences in past renal disease.

Physical Examination Data

No physical examination procedures were used to evaluate the renal system as most procedures are invasive and beyond the scope of this voluntary examination. Accordingly, the renal system was evaluated primarily by laboratory data.

Laboratory Data

Five renal variables were quantitated by general laboratory procedures to assess nonspecific renal system function. The presence or absence of urine protein was determined by standard reagent strip testing. Hematuria and leukocyturia were measured by high-power microscopic examination after centrifugation for 5 minutes. Urine specific gravities were measured by Ames' Multisticks; those urines exceeding normal limits were remeasured by standardized refractometers. BUN levels were assayed by a DuPont Automated Chemical Analyzer, model 500. The SCRF laboratory normal values from these variables are given in Table 17-3.

TABLE 17-3.

Laboratory Norms for Five Renal Variables

Renal Variable	Normal	Abnormal
Urine Protein	Absent	Present
Occult Blood	Absent	$\geq$1 RBC/HPF
WBC/HPF	$\leq$2	>2
BUN (mg/dl)	7-22	$\geq$23
Specific Gravity	1.005-1.03	$\leq$1.004

In this section, urinary protein, hematuria, and leukocyturia were analyzed as discrete variables, whereas BUN and urine specific gravity were analyzed as continuous variables. The number and percent of subjects with abnormal values for the discrete variables are displayed in the summary Table 17-4, along with the number of participants, the unadjusted means, and standard errors of the continuous variables.

TABLE 17-4.

Summary of Renal Laboratory Variables by Group

Renal Variable	Group: Ranch Hand Number Abnormal	Ranch Hand Percent Abnormal	Comparison Number Abnormal	Comparison Percent Abnormal	Unadjusted p-Value
Urine Protein	37	3.6	40	3.1	0.485
Occult Blood	182	17.9	208	16.1	0.239
WBC/HPF	102	10.0	107	8.3	0.145

Renal Variable	Unadjusted Mean (Sample Size)	Standard Error	Unadjusted Mean (Sample Size)	Standard Error	Unadjusted p-Value
BUN (mg/dl)	14.21* (1,016)	--	14.30* (1,293)	--	0.554
Specific Gravity	1.0157 (1,016)	0.0002	1.0152 (1,292)	0.0002	0.082

*Arithmetic mean calculated on square root scale and transformed to original units.

--Standard error not given, since analysis performed on square root scale.

The following statistical power statements apply to several variables displayed in Table 17-4. At a standard α-level of 0.05 and a power of 0.80, the sample sizes were sufficient to detect a 1.28-fold increase in the frequency of percent abnormal values for urinary occult blood, and a 1.43-fold increase in the percentage of leukocyturia, both over that observed in the Comparison group. Further, the sample sizes were adequate to reveal a 2.9 percent mean shift in the BUN value relative to the mean observed in the Comparison group.

Urinary Protein

As displayed in Table 17-4, the Ranch Hand group had a prevalence rate of urinary protein of 3.6 percent versus 3.1 percent in the Comparison group (Est. RR: 1.18, 95% C.I.: [0.75,1.86], p=0.485). This difference was not significant.

Tests of association were conducted with pooled participant data using the covariates of race, occupation, diabetic class, and age. These tests are presented in Table 17-5.

TABLE 17-5.

Association Between Urinary Protein and Age, Race, Occupation, and Diabetic Class in the Combined Ranch Hand and Comparison Groups

		Presence of Urinary Protein					
		Yes		No			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	34	3.5	927	96.5	961	0.641[a]
	Born <1942	43	3.2	1,304	96.8	1,347	
Race	Nonblack	65	3.0	2,100	97.0	2,165	0.002[a]
	Black	12	8.4	131	91.6	143	
Occupation	Officer	18	2.1	845	97.9	863	
	Enlisted Flyer	11	2.8	376	97.2	387	0.010[b]
	Enlisted Groundcrew	48	4.5	1,010	95.5	1,058	
Diabetic* Class	Diabetic	20	11.4	155	88.6	175	
	Impaired	18	6.4	264	93.6	282	<0.001[b]
	Normal	39	2.1	1,808	97.9	1,847	

[a]Fisher's exact test.

[b]Pearson's chi-square test.

*Unable to classify four participants, due to missing 2-hour postprandial glucose level and no historical evidence of diabetes.

These results suggested no age effect, but significant associations for the covariates of race (p=0.002), occupation (p=0.010), and diabetic class (p<0.001) were noted. The significant covariate effects were attributable to higher percentages of urinary protein abnormalities in Blacks versus non-blacks, enlisted groundcrew versus officers or enlisted flyers, and diabetes (past history [unverified] or greater than or equal to 200 mg/dl glucose) versus impaired glucose tolerance (at least 140 but less than 200 mg/dl glucose) versus normal glucose tolerance (less than 140 mg/dl glucose).

The prevalence rates of urinary protein abnormalities were adjusted by logistic regression models using the above four covariates. Race and occupation demonstrated significant effects (p=0.023 and p=0.023, respectively), while age did not (p=0.294). Because of a significant interaction between group and diabetic class (p=0.047), stratified analyses were conducted to provide further clarification. The results are shown in Table 17-6.

The adjusted relative risk, 95 percent confidence interval, and group p-value for each diabetic class are shown in Table 17-7.

TABLE 17-6.

Frequency of Urinary Protein by Diabetic Class and Group

		Presence of Urinary Protein				
		Yes		No		
Diabetic Class	Group	Number	Percent	Number	Percent	Total
Diabetic	Ranch Hand	7	9.0	71	91.0	78
	Comparison	13	13.4	84	86.6	97
Impaired	Ranch Hand	5	4.7	101	95.3	106
	Comparison	13	7.4	163	92.6	176
Normal	Ranch Hand	25	3.0	807	97.0	832
	Comparison	14	1.4	1,001	98.6	1,015

TABLE 17-7.

Adjusted Relative Risks for Urinary Protein by Diabetic Class

Diabetic Class	Adjusted Relative Risk	95% C.I.	p-Value
Diabetic	0.66	(0.25, 1.77)	0.414
Impaired	0.66	(0.23, 1.93)	0.453
Normal	2.23	(1.15, 4.32)	0.018

This analysis showed that the estimated prevalence of urinary protein is lower in the Ranch Hand group than in the Comparison group for the diabetic and glucose-impaired strata. Conversely, for the normal diabetic class, the Ranch Hand group manifested a significant increased prevalence of positive urinary protein as contrasted with the Comparison group.

These followup examination results were different from the 1982 Baseline examination, which showed significantly more proteinuria in the Comparison group. The prevalence of proteinuria in the followup examination was about 75 percent higher than the prevalence observed in the Baseline study. The interaction of group and diabetic class suggested Ranch Hand increases in proteinuria for normal glucose tolerance participants.

Urinary Occult Blood

Hematuria was determined by microscopic examination. For both groups combined, the frequency distribution of RBC count data was: 0 RBC/HPF, 82.15 percent; 1-2 RBC/HPF, 15.13 percent; 3-5 RBC/HPF, 2.03 percent; and greater than 5 RBC/HPF, 0.69 percent.

As noted in Table 17-4, the prevalence of urinary occult blood in the Ranch Hand group (17.9%) was slightly higher than the rate observed for the Comparison group (16.1%). The unadjusted analysis showed no significant group differences for occult blood (Est. RR: 1.14, 95% C.I.: [0.91,1.42], p=0.239).

Tests of association with the covariates of race, occupation, diabetic class, and age were conducted using combined group data for urinary occult blood, and these results are given in Table 17-8.

TABLE 17-8.

Association Between Urinary Occult Blood and Age, Race, Occupation, and Diabetic Class in the Combined Ranch Hand and Comparison Groups

		Presence of Urinary Occult Blood					
		Yes		No			
Covariate	Covariate Category	Number	Percent	Number	Percent	Total	p-Value
Age	Born ≥1942	148	15.4	812	84.6	960	0.115[a]
	Born <1942	242	18.0	1,105	82.0	1,347	
Race	Nonblack	355	16.4	1,809	83.6	2,164	0.016[a]
	Black	35	24.5	108	75.5	143	
Occupation	Officer	118	13.7	745	86.3	863	
	Enlisted Flyer	76	19.6	311	80.4	387	0.005[b]
	Enlisted Groundcrew	196	18.5	861	81.5	1,057	
Diabetic Class*	Diabetic	33	18.9	142	81.1	175	
	Impaired	52	18.5	229	81.5	281	0.296[b]
	Normal	305	16.5	1,542	83.5	1,847	

[a]Fisher's exact test.

[b]Pearson's chi-square test.

*Unable to classify four participants, due to missing 2-hour postprandial glucose level and no historical evidence of diabetes.

As reflected in Table 17-8, there was no significant effect due to diabetic class or age. However, Blacks had a significantly higher prevalence of urinary occult blood than nonblacks (p=0.016), and significant effects were also due to occupation (p=0.005), with officers having a lower proportion of positive occult blood determinations than enlisted personnel.

An adjusted analysis of urinary occult blood proportions was conducted by logistic regression techniques. Multiple significant three-factor interactions were noted, e.g., group-by-occupation-by-race (p=0.008), group-by-age-by-diabetic class (p=0.045), and group-by-occupation-by-diabetic class (p=0.017). Consequently, a series of analyses stratified by race were performed to determine adjusted relative risks for nonblacks and Blacks separately. The adjusted results for nonblack participants are given in Table 17-9.

TABLE 17-9.

Adjusted Analysis for Urinary Occult Blood for Nonblacks by Group

	Presence of Urinary Occult Blood					
	Yes		No			
Group	Number	Percent	Number	Percent	Total	Summary Statistics
Ranch Hand	166	17.4	789	82.6	955	Adj. RR: 1.13
Comparison	189	15.6	1,020	84.4	1,209	95% C.I.: (0.91,1.42), p-Value: 0.291

The covariates of occupation and age contributed significant effects ($p<0.001$ and $p=0.002$, respectively) to this analysis. Diabetic class was not significant ($p=0.863$), and was consequently not included in the final model. No significant group differences were found ($p=0.291$).

Table 17-10 shows the frequencies for Black participants.

The adjusted analysis of the data on Blacks showed a significant interaction of group and occupation ($p=0.003$). Table 17-11 presents frequencies and percents for the presence of urinary occult blood for each group, stratified by occupation.

This table demonstrates that the group-by-occupation interaction for Blacks was due to the Ranch Hand officers having a lesser prevalence of occult blood abnormalities than Comparison officers, while conversely, Ranch Hand enlisted personnel showed a higher prevalence of abnormalities than enlisted Comparisons. Because of the absence of hematuria in Black Ranch Hand officers, no relative risk was calculated. Consequently, the Black enlisted occupational categories were combined and investigated further through logistic regression techniques. This analysis did not show a difference of urinary occult blood percentages in the Ranch Hand Black

TABLE 17-10.

Frequency of Urinary Occult Blood for Blacks by Group

Group	Presence of Urinary Occult Blood: Yes Number	Yes Percent	No Number	No Percent	Total
Ranch Hand	16	26.7	44	73.3	60
Comparison	19	22.9	64	77.1	83

TABLE 17-11.

Frequency of Urinary Occult Blood for Blacks by Occupation and Group

Occupation	Group	Presence of Urinary Occult Blood: Yes Number	Yes Percent	No Number	No Percent	Total
Officer	Ranch Hand	0	0.0	7	100.0	7
	Comparison	3	42.9	4	57.1	7
Enlisted Flyer	Ranch Hand	3	30.0	7	70.0	10
	Comparison	1	5.9	16	94.1	17
Enlisted Groundcrew	Ranch Hand	13	30.2	30	69.8	43
	Comparison	15	25.4	44	74.6	59

enlisted and the Comparison Black enlisted strata (Est. RR: 1.62, 95% C.I.: [0.73,3.63], (p=0.239). The effects of age (p=0.817), occupation (p=0.171), and diabetic class (p=0.145) were not statistically significant, and were not included in the final adjusted analysis.

In conclusion, both unadjusted and adjusted stratified analyses (by race) did not reveal a consistent and plausible excess of hematuria in the Ranch Hand group. The tenfold or greater increase in the cross-sectional prevalence of hematuria compared to the Baseline examination (1.3% of both groups) to this followup examination may be due to a different sensitivity of the laboratory techniques of reagent-strip testing versus microscopic observation. Nonetheless, an approximate prevalence of 17 percent hematuria merits reevaluation at the next followup examination.

Urinary White Blood Cell Count

Leukocyturia was assessed by microscopic examination. As noted in Table 17-3, more than two white blood cells per high-power field (WBC/HPF) were considered abnormal by the SCRF laboratory. This is in distinct contrast to the cutpoint of five WBC/HPF used at the Baseline examination.

Table 17-4 shows the group frequencies of abnormal urine WBC's. The unadjusted analysis revealed a nonsignificant group effect (Est. RR: 1.24, 95% C.I.: [0.93,1.64], p=0.145).

Tests of association were conducted between the frequency of abnormal WBC counts in both groups and the covariates of race, occupation, diabetic class, and age. The results revealed a significantly higher prevalence of abnormal counts for Blacks than nonblacks ($p<0.001$), an effect due to occupation ($p=0.023$), with a lower prevalence of abnormalities for officers than enlisted personnel and an effect due to diabetic class ($p=0.046$), with a lower prevalence of abnormal WBC counts in the normal diabetic class than in either the impaired or diabetic classifications. Age was noncontributory ($p=0.508$).

Adjusted analyses of leukocyturia by group were performed by logistic regression techniques. A significant three-way interaction for group, age, and race was detected ($p=0.004$), requiring further stratified analyses. A summary of the frequencies for nonblacks is presented in Table 17-12.

TABLE 17-12.

Frequency of Urinary WBC/HPF for Nonblacks by Group

	Urinary WBC/HPF				
	Abnormal		Normal		
Group	Number	Percent	Number	Percent	Total
Ranch Hand	92	9.6	864	90.4	956
Comparison	88	7.3	1,121	92.7	1,209

The logistic regression adjustment of the data for nonblacks showed significant covariate effects for occupation ($p=0.046$) and diabetic class ($p=0.031$), and a significant interaction between group and age ($p=0.018$). Consequently, additional analyses were conducted stratifying by age (born in or after 1942, born before 1942), and are shown in Table 17-13.

TABLE 17-13.

Adjusted Analyses for Urinary WBC/HPF for Nonblacks
by Age Category and Group

Age	Group	Urinary WBC/HPF: Abnormal Number	Abnormal Percent	Normal Number	Normal Percent	Total	Summary Statistics
Born ≥1942	Ranch Hand	41	10.8	339	89.2	380	Adj. RR: 2.42
	Comparison	24	4.8	478	95.2	502	95% C.I.: (1.43,4.09)
							p-Value: 0.001
Born <1942	Ranch Hand	51	8.9	525	91.1	576	Adj. RR: 0.99
	Comparison	64	9.1	643	90.9	707	95% C.I.: (0.67,1.46)
							p-Value: 0.956

As depicted by the above table, the adjusted rate of nonblack young Ranch Hands with abnormal urinary white blood cell counts was significantly greater than that for nonblack Comparisons (p=0.001 adjusted for occupation and diabetic class). Demonstrating the interaction involving age and group, the adjusted rate of nonblack older Ranch Hands with abnormal urinary WBC counts was nonsignificant and less than older nonblack Comparisons (p=0.956 adjusted for occupation and diabetic class).

Similar analyses were conducted for Black participants. Rates of abnormal urinary white blood cell count levels were 16.7 percent and 22.9 percent (n=60 and 83) for Black Ranch Hands and Black Comparisons, respectively. Significant interactions involving group and occupation (p=0.002) and group and age (p=0.001) were found. Additional analyses stratified by occupation were performed. Frequencies stratified by occupation are shown in Table 17-14.

This table clearly shows how the proportions of WBC abnormalities vary by group within the various occupational categories. However, because of the lack of abnormalities in the Black Ranch Hand officer stratum, an adjusted relative risk was not calculated for this occupation. Thus, Black enlisted categories were combined and subjected to further logistic regression techniques. The analysis showed yet another interaction, between group and age (p=0.026), requiring an additional stratification by age. Results of these analyses are presented in Table 17-15.

TABLE 17-14.

Frequency of Urinary WBC for Blacks
by Occupational Category and Group

		Urinary WBC/HPF Count				
		Abnormal		Normal		
Occupation	Group	Number	Percent	Number	Percent	Total
Officer	Ranch Hand	0	0.0	7	100.0	7
	Comparison	2	28.6	5	71.4	7
Enlisted Flyer	Ranch Hand	3	30.0	7	70.0	10
	Comparison	3	17.6	14	82.4	17
Enlisted Groundcrew	Ranch Hand	7	16.3	36	83.7	43
	Comparison	14	23.7	45	76.3	59

TABLE 17-15.

Adjusted Analyses for Urinary WBC/HPF for Black
Enlisted Flyers and Groundcrew by Age and Group

		Urinary WBC/HPF Count					
		Abnormal		Normal			
Age	Group	Number	Percent	Number	Percent	Total	Summary Statistics
Born ≥1942	Ranch Hand	4	13.8	25	86.2	29	Adj. RR: 0.41
	Comparison	13	28.3	33	71.7	46	95% C.I.: (0.12,1.40)
							p-Value: 0.153
Born <1942	Ranch Hand	6	25.0	18	75.0	24	Adj. RR: 2.17
	Comparison	4	13.3	26	86.7	30	95% C.I.: (0.53,8.79)
							p-Value: 0.279

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

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

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

Blood Urea Nitrogen (BUN)

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

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

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

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

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

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

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

TABLE 17-16.

Adjusted Analysis of BUN by Race and Group

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

*Converted from square root scale.

Urinary Specific Gravity

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

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

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

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

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

TABLE 17-17.

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

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

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

EXPOSURE INDEX ANALYSES

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

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

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

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

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

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

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

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

TABLE 17-18.

Adjusted Categorical Exposure Index Analyses for Renal Variables by Occupation

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

TABLE 17-18. (continued)

Adjusted Categorical Exposure Index Analyses for Renal Variables by Occupation

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

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

TABLE 17-19.

Adjusted Continuous Exposure Index Analyses for Renal Variables

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

TABLE 17-19. (continued)

Adjusted Continuous Exposure Index Analyses for Renal Variables

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

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

TABLE 17-20.

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

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

LONGITUDINAL ANALYSES

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

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

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

SUMMARY AND CONCLUSIONS

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

TABLE 17-21.

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

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

TABLE 17-22.

Overall Summary Results of Unadjusted and Adjusted Analyses for Renal Variables

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

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

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

****Group-by-covariate interaction.

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

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

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

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

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

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

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

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

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

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

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

CHAPTER 17

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CHAPTER 18

ENDOCRINE ASSESSMENT

INTRODUCTION

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

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

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

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

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

Baseline Summary Results

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

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

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

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

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

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

Parameters of the 1985 Endocrine Assessment

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

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

RESULTS AND DISCUSSION

Questionnaire Data

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

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

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

Physical Examination Data

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

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

TABLE 18-1.

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

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

*Fisher's exact test.

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

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

TABLE 18-2.

Medical Record Verification Results of Reported Thyroid Disease by Group

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

TABLE 18-3.

Unadjusted Analysis for Thyroid and Testicular Conditions by Group

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

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

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

Laboratory Test Data

General

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

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

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

TABLE 18-4.

Laboratory Endocrinological Variables:
SCRF Normal and Abnormal Ranges

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

TABLE 18-5.

Unadjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

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

TABLE 18-5. (continued)

Unadjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

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

TABLE 18-5. (continued)

Unadjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

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

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

[a]t-test.

[b]Chi-square test.

[c]Fisher's exact test.

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

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

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

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

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

T_3 % Uptake

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

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

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

TABLE 18-6.

Adjusted Continuous and Categorical Analyses for Laboratory Endocrinological Variables by Group

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

TABLE 18-6. (continued)

Adjusted Continuous and Categorical Analyses for
Laboratory Endocrinological Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Differential	n	1,004	1,280				GRP*AGE*RACE Cortisol (p=0.032)
	Adj. Mean	****	****		—	****	PERSTYPE (p=0.005)
	95% C.I.	****	****				%BFAT (p<0.001)
2-Hour Post-prandial Glucose	n	976	1,234				%BFAT (p<0.001)
	Adj. Mean	114.4	115.3		—	0.487	OCC (p<0.001)
	95% C.I.	(107.3,122.0)	(108.2,123.0)				AGE*RACE (p=0.002)
				Overall		0.034	AGE (p<0.001)
				Impaired vs. Normal	0.73 (0.56,0.96)	0:022	RACE (p=<0.016)
				Diabetic vs. Normal	1.26 (0.72,2.22)	0.421	%BFAT (p<0.001)
Diabetes (Composite Indicator)	n	1,016	1,292				%BFAT (p<0.001)
				Diseased vs. Normal	1.12 (0.80,1.56)	0.500	AGE*RACE (p=0.005)

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

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

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

TABLE 18-7.

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

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

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

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

Thyroid Stimulating Hormone (TSH)

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

TABLE 18-8.

Adjusted Categorical Analysis for T_3 % Uptake

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

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

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

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

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

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

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

TABLE 18-9.

Adjusted Categorical Analysis for TSH

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

TABLE 18-10.

Adjusted Continuous Analysis for TSH by Group

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

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

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

Testosterone

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

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

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

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

TABLE 18-11.

Adjusted Categorical Analysis for Testosterone

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

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

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

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

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

Cortisol: Initial, 2-Hour, and Differential

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

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

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

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

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

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

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

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

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

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

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

TABLE 18-12.

Adjusted Continuous Analysis for Initial Cortisol by Group

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

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

TABLE 18-13.

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

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

[a]By t-test.

[b]By analysis of variance.

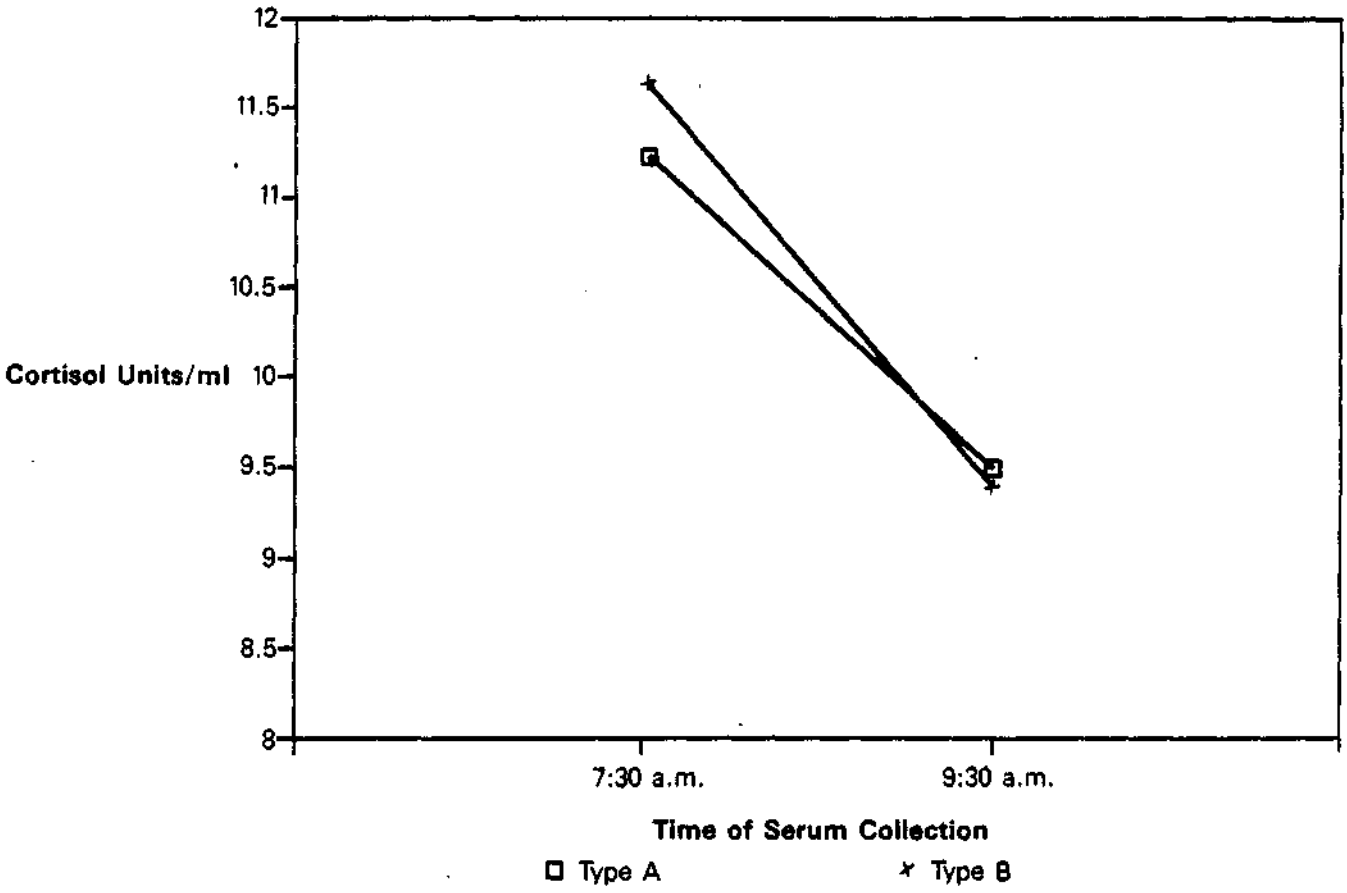

Figure 18-1.
Mean Cortisol Levels by Personality Type, Adjusted for Age and Percent Body Fat, by Time of Specimen Collection

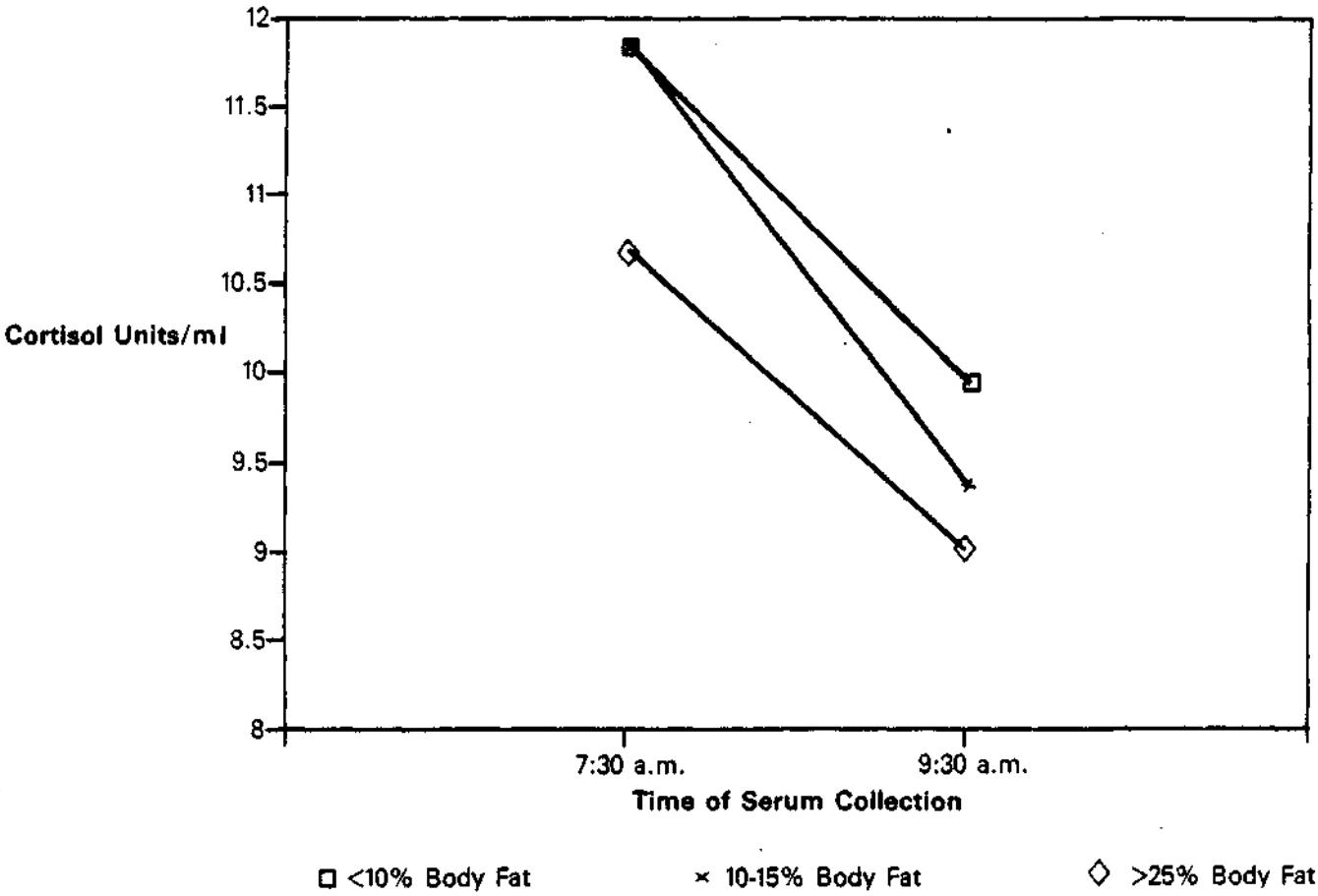

Figure 18-2.
Mean Cortisol Levels by Percent Body Fat, Adjusted for Age and Personality Type, by Time of Specimen Collection

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

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

2-Hour Postprandial Glucose

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

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

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

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

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

TABLE 18-14.

Adjusted Categorical Analysis for 2-Hour Postprandial Glucose

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

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

TABLE 18-15.

Adjusted Continuous Analysis for 2-Hour Postprandial Glucose by Group

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

Composite Diabetes Indicator

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

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

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

EXPOSURE INDEX ANALYSES

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

TABLE 18-16.

Adjusted Analysis for Diabetes (Composite Indicator)

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

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

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

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

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

LONGITUDINAL ANALYSES

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

TABLE 18-17.

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

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

TABLE 18-17. (continued)

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

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

TABLE 18-17. (continued)

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

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

TABLE 18-17. (continued)

Adjusted Exposure Index Analyses for Endocrinological Variables by Occupation

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

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

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

[b]Exposure index-by-race interaction.

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

TABLE 18-18.

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

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

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

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

SUMMARY AND CONCLUSIONS

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

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

TABLE 18-19.

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

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

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

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

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

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

TABLE 18-20.

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

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

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

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

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

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

Chapter 18

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CHAPTER 19

IMMUNOLOGICAL EVALUATION

INTRODUCTION

Overt damage to organs of the immune system and depressed immunologic function have been noted in a variety of animals exposed to TCDD. As the fields of immunology and immunotoxicology have grown within the past 10 years, a significant spectrum of subtle immunotoxic effects has also been described in animals, but for many possible reasons, comparable adverse effects have not been consistently recorded in exposed human individuals or cohorts.

Thus, an intensive search is underway to ascertain the effects of TCDD on the human immune system, particularly with respect to the development of cancer. Every major ongoing dioxin morbidity study in the United States has now incorporated comprehensive laboratory assessments of the immune system.

Numerous animal studies have demonstrated significant immunotoxicity following the administration of TCDD. The relatively consistent observations of decreased thymus weight (with cortical atrophy and a depletion of lymphocytes), atrophy of other lymphoid tissue, depressed cellular bone marrow, and decreased humoral and cell-mediated immunity and increased susceptibility to infection have been noted in a variety of animals, including monkeys, rabbits, guinea pigs, rats, and mice.[1-12] The immune-response effects varied by species, species strain, age, integrity of the endocrine system, dose, and route of administration. Generally, the immunologic parameters returned to normal or approximate normal values over time, even following moderate to high doses of TCDD. While experiments have been conducted to assess the immunotoxicity of TCDD, little has been published on the immunotoxicity of 2,4-D or 2,4,5-T.

The immune system is so sensitive to TCDD that immune function has frequently been used as a marker of toxicity in the absence of other biologic effects.[13] The mechanism of TCDD immunotoxicity is under intensive investigation by molecular biologists, pathologists, and geneticists. In general, TCDD toxicity is probably linked to the Ah receptor, and specifically to the Ah^b allele which governs microsomal enzyme induction as reflected by aryl hydrocarbon hydroxylase and cytochrome P-448/450 levels.[14] This premise underscores the questions of the degree to which the human response to TCDD is dependent upon the Ah locus or other genetic receptors, and how this response is manifested in the immune system.

Animal studies and several observational studies in humans have shown variable results. Data from the Times Beach, Missouri, episode disclosed no group differences for various T lymphocyte populations, proliferative responses to PHA, concanavalin A, pokeweed or tetanus toxoid stimulation, and in skin testing with seven antigens.[15] A report of the assessment of the immune system of men exposed to TCDD in an industrial accident in Britain

did not discuss the results of the measurement of the immunoglobulin profile, lymphocytes, T and B cells, response to PHA, and three hematologic variables.[16] A prior publication on the same cohort cited unpublished findings of Ward, suggesting a reduction in the capacity of the "primary" immune system.[17]

A longitudinal evaluation of 48 highly exposed children (one-half with chloracne) from the Seveso incident showed significantly elevated complement hemolytic activity over six measurements during the period 1976 to 1979 (although the biologic significance of this is unknown) and an increased proliferative response to PHA and pokeweed during the first three screenings.[18] This study (as others) was characterized by shifting a study population over the observation period and by excessive laboratory variation that may have masked other true group differences. Nonetheless, the Seveso data may be interpreted as indicative of a stimulated immune system, particularly cell-mediated immunity, differing substantially from the bulk of animal studies, which showed decreased activity.

A recent study of residents of the TCDD-contaminated Quail Run Mobile Home Park in Missouri also revealed data that conflicted with the Seveso experience.[19] A statistically significant amount of anergy and relative anergy was detected in the TCDD-exposed group, as determined by the multitest applicator (seven-antigen test system). Inter-reader variation presented major interpretive difficulties. Nevertheless, findings suggestive of decreased cell-mediated immunity were provided by decreased T_3, T_4, and T_{11} cell percentages. Also noted was an increased lymphoproliferative response to pokeweed mitogen (PWM). The overall depression of immunologic response was not correlated with an increase in clinical disease.

Baseline Summary Results

Immunologic function and phenotypic marker studies were performed on 592 participants (297 Ranch Hands, 295 Comparisons) randomly selected by the terminal digit of their case number. Because of laboratory problems, e.g., fluctuating quality control and lack of simultaneous differential counts on the peripheral mononuclear cells, a special Immunology Review Committee was convened to determine which data were relevant for analysis. Such decisions were made on a case-by-case basis without knowledge of Ranch Hand or Comparison group membership. The Committee concluded that the data could be analyzed on a group basis, but interpretation of data on an individual basis was inappropriate.

Analyses of the cell surface markers (T_{11}, T_3, T_4, T_8, B, the T_4/T_8 ratio, and the total lymphocyte count [TLC]) showed no significant group differences. However, the increased smoking was significantly associated with increases in cell counts but not with the T_4/T_8 ratio and B_1 cells, whereas increasing age was significantly associated with decreasing TLC and T_8 cells.

Functional studies of T and B cells via reaction to antigenic (tetanus toxoid) or mitogen (phytohemagglutinin, concanavalin A, and pokeweed) stimulation showed no group differences. Similarly, unadjusted and adjusted mean values of the four assays were not significantly different between groups, but one unstimulated control value (reflecting Baseline thymidine uptake by T cells) was significantly decreased in the Ranch Hands. The biologic relevance of this finding was unclear.

Further, in the covariate analysis of the functional studies, group-by-smoking and group-by-alcohol interactions were noted. Of greater importance, however, was the finding that lymphocytic response increased with increased smoking, but was depressed in association with increasing age.

In summary, both immunologic function and cell marker studies did not show significant impairment in the Ranch Hand group, or patterns supportive of an herbicide effect. Smoking, for the first time to the knowledge of the authors, was associated with a significant increase in the marker cells T_{11}, T_3, T_4, and T_8, and in the total lymphocyte count, with a concomitant increase in lymphocytic response to PWM.

Parameters of the 1985 Immunologic Profile

The format for the 1985 AFHS physical examination placed more emphasis on the immunologic assessment than did the 1982 Baseline profile. The random sampling scheme was expanded to produce an approximate 50-percent sample of the cohorts, and included the same terminal digits of the case number used at Baseline in order to include all individuals evaluated in 1982 and thus establish a longitudinal data base.

All immunologic tests were performed at the Scripps Immunology Reference Laboratory (SIRL). The battery of phenotypic marker assays and functional tests was slightly modified from the Baseline profile. The assay for HLA-DR cells was added to the battery of marker studies, and a functional test for natural killer cells (with and without interferon) was substituted for the concanavalin A stimulation assay. A comprehensive set of skin tests for the antigens Candida, mumps, Trichophyton, and staph-phage-lysate was added to evaluate the integrity of the delayed hypersensitivity response.

The dependent variables of the analyses in this chapter arise from three distinct measurement systems: phenotypic marker studies, functional studies, and skin testing. There were more covariates than in the Baseline study, namely age, race, occupational category, exposure index, and new smoking and alcohol data from the 1985 questionnaire.

Participants deleted from the immunological analyses included those with recent radiation or chemotherapy, and those individuals on immunosuppressive or systemic steroid medication. Marginal totals in the tables below vary somewhat due to missing covariate data. Thus, numbers in the table also vary according to which immunologic data sources were used in the analysis. In general, most analyses are based upon data from 465 Ranch Hands and 585 Comparisons. Analytic tests included t-tests, general linear models (SAS®-GLM), logistic regression (BMDP®-LR), and Fisher's exact test. Parallel analyses using Original Comparisons are in Tables Q-5 through Q-10 of Appendix Q.

Rationale of the Immunologic Measurements

Because of rapid changes in our knowledge of the immune system, Table 19-1 is provided as an aid in interpreting the medical significance of the immunological data.

TABLE 19-1.

Medical Significance of the Immunological Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
MARKER STUDIES		
OKT_{11}	Measures total T cells coincident with sheep rosette receptor on cell surface (most are T_4 and T_8 cells).	Decreased in immune deficiency/ increased with lymphoproliferative disorders.
Leu 12	Measures peripheral blood B cells, no reaction with T cells, granulocytes, or monocytes.	Decreased in immunodeficiency/ increased in lymphoproliferative disorders.
OKT_4	Measures T cells which exhibit helper/ inducer phenotype.	Decreased in AIDS/increased in autoimmune diseases.
OKT_8	Measures T cells which exhibit suppressor/ cytotoxic functions.	Variable in autoimmune diseases. Increased in some viral illnesses and immunodeficiencies.
Leu M3	Measures mature monocytes in peripheral blood.	Increases with inflammation.
HLA-DR	Measures cells expressing HLA-DR antigen; includes B cells and monocytes.	B cell deficiency/ Agammaglobulinemia.
FUNCTIONAL STUDIES		
Mixed Leukocyte Culture (MLC)	Measures reactivity of T cells to foreign histocompatiblity antigens on unrelated lymphocytes.	HLA sensitization/transplantation.
PHA	Measures functional capability of T cells to become activated by mitogen and undergo proliferation.	T cell deficiency.
NKC (with interferon) NKC (without interferon)	Measures natural killer cell lytic activity with and without interferon treatment of the natural killer cells.	Decreased natural defenses.

TABLE 19-1. (continued)

Medical Significance of the Immunological Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
FUNCTIONAL STUDIES (continued)		
PWM	Measures functional capability of T cells to become activated by mitogen and undergo proliferation.	T cell deficiencies.
SKIN TESTS		
Candida Mumps Tricophyton Staph-phage-lysate	Each measures skin reactivity induced by specific antigen injected intradermally and correlates with recall T cell sensitivity to the antigen.	Antigen reactivity or sensitivity/ Anergy.

Immunology Methodologies

The isolation of peripheral blood mononuclear (PBM) cells was the first step to prepare for testing immune competence and enumeration of phenotypic markers. Heparinized whole blood was obtained from each patient. PBM's were isolated by Ficoll-Hypaque density gradient centrifugation. The PBM's were then washed and resuspended in HB101 media (HANA Biologics, Inc.) supplemented with 10M units/ml penicillin, 10,000 mcg/ml streptomycin, 1 percent sodium pyruvate (100 mM), and 1 percent L-glutamine (200 mM). To determine percent monocyte and granulocyte contamination of the PBM cell preparations, an aliquot of the cells was stained with a nonspecific esterase stain. PBM concentration was adjusted for each individual assay.

Cell Surface Marker Analysis

Mouse monoclonal antibodies directed against specific surface markers were used to identify and quantitate different cell populations in the peripheral blood of the participants. Mononuclear cell concentrations adjusted to 1.0×10^6 cells/ml were incubated with the following fluorescein isothiocyanate conjugated monoclonal antibodies: CD2(OKT11*), CD4(OKT4*), CD8(OKT8*), CD19(Leu12**), CD14(LeuM3**), and HLA-DR(OKDR*). These cell surface antibodies measure total numbers of T and B lymphocytes, monocytes, helper T lymphocytes, suppressor T lymphocytes, and those cells carrying the HLA-DR antigen. A flow cytometer (Spectrum III, Ortho Diagnostic Systems, Raritan, New Jersey) was used to measure percent positive for each specific surface marker and absolute numbers were calculated.

Phytohemagglutinin (PHA) and Pokeweed Mitogen Stimulation Assays

Mitogens were used to stimulate the proliferation of lymphocytes in vitro. During the proliferative response, the lymphocytes undergo blast transformation and incorporate radioactive thymidine into their DNA. Participant lymphocyte concentrations were adjusted to 2.0×10^6 cells/ml in supplemented HB101 media. Samples were cultured in quadruplicate. Individual cultures consisted of 0.1 ml of cell suspension and 0.1 ml of mitogen solution in microtiter plates. The cultures were incubated in an atmosphere of 5 percent CO_2 at 37 degrees Centigrade. Participant cells were cultured with PHA (12 µg/ml, Sigma Chemical Co., St. Louis, Missouri) for a total of 4 days and pokeweed mitogen (0.05 µg/ml, Sigma Chemical Co., St. Louis, Missouri) for a total of 5 days. The cultures were pulsed with tritiated thymidine (1.0 µCi/ microtiter well) for 4 hours and then harvested on a multiple automated harvester. Cellular proliferation was assessed by tritiated thymidine uptake measured by liquid scintillation counting.

Mixed Lymphocyte Reaction

Histocompatibility antigens (HLA) can also stimulate lymphocytes causing blast transformation. Donor lymphocytes were used to stimulate the proliferation of participants' lymphocytes in vitro. A pool of donor lymphocytes

*Ortho Diagnostic Systems, Raritan, New Jersey
**Becton Dickinson Monoclonal Center, Inc., Mountain View, California

was frozen and used as a stimulator pool throughout the course of the study. An aliquot of this pool was thawed daily. Viability of this pool was assessed by trypan blue exclusion. A pool of freshly isolated lymphocytes was prepared daily and also used as stimulator cells. Both pools of stimulator cells were inactivated by irradiation (3,000 rad). Stimulator pools and participant lymphocyte concentrations were adjusted to 1.0 x 10^6 cells/ml in supplemented HB101 media. Samples were cultured in quadruplicate. Individual cultures consisted of 0.1 ml of participant cell suspension and 0.1 ml of stimulator cell suspension, in microtiter plates. The cultures were incubated in an atmosphere of 5 percent CO_2 at 37 degrees Centigrade for 6 days. The cultures were pulsed with tritiated thymidine (1.0 µCi/ microtiter well) for 16 hours and then harvested on a multiple automated cell harvester. Cellular proliferation was assessed by tritiated thymidine uptake measured by liquid scintillation counting.

Natural Killer Cell Assays

Mononuclear cells from the participant were evaluated to assess the ability of certain peripheral blood cells to kill target cells from a K-562 leukemia cell line. The K-562 target cells were preincubated with radioactive chromium (^{51}Cr) at 37 degrees Centigrade in 5 percent CO_2 for 1 hour, washed, and the cell concentration adjusted to 1.6 x 10^5 cells/ml. A 50 µl aliquot of radioactive K-562 cells was added to each microtiter well. Participant lymphocytes were adjusted to three different concentrations: 0.53, 1.6, and 2.7 x 10^6 cells/ml. One ml of each of these concentrations was incubated with 20 units of recombinant γ-interferon (Genentech, Inc., San Francisco, California) for 1 hour at about 37 degrees Centigrade. Quadruplicate 150 µl aliquots of each concentration, with and without interferon preincubation, were dispensed in a microtiter plate. Four wells contained media alone to determine the spontaneous release of radioactivity from the K-562 cells. Four wells contained 1 percent Triton X-100 to determine the maximal release of radioactivity. The final effector to target ratios were 50:1, 30:1, and 10:1. The microtiter plates were centrifuged briefly at low speed and incubated at 37 degrees Centigrade in 5 percent CO_2 for 3 hours. A 100 µl aliquot of the supernatant was removed from each well and counted on a gamma counter. Percent chromium release from the K-562 target cells was determined for each effector:target cell ratio.

Interpretive Considerations

The values of the results of assays of immunologic status are more variable than those found in routine single reactant clinical chemistry assays. Often there are numerous biochemical factors/metabolites that affect the immunologic assay results so that interpretations of normalcy must be in the context of those obtained concurrently in a normal control cohort group. Such controls allow for proper adjustments of the raw assay data in order to minimize the broad range of technical and reagent effects in the various immunologic assays. These adjustments in the raw assay data results will correct for such variability and allow for the detection of any significant biologic abnormalities. Because of the need for these control adjustments, the immunologic assay results cannot be meaningfully compared to existing normal ranges determined on different groups of individuals at other times.

RESULTS AND DISCUSSION

Cell Surface Marker (Phenotypic) Studies

Immunological tests were carried out on 47 percent (1,085) of the participants because of the complexity of the assay and the expense of these tests. The participants were randomly selected so that approximately 50 percent of each group of participants arriving for the physical examination had blood drawn for the immunological tests. Logistical delay during the initial weeks of the examination reduced the number to less than 50 percent. Within each group, blood was drawn for the immunological tests from about one-half of the selected participants on the first day of the physical examination, and from the remainder on the following day. Skin tests, which were scheduled for the first day, were therefore carried out after the blood draw on the first day for the first half of the immuno-tested participants. Skin tests were not done for those participants selected for immunological testing on day two in order to avoid any effect the skin test antigens might have on the cell counts and functions. Thus, 553 participants received both the immunological tests and the skin tests, 532 received the immunological tests but not the skin tests, 1,206 received the skin tests but not the immunological tests, and 18 received neither. Table 19-2 gives the frequencies of the participants in each exposure group who had the tests.

Participants who were taking anti-inflammatory or immunosuppression medication or who had recently received x-ray treatment or chemotherapy for cancer were excluded from all the analyses. Participants taking aspirin, however, were not excluded.

TABLE 19-2.

Frequencies of Participants Who Took the Immunological Tests and the Skin Tests, by Group

Group	Immunology Tests	Skin Tests: No	Skin Tests: Yes	Total
Ranch Hand	No	9	524	533
	Yes	218	265	483
	Total	227	789	1,016
Comparison	No	9	682	691
	Yes	314	288	602
	Total	323	970	1,293

For those participants who were given the immunological tests, the following dependent variables were examined: total T cells, helper T cells, suppressor T cells, B cells, monocytes, HLA-DR cells, and the T_4/T_8 (helper/suppressor cell) ratio. These variables were treated as continuous in the analysis.

The covariates considered in the analysis were the matching variables (age, race, occupation), smoking history (current cigarettes/day and total pack-years of smoking), and alcohol consumption (average number of drinks per day during the 2 weeks prior to the physical examination and total drink-years). The covariates age and the smoking history and alcohol consumption variables were used as continuous variables in the analyses since the relationships between the dependent variables and the covariates were generally monotonic.

Considerable day-to-day variation exists in the results of immunological tests due to a number of extraneous factors, including temperature, humidity, and sensitivity of the instrumentation. Significant batch-to-batch variation (among examination groups) was apparent for total T cells, suppressor T cells, B cells, and the T_4/T_8 ratio, and significant blood-draw day variation was apparent for helper T cells, monocytes, and HLA-DR cells. Adjustments in the analyses were made for these sources of variation by using batch or blooddraw day indicators. Throughout this section, appropriate adjustment was carried out in the assessment of group differences of the dependent variables; this analysis was unadjusted for the covariates listed above and is referred to as the "unadjusted" analysis. Adjustment was also made for batch-to-batch or blood-draw day variation in the analyses of the associations of the dependent variables with the covariates. Further, this adjustment was also used in the fitting of general linear models to assess the group differences, adjusted for the covariates.

Prior to analysis, group data were pooled for each continuous variable and were examined to determine whether transformation would enhance normality or distributional symmetry. The following transformations were used in the analyses:

Variable	Transformation
Total T cells	Square root
Helper T cells	Square root
Suppressor T cells	Logarithm
B cells	Square root
Monocytes	Logarithm
HLA-DR cells	Square root
T_4/T_8 ratio	Logarithm

The results of the analyses in this section are summarized in Tables 19-3 through 19-5. Table 19-3 presents the unadjusted analyses for the cell surface markers, Table 19-4 displays the covariate associations, and Table 19-5 gives the adjusted results. These tables are accompanied by

TABLE 19-3.

Unadjusted Analyses for Cell Surface Markers by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value
Total T Cells (T_{11})	n	464	581	
	Mean	1,616	1,604	0.736
	95% C.I.	(1,561, 1,671)	(1,556, 1,653)	
Helper T Cells (T_4)	n	461	580	
	Mean	874.6	863.3	0.610
	95% C.I.	(839.9, 909.9)	(833.3, 893.9)	
Suppressor T Cells (T_8)	n	465	582	
	Mean	523.6	530.0	0.671
	95% C.I.	(500.1, 548.1)	(508.9, 552.0)	
B Cells	n	457	575	
	Mean	185.6	189.5	0.594
	95% C.I.	(174.1, 197.4)	(179.2, 200.1)	
Monocytes	n	462	582	
	Mean	46.08	44.49	0.427
	95% C.I.	(42.99, 49.39)	(41.88, 47.27)	
HLA-DR Cells	n	462	582	
	Mean	571.4	568.4	0.842
	95% C.I.	(547.9, 595.3)	(548.1, 589.1)	
T_4/T_8 Ratio	n	461	577	
	Mean	1.600	1.570	0.499
	95% C.I.	(1.531, 1.672)	(1.510, 1.633)	

TABLE 19-4.

Association Between Cell Surface Marker Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Directionality Shown)

Variable	Race	Occupation	Age	Current Alcohol (Drinks/Day)	Drink-Years	Current Smoking (Cigarettes/Day)	Lifetime Smoking (Pack-years)
Total T Cells	NS	0.005 O<E	0.002[a]	0.069[a]	NS	<0.001[b]	<0.001[c]
Helper T Cells	NS	0.024 O<E	<0.001[a]	NS	NS	<0.001[b]	<0.001[c]
Suppressor T Cells	NS	<0.001 O<G<F	<0.001[a]	0.058[d]	NS	<0.001[e]	0.076[c]
B Cells	NS	<0.001 O<E	<0.001[a]	0.001[a]	0.047[f]	<0.001[e]	0.005[c]
Monocytes	0.027 N>B	0.019 O<F<G	NS	0.031[g]	<0.001[h]	<0.001[c]	<0.001[c]
HLA-DR Cells	NS	<0.001 O<E	0.010[a]	NS	0.083[c]	<0.001[c]	<0.001[c]
T_4/T_8 Ratio	NS	0.063 F<G<O	NS	NS	0.049[c]	<0.001[c]	0.001[c]

[a]Monotone decreasing.

[b]Increases, drop-off at highest category.

[c]Monotone increasing.

[d]Generally decreasing trend.

[e]Increases from 0 category, then decreases, but not back to same level.

[f]Increases from 0 category, then steady decrease with increasing levels.

[g]Generally increasing trend.

[h]Flat for 0 and first few categories, then increases.

NS: Not significant (p>0.10)
N: Nonblack
B: Black
O: Officer
E: Enlisted personnel (flyer and groundcrew)
F: Enlisted flyer
G: Enlisted groundcrew

TABLE 19-5.

Adjusted Analyses for Cell Surface Markers by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks*
Total T Cells	n	442	567		BATCH (p=0.029)
	Adj. Mean	****	****	****	AGE (p=0.009)
	95% C.I.	****	****		ALC (p=0.001)
					CSMOK (p<0.001)
					GRP*RACE (p=0.033)
					DRKYR*PACKYR (p=0.015)
Helper T Cells	n	439	566		BATCH (p=0.021)
	Adj. Mean	869.4	878.5	0.662	DAY(BATCH) (p=0.014)
	95% C.I.	(836.1, 903.2)	(849.2, 908.4)		AGE (p<0.001)
					ALC*OCC (p=0.008)
					CSMOK*OCC (p=0.023)
					ALC*CSMOK (p=0.006)
					DRKYR*PACKYR (p=0.012)
Suppressor T Cells	n	463	580		BATCH (p<0.001)
	Adj. Mean	530.8	537.9	0.640	OCC (p=0.014)
	95% C.I.	(506.8, 556.0)	(516.1, 560.5)		AGE (p=0.004)
					ALC (p=0.020)
					CSMOK (p<0.001)
B Cells	n	435	561		BATCH (p<0.001)
	Adj. Mean	****	****	****	ALC (p=0.006)
	95% C.I.	****	****		AGE*CSMOK (p=0.025)
					DRKYR*RACE (p=0.026)
					GRP*PACKYR (p=0.018)
					GRP*RACE*OCC (p=0.046)
Monocytes	n	440	568		BATCH (p<0.001)
	Adj. Mean	****	****	****	DAY(BATCH) (p<0.001)
	95% C.I.	****	****		RACE (p=0.032)
					DRKYR (p=0.013)
					CSMOK (p<0.001)
					PACKYR (p=0.006)
					GRP*OCC (p=0.044)
					GRP*ALC (p=0.010)

TABLE 19-5. (continued)

Adjusted Analyses for Cell Surface Markers by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks*
HLA-DR Cells	n	459	580		BATCH (p<0.001)
	Adj. Mean	****	****	****	DAY(BATCH) (p=0.004)
	95% C.I.	****	****		OCC (p=0.035)
					CSMOK (p<0.001)
					GRP*ALC (p=0.045)
					AGE*PACKYR (p=0.005)
T_4/T_8 Ratio	n	461	577		BATCH (p<0.001)
	Adj. Mean	1.570	1.552	0.678	OCC (p=0.020)
	95% C.I.	(1.501, 1.643)	(1.491, 1.616)		CSMOK (p<0.001)

*Abbreviations
BATCH: batch-to-batch variation among examination groups
DAY(BATCH): blood-draw day variation
ALC: current alcohol use
CSMOK: current smoking
OCC: occupation
GRP: group
DRKYR: lifetime alcohol use (drink-years)
PACKYR: lifetime smoking (pack-years)

****Significant group-by-covariate interaction—adjusted mean, confidence interval, and p-value not presented.

discussion of each variable. The results of adjusted analyses with group-by-covariate interactions are found in Table Q-1 of Appendix Q.

Total T Cells (T_{11})

No significant difference was found between groups in the mean values of total T cells (p=0.736). These data were analyzed without adjustment for any covariates except batch-to-batch variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found with occupation (p=0.005), age (p=0.002), current smoking (p<0.001), and pack-years (p<0.001). A marginal association (p=0.069) was found with current alcohol use due to a steady decrease in mean counts with higher drinking levels. Officers had a lower mean count (1,539 cells/mm^3) than enlisted flyers (1,668 cells/mm^3), or enlisted groundcrew (1,647 cells/mm^3). The mean count decreased with age: 1,663 cells/mm^3, 1,582 cells/mm^3, and 1,404 cells/mm^3 for those born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. The mean count increased with increasing current smoking and increasing lifetime smoking history (pack-years).

A general linear model was fitted to assess the group difference in mean count of total T cells with adjustment for each covariate and any interactions that made significant contributions to the model. Batch-to-batch variation was a significant covariate (p=0.029).

A significant group-by-race interaction was found (p=0.033); Black Ranch Hands had a significantly lower adjusted mean count than Black Comparisons (1,566 cells/mm^3 versus 1,888 cells/mm^3; p=0.039), but the group difference for nonblacks was not significant (p=0.619) (see Table Q-1 of Appendix Q). The following covariates were significant: age (p=0.009), current alcohol use (p=0.001), current smoking (p<0.001), and a drink-year-by-pack-year interaction (p=0.015). Analyses using only Original Comparisons showed the same results as when using the total Comparison group (see Tables Q-6 and Q-7 of Appendix Q), with a group-by-race interaction present (p=0.028).

Helper T Cells (T_4)

No significant difference was found between groups in the mean values of helper T cells (p=0.610). This contrast was analyzed without adjustment for any covariates except blood-draw day variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found with occupation (p=0.024), age (p<0.001), current smoking (p<0.001), and pack-years (p<0.001). Officers had a lower mean count (831 cells/mm^3) than enlisted flyers (885 cells/mm^3) or enlisted groundcrew (894 cells/mm^3). There was a decrease in the mean count with increasing age: 907 cells/mm^3, 850 cells/mm^3, and 713 cells/mm^3 for those born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. The mean count increased with increasing levels of current smoking and with increasing pack-years of lifetime smoking.

Adjusted analyses assessed the group difference in mean count of helper T cells with adjustment for each covariate and any significant interactions. Adjustment for the blood-draw day variation was included. Age made a significant contribution to the model ($p<0.001$). The following interactions between covariates were significant: current alcohol use-by-occupation ($p=0.008$), current smoking-by-occupation ($p=0.023$), current alcohol use-by-current smoking ($p=0.006$), and drink-years-by-pack-years ($p=0.012$). The adjusted group difference in mean count was not significant ($p=0.662$): 869 cells/mm^3 for the Ranch Hand group versus 879 cells/mm^3 for the Comparison group. Adjusted analyses using Original Comparisons (Table Q-6 of Appendix Q) also revealed a nonsignificant group difference ($p=0.835$).

Suppressor T Cells (T_8)

No significant difference was found between groups in the mean values of suppressor T cells ($p=0.671$). This contrast was analyzed without adjustment for any covariates except batch-to-batch variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found with occupation ($p<0.001$), age ($p<0.001$), and current smoking ($p<0.001$). The mean count for officers was less than the mean count for enlisted groundcrew, which was in turn less than the mean count for enlisted flyers; the means were 492 cells/mm^3, 540 cells/mm^3, and 575 cells/mm^3, respectively. The mean counts decreased with increasing age: 557 cells/mm^3, 512 cells/mm^3, and 439 cells/mm^3 for participants born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. The mean counts increased with increasing levels of current smoking. Marginally significant associations were found with current alcohol use ($p=0.058$, mean T_8 counts decreased with increasing current levels of drinking) and pack-years ($p=0.076$, mean counts increased with increasing pack-years).

The adjusted analysis of group differences in mean count of suppressor T cells was made with adjustment for each covariate and any interactions that made significant contributions, including significant batch-to-batch variation ($p<0.001$). Significant adjusting covariates were occupation ($p=0.014$), age ($p=0.004$), current alcohol use ($p=0.020$), and current smoking ($p<0.001$). The adjusted group difference was not significant ($p=0.640$).

A marginal ($p=0.063$) group-by-race interaction was not retained in the final model, but was explored. Black Ranch Hands had a lower adjusted mean count than Black Comparisons (512 cells/mm^3 versus 649 cells/mm^3, $p=0.056$), whereas the difference between nonblack groups was negligible (531 cells/mm^3 for Ranch Hands and 532 cells/mm^3 for Comparisons, $p=0.974$). Analyses involving the Original Comparisons showed a significant interaction between group and race ($p=0.010$) (see Tables Q-6 and Q-7 of Appendix Q), with the same pattern seen for the group-by-race interaction for the total Comparison group.

B Cells

No significant difference was found between groups in the mean values of B cells ($p=0.594$). This contrast was analyzed without adjustment for any covariates except batch-to-batch variation.

Significant associations using pooled data were found between B cells and occupation ($p<0.001$), age ($p<0.001$), current alcohol use ($p=0.001$), drink-years ($p=0.047$), current smoking ($p<0.001$), and pack-years ($p=0.005$). Officers had a lower mean count than enlisted flyers and groundcrew (166 cells/mm^3, 205 cells/mm^3, and 201 cells/mm^3, respectively). The mean count decreased with increasing age: 206 cells/mm^3, 177 cells/mm^3, and 146 cells/mm^3 for those born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. The mean counts decreased with an increasing number of drinks per day, and also with higher levels of total lifetime drinking, except for the "never-drinkers," whose level was lower than the greater than 30 to 100 drink-year group; the means for the drink-year categories were: 0, 180 cells/mm^3; greater than 0 to 5, 199 cells/mm^3; greater than 5 to 30, 189 cells/mm^3; greater than 30 to 100, 183 cells/mm^3; and greater than 100, 150 cells/mm^3. The nonsmokers had a lower mean count than current smokers, whereas among the smokers the mean counts decreased with higher current smoking levels. The means for the different current-smoking (cigarettes/day) categories were: 0, 166 cells/mm^3; greater than 0 to 20, 237 cells/mm^3; greater than 20 to 40, 222 cells/mm^3; and greater than 40, 202 cells/mm^3. Lifetime smokers had a higher mean count than "never-smokers"; otherwise the pattern was not clear.

Adjusted analyses, including adjustment for the significant ($p<0.001$) batch-to-batch variation, were used to investigate the mean count of B cells. Adjustment was made for each covariate and any interactions that made significant contributions. A significant group-by-race-by-occupation interaction was found ($p=0.046$), along with a group-by-pack-year interaction ($p=0.018$). Significant contributions were made by current alcohol use ($p=0.006$), an age-by-current smoking interaction ($p=0.025$), and a drink-years-by-race interaction ($p=0.026$).

The analysis consequently was performed separately for nonblacks and Blacks. For nonblacks, the group-by-pack-year interaction persisted ($p=0.021$) (see Table Q-1 of Appendix Q). Ranch Hands who had never smoked had a much lower adjusted mean count than the corresponding Comparisons, 154 cells/mm^3 versus 190 cells/mm^3 ($p=0.004$). Among smokers, the adjusted mean count for the greater than 0 to 20 pack-year category was less for Ranch Hands than for Comparisons. For both the greater than 20 to 40 and the greater than 40 pack-year categories, the adjusted mean count was higher for Ranch Hands than for Comparisons. The p-values for these three contrasts were greater than 0.10. For Blacks, the unadjusted group difference was not significant ($p=0.808$; Ranch Hands, 186 cells/mm^3, versus Comparisons, 194 cells/mm^3). Adjusted means were not calculated because no covariates made any significant contribution to an adjusted model, and moreover, adjustment for batch-to-batch variation was not possible because of the small number of Black participants.

Other significant covariates and interactions in the adjustment for nonblacks included occupation ($p=0.047$), drink-years ($p<0.001$), and an age-by-current smoking interaction ($p=0.039$).

Monocytes

No significant difference was found between groups in the mean value of monocytes ($p=0.427$). This contrast was analyzed without adjustment for any covariates except blood-draw day variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found with race ($p=0.027$), occupation ($p=0.019$), current drinking ($p=0.031$), drink-years ($p<0.001$), current smoking ($p<0.001$), and pack-years ($p<0.001$). Blacks had a lower mean count than nonblacks (37.1 cells/mm^3 versus 45.7 cells/mm^3, respectively). Officers had a lower mean count (42.3 cells/mm^3) than enlisted flyers (44.4 cells/mm^3), who had a lower mean count than enlisted groundcrew (48.2 cells/mm^3). Higher mean counts were associated with higher current drinking levels. There were increases in mean counts with higher drink-years and with increasing amounts of both current and lifetime smoking.

Assessment of the group difference in mean count of monocytes was done with adjustment for each covariate and any interactions that made significant contributions, including blood-draw day variation.

A significant group-by-occupation interaction ($p=0.044$) and a significant group-by-current alcohol use interaction ($p=0.010$) were found. For interpretation, these were explored in a model including the group-by-occupation-by-current alcohol use interaction, with the alcohol variable discretized (see Table Q-1 of Appendix Q). Except for those men consuming more than two to four drinks per day, Ranch Hand officers had a higher adjusted mean count than Comparison officers, the difference being large (44.2 cells/mm^3 versus 32.3 cells/mm^3) for nondrinkers, ($p=0.060$). For enlisted flyers, except those in the greater than four drinks per day category, Ranch Hands had a lower adjusted mean count than corresponding Comparisons. For the greater than two to four drinks per day category, a large difference between adjusted means (32.7 cells/mm^3 for Ranch Hands, 56.2 cells/mm^3 for Comparisons) was observed ($p=0.097$). Further, it was found that for enlisted groundcrew not currently drinking, Ranch Hands had a lower adjusted mean count than the corresponding Comparisons, whereas the Ranch Hand current drinkers had higher adjusted mean counts than the corresponding Comparisons. The difference was large (68.9 cells/mm^3 versus 35.3 cells/mm^3) for the greater than four drinks per day category ($p=0.003$).

Significant effects on the monocyte counts were also seen for race ($p=0.032$), drink-years ($p=0.013$), current smoking ($p<0.001$), and pack-years ($p=0.006$). Analyses using Original Comparisons revealed a significant ($p=0.040$) group-by-age interaction (see Tables Q-6 and Q-7 of Appendix Q). This was due to a lower count for Ranch Hands than Comparisons for those born in or after 1942 (41.4 cells/mm^3 versus 48.0 cells/mm^3, $p=0.048$), a higher count for Ranch Hands than Comparisons for those born between 1923 and 1941 (48.2 cells/mm^3 versus 42.8 cells/mm^3, $p=0.058$), and very little difference for those born in or before 1922 ($p=0.924$).

HLA-DR Cells

No significant difference was found between groups in the mean values of HLA-DR cells ($p=0.842$). This contrast was analyzed without adjustment for any covariates except blood-draw day variation.

Significant associations were found using pooled data with occupation ($p<0.001$), age ($p=0.010$), current smoking ($p<0.001$), and pack-years ($p<0.001$). Officers had a lower mean count than enlisted participants (526 cells/mm^3 versus 597 cells/mm^3 for flyers and 598 cells/mm^3 for groundcrew). The average mean count was higher for younger participants than for

older participants: 588 cells/mm^3, 557 cells/mm^3, and 555 cells/mm^3 for those born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. There was a significant increase in average mean counts with increasing levels of both current and lifetime smoking. There was a marginally significant increase in mean cell counts with drink-years (p=0.083).

Analyses, with adjustment for blood-draw day, each covariate, and any interactions, were carried out to assess the group difference in mean count of HLA-DR cells. A significant group-by-current alcohol use interaction was found (p=0.045); for Ranch Hands drinking more than four drinks per day, the adjusted mean count was greater, 564 cells/mm^3 versus 473 cells/mm^3, than for Comparisons (p=0.052), whereas no appreciable group differences were apparent for the participants drinking four or fewer drinks per day (see Table Q-1 of Appendix Q). Significant effects were seen with occupation (p=0.035), current smoking (p<0.001), and an age-by-pack-year interaction (p=0.005).

Analyses using Original Comparisons (Table Q-6 of Appendix Q) did not show a significant group-by-current alcohol use interaction (p=0.152), and no significant difference between groups was observed (p=0.887).

T_4/T_8 Ratio

No significant difference was found between groups in the mean value of the T_4/T_8 ratio (p=0.499). This contrast was analyzed without adjustment for any covariates except batch-to-batch variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found with drink-years (p=0.049), current smoking (p<0.001), and pack-years (p=0.001). The mean T_4/T_8 ratio generally increased with increasing drink-years, and increased with increasing amounts of current smoking and total pack-years. There was a marginally significant association with occupation (p=0.063). Enlisted flyers had a lower average ratio than officers and enlisted groundcrew (1.48 versus 1.62 and 1.60, respectively).

The adjusted group difference in the T_4/T_8 ratio was not significant (p=0.678; Ranch Hands 1.57 versus Comparisons 1.55). Significant effects were seen for occupation (p=0.020), current smoking (p<0.001), and batch-to-batch variation (p<0.001).

In the analysis of the Original Comparisons, a significant group-by-current smoking interaction was found (p=0.016). Further analysis showed a significant difference between groups (Ranch Hand mean ratio of 1.84 versus Original Comparison mean ratio of 1.51, p=0.004), for the greater than 20 to 40 cigarettes per day category (see Tables Q-6 and Q-7 of Appendix Q).

Functional Stimulation Studies

Statistical analyses were performed on cell function responses to PHA, PWM, and MLC. For each stimulated cell population, autologous controls were also studied. The measurements resulting from each test were the average counts over four samples for the stimulated cell population and for the autologous controls. The net average count, defined as the difference

between the average counts per minute (CPM) for the stimulated and the control cells, was also calculated.

Cell response data were obtained from the 1,085 immunologically tested participants. The exclusion conditions were the same as in the previous section, namely, participants who were taking anti-inflammatory or immunosuppressant medication, or who had recently experienced radiation therapy or chemotherapy for cancer.

Review of the immunological data base by the Air Force and SIRL resulted in certain test exclusions due to technical error, and equipment malfunction, those identified by quality control procedures (Grubbs' test[20]), and unexplained outliers. For the mean cell counts per minute (CPM) analyzed for this section, a total of 17 data points were excluded as unexplained outliers from the data base, involving eight participants (three Ranch Hands and five Comparisons): 1 point was invalid due to technical error in the assay for MLC stimulated cells (Ranch Hand) and the remainder were outliers in the PWM controls or stimulated cells (two Ranch Hand controls, 13 Comparison controls, and one Ranch Hand stimulated cells). This meant that, for one participant, the PWM control mean was omitted from the analysis and, for the other seven participants, the means were calculated from fewer than four points. No unexplained data points were found for the PHA-stimulated cells or corresponding controls.

All analyses were adjusted for significant blood-draw day variation, and the same covariates were used as in the adjusted analyses of the cell surface markers. The covariates age, current smoking, pack-years, current alcohol use, and drink-years were discretized because marginal examination showed generally nonlinear responses of the cell function variables with these covariates. Thus, the p-values given in this section for the marginal association of the variables with each covariate indicate the significance of the differences among the categories defined by the levels of the covariate.

Prior to analysis, the data were transformed to enhance normality or at least distributional symmetry. The following transformations were used:

Variable	Transformation
Unstimulated Response (PHA)	logarithm
PHA Net Response	none
Pokeweed Net Response	square root
MLC Net Response	square root

The summarized results of this section are given in Tables 19-6 through 19-8 (see Table Q-1 of Appendix Q for results involving group-by-covariate interactions). Only results for the unstimulated controls for the PHA assay are presented as an assessment of the function of the immune system in the unchallenged state. However, separate controls were run for each assay since incubation periods vary for each test procedure. In the analysis of data on the net response for each assay, the appropriate control was used. Analysis of each control assay was performed, and no significant group differences were noted.

TABLE 19-6.

Unadjusted Analyses for Functional Stimulation Tests by Group

Variable	Statistic*	Group: Ranch Hand	Group: Comparison	p-Value
Unstimulated Response (PHA)	n	464	584	
	Mean	1,656	1,657	0.979
	95% C.I.	(1,578, 1,737)	(1,589, 1,728)	
PHA Net Response	n	463	583	
	Mean	212,323	208,782	0.339
	95% C.I.	(206,484, 218,161)	(203,689, 213,875)	
Pokeweed Net Response	n	465	584	
	Mean	85,655	83,019	0.317
	95% C.I.	(81,528, 89,883)	(79,467, 86,648)	
MLC Net Response	n	452	564	
	Mean	79,132	82,460	0.185
	95% C.I.	(75,269, 83,092)	(79,010, 85,983)	

*Group means and confidence intervals expressed as counts per minute (CPM).

Unstimulated Response (PHA)

No significant difference was found between groups in the mean values of PHA unstimulated responses ($p=0.979$). These control values were derived from unstimulated cells and reflect baseline cell function. This contrast was analyzed without adjustment for any covariates except blood-draw day variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found with race ($p<0.001$), age ($p<0.001$), and drink-years ($p=0.048$). The average mean count for nonblacks was lower than for Blacks: 1,629 CPM and 2,210 CPM, respectively. There was a strong decrease in mean count with increasing age. For those born in or after 1942, the mean was 1,770 CPM; for those born between 1923 and 1941, the mean was 1,606 CPM; and for those born in or before 1922, the mean count was 1,238 CPM. The mean count generally decreased with increasing drink-years, with a maximum mean count of 1,726 CPM for non-drinkers and a minimum mean count of 1,414 CPM for participants with greater than 100 drink-years. A marginally significant association was found with occupation ($p=0.086$). The average mean count for officers was lower than that for enlisted flyers, which was in turn lower than that for enlisted ground-crew: the means were, respectively, 1,592 CPM, 1,662 CPM, and 1,713 CPM. This relationship with occupation was not seen with the PWM or MLC unstimulated responses. Since these values were derived from the same blood specimens and were unstimulated, this observation may represent a chance occurrence. There was a marginally significant association with pack-years ($p=0.051$); the response generally increased with increasing pack-years.

TABLE 19-7.

Association Between Functional Stimulation Test Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Directionality Shown)

Variable	Race	Occupation	Age	Current Alcohol (Drinks/Day)	Drink-Years	Current Smoking (Cigarettes/Day)	Lifetime Smoking Pack-years
Unstimulated Response (PHA)	<0.001 N<B	0.086 O<F<G	<0.001[a]	NS	0.048[b]	NS	0.051[c]
PHA Net Response	0.002 N<B	NS	<0.001[a]	<0.001[d]	0.002[d]	NS	NS
Pokeweed Net Response	NS	NS	NS	NS	0.038[e]	<0.001[f]	0.001[f]
MLC Net Response	NS	NS	0.035[b]	NS	0.008[g]	<0.001[f]	0.015[f]

[a]Monotone decreasing.
[b]Generally decreasing trend.
[c]Flat for 0 and first few categories, then increases.
[d]Increases, drop-off at highest category.
[e]Generally increasing trend.
[f]Monotone increasing.
[g]Increases from 0 category, then decreases, but not back to same level.

NS: Not significant (p>0.10).
N: Nonblack
B: Black
O: Officer
F: Enlisted flyer
G: Enlisted groundcrew

TABLE 19-8.

Adjusted Analyses for Functional Stimulation Tests by Group

Variable	Statistic*	Group: Ranch Hand	Group: Comparison	p-Value	Covariate Remarks
Unstimulated Response (PHA)	n	464	584	0.855	BATCH (p<0.001)
	Mean	1,741	1,731		DAY (BATCH) (p<0.001)
	95% C.I.	(1,595, 1,901)	(1,593, 1,882)		RACE (p<0.001)
					AGE (p<0.001)
PHA Net Response	n	461	581	0.233	BATCH (p<0.001)
	Adj. Mean	193,280	188,952		DAY (BATCH) (p<0.001)
	95% C.I.	(176,032, 210,529)	(171,889, 206,014)		RACE (p=0.011)
					AGE*CSMOK (p=0.007)
					ALC*CSMOK (p=0.008)
Net Pokeweed Response	n	463	582	0.579	BATCH (p<0.001)
	Mean	91,567	90,097		DAY (BATCH) (p<0.001)
	95% C.I.	(82,189 101,451)	(81,008, 99,669)		RACE*OCC (p=0.024)
					ALC*OCC (p=0.036)
					ALC*CSMOK (p=0.009)
Net MLC Response	n	430	550	****	BATCH (p<0.001)
	Adj. Mean	****	****		DAY (BATCH) (p=0.001)
	95% C.I.	****	****		DRKYR (p<0.001)
					ALC (p=0.001)
					GRP*PACKYR (p=0.046)
					RACE*CSMOK (p=0.043)

*Group means and confidence intervals expressed as counts per minute (CPM).
****Group-by-covariate interaction--adjusted mean, confidence interval, and p-value not presented.

(The means were 1,657 CPM, 1,696 CPM, 1,519 CPM, and 1,712 CPM for 0, greater than 0 to 20, greater than 20 to 40, and greater than 40 pack-years, respectively.)

Adjusted analyses to assess the group difference in mean counts of PHA controls were performed with adjustment for each covariate and any interactions that made significant contributions, including significant blood-draw day variation. The group difference in adjusted mean count was not significant ($p=0.855$; Ranch Hand group mean of 1,741 CPM versus Comparison group mean of 1,731 CPM). Race and age were significant covariates ($p<0.001$ for both).

Adjusted and unadjusted analyses using the Original Comparisons (see Tables Q-8 and Q-9 of Appendix Q) showed similar results; i.e., no significant group difference ($p=0.608$, unadjusted; $p=0.613$, adjusted).

PHA Net Response

No significant difference was found between groups in the mean values of net response to PHA ($p=0.339$). This contrast was analyzed without adjustment for any covariates except blood-draw day variation.

The data were pooled for the two groups and the relationship with the covariates was examined. Significant associations were found for race ($p=0.002$), age ($p<0.001$), current alcohol use ($p<0.001$), and drink-years ($p=0.002$). Nonblacks had a lower net count than Blacks (208,953 CPM, 233,622 CPM, respectively). There was a steady decrease in net count with increasing age: the means were 217,003 CPM, 206,901 CPM, and 184,419 CPM for those born in or after 1942, born between 1923 and 1941, and born in or before 1922, respectively. Those currently drinking more than four drinks per day had a lower mean net count than those drinking less. The participants in the greater than 100 drink-year category had a lower mean net count than those with fewer drink-years.

Using a general linear model with adjustment for each covariate and any significant interactions including blood-draw day variation, the adjusted group difference was found to be not significant ($p=0.233$; Ranch Hand count of 193,280 CPM versus Comparison count of 188,952 CPM). Significant contributions were made by race ($p=0.011$), an age-by-current smoking interaction ($p=0.007$), and a current alcohol use-by-current smoking interaction ($p=0.008$).

A marginally significant ($p=0.057$) group-by-occupation interaction was excluded from the final model. However, this interaction was explored, and was found to be due to a group difference among enlisted flyers ($p=0.014$); the adjusted mean Ranch Hand net stimulated count was greater than that of the Comparisons (207,050 CPM and 185,344 CPM, respectively).

Analyses using the Original Comparisons (see Tables Q-9 and Q-10 of Appendix Q) revealed a significant group-by-occupation interaction ($p=0.017$), with results similar to the Ranch Hand versus total Comparison contrast of net counts; namely, enlisted flyer Ranch Hands had an adjusted mean count greater than enlisted flyer Original Comparisons ($p=0.003$).

Pokeweed Net Response

No significant difference was found between groups in the mean values of net response to pokeweed ($p=0.317$). These data were analyzed without adjustment for any covariates except blood-draw day variation.

Significant associations were found using the pooled group data with drink-years ($p=0.038$), current smoking ($p<0.001$), and pack-years ($p=0.001$). The mean count was higher for those with greater than 100 drink-years and lower for never-drinkers, but with no pattern for the in between categories. For both current and lifetime smoking (pack-years), there was a steady upward trend in mean counts with increasing levels of smoking.

The difference in adjusted group means was not significant: Ranch Hands, 91,567 CPM, and Comparisons, 90,097 CPM ($p=0.579$). The following interactions were significant: race-by-occupation ($p=0.024$), current alcohol use-by-occupation ($p=0.036$), and current alcohol use-by-current smoking ($p=0.009$).

Net Response to MLC Stimulation

No significant difference was found between groups in the mean response to MLC stimulation ($p=0.185$). These data were analyzed without adjustment for any covariates except blood-draw day variation.

The data were pooled for the two groups, and the relationship with the covariates was examined. Significant associations were found for age ($p=0.035$), drink-years ($p=0.008$), current smoking ($p<0.001$), and pack-years ($p=0.015$). The net mean count generally decreased with increasing age: 84,543 CPM, 72,408 CPM, and 79,081 CPM for those born in or after 1942, between 1923 and 1941, and in or before 1922, respectively. The net mean count was lowest for never-drinkers, with no clear pattern among the drinkers: 66,933 CPM, 78,555 CPM, 80,713 CPM, 84,236 CPM, and 80,416 CPM for the 0, greater than 0 to 5, greater than 5 to 30, greater than 30 to 100, and greater than 100 drink-year categories, respectively. There was a monotonically increasing trend in net average count with current smoking, the nonsmokers having a much lower value than the smokers. An equivalent pattern was found for lifetime smoking (pack-years).

Adjusted analyses were carried out to assess the group difference in mean counts of MLC net response, including adjustment for the significant blood-draw day variation. A significant group by pack-year interaction was found ($p=0.046$). Never-smoking Ranch Hands had a lower adjusted mean count (68,921 CPM) than the corresponding Comparisons (77,232 CPM) ($p=0.053$). Ranch Hands in the greater than 0 to 20 pack-year category had a lower adjusted mean count (67,976 CPM) than the corresponding Comparisons (74,333 CPM) ($p=0.057$). The adjusted means for the Comparisons decreased with increasing pack-years, whereas those of the Ranch Hands generally increased (see Table Q-1 of Appendix Q). Significant contributions were made to the model by drink-years ($p<0.001$), current alcohol use ($p=0.001$), and a race-by-current smoking interaction ($p=0.043$).

Discussion

The performance of the phenotypic and cell stimulation studies was monitored daily by highly structured quality assurance techniques (see Chapter 6). This resulted in a remarkably error-free data set, in contrast to the immunologic tests at the Baseline study that required the assistance of a review group to determine which data were appropriate for analysis. The finding of significant blood-draw day and batch-to-batch variation at the followup examination was judged to be totally normal and inherent within the test procedures; only a few data points within specific variables were omitted because of outlying values. The unique use of a "batch" variable for adjustment of all the phenotypic and stimulation studies permitted unadjusted and covariate-adjusted group contrasts while controlling for inherent laboratory variation.

All unadjusted and adjusted analyses (without group interactions) showed no significant group differences. Analysis of MLC revealed a group-by-pack-year of smoking interaction with lower counts in the Ranch Hand group than in the Comparison group for 0 and greater than 0 to 20 pack-year categories. Despite differences in the quality of Baseline and followup results, slight changes in cohort numbers, and different mathematical models, there was remarkable concordance in the immunologic results of both examinations, both for the dependent variables and for the effects of the covariates. No judgment of adverse immunologic competence was made for any variable, or sets of variables, or in substrata examined because of group-by-covariate interactions for the cell surface marker and cell stimulation studies.

EXPOSURE INDEX ANALYSES

Within each occupational category, exposure index analyses were conducted to assess possible dose-response relationships (see details in Chapter 8). Analyses were performed for the cell surface marker variables (total T cells, helper T cells, suppressor T cells, B cells, monocytes, HLA-DR cells, and the T_4/T_8 ratio) and for the functional stimulation tests (the control counts per minute for the PHA test, and the net PHA, PWM, and MLC counts per minute). Analyses were not done for the skin test responses.

Unadjusted and adjusted analyses were performed using general linear models. Exposure index-by-covariate interactions were explored in the adjusted analyses. Covariates were age, race, current and lifetime alcohol use (drink-years), and current and lifetime cigarette smoking (pack-years). For each analysis, an overall test was made of the differences among the means corresponding to the low, medium, and high exposure index levels. Medium versus low and high versus low contrasts of means were also made.

Results of the adjusted analyses are presented in Table 19-9 for cell surface markers and 19-10 for functional stimulation tests. Parallel results of unadjusted analyses are given in Tables Q-2 and Q-3, Appendix Q. Results of exposure index-by-covariate interactions are also given in Table Q-4 of Appendix Q.

TABLE 19-9.

Adjusted Exposure Index Analyses for Cell Surface Markers by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Contrast	p-Value
Total T Cells	Officer	n	62	62	55	Overall	0.672
		Adj. Mean	1,745	1,674	1,673	M vs. L	0.443
		95% C.I.	(1384,2148)	(1342,2042)	(1318,2069)	H vs. L	0.442
	Enlisted Flyer	n	21	24	24	Overall	0.874
		Adj. Mean	1,538	1,470	1,516	M vs. L	0.613
		95% C.I.	(1191,1928)	(1138,1845)	(1218,1847)	H vs. L	0.875
	Enlisted Groundcrew	n	65	76	53	Overall	0.068
		Adj. Mean	1,737	1,533	1,558	M vs. L	0.029
		95% C.I.	(1550,1935)	(1367,1709)	(1372,1756)	H vs. L	0.085
Helper T Cells	Officer	n	62	62	54	Overall	0.878
		Adj. Mean	798.2	801.1	774.3	M vs. L	0.960
		95% C.I.	(585.3,1044.1)	(600.8,1030.1)	(564.0,1071.9)	H vs. L	0.676
	Enlisted Flyer	n	21	25	23	Overall	0.726
		Adj. Mean	824.1	760.0	788.4	M vs. L	0.426
		95% C.I.	(612.8,1066.7)	(561.6,988.4)	(609.2,990.7)	H vs. L	0.672
	Enlisted Groundcrew	n	65	74	53	Overall	0.150
		Adj. Mean	968.6	874.2	867.7	M vs. L	0.090
		95% C.I.	(858.0,1086.0)	(774.4,980.1)	(758.1,984.7)	H vs. L	0.101

TABLE 19-9. (continued)

Adjusted Exposure Index Analyses for Cell Surface Markers by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
Suppressor T Cells	Officer	n	62	63	55	Overall	0.269
		Adj. Mean	648.1	566.9	606.3	M vs. L	0.106
		95% C.I.	(463.9,905.4)	(414.7,774.9)	(433.4,848.1)	H vs. L	0.425
	Enlisted Flyer	n	21	25	24	Overall	0.930
		Adj. Mean	500.5	493.5	518.8	M vs. L	0.915
		95% C.I.	(347.5,720.8)	(345.1,705.5)	(379.0,710.1)	H vs. L	0.792
	Enlisted Groundcrew	n	65	75	53	Overall	0.088
		Adj. Mean	558.6	480.8	483.7	M vs. L	0.044
		95% C.I.	(481.4,648.2)	(417.6,553.6)	(413.6,565.5)	H vs. L	0.081
B Cells	Officer	n	62	63	54	Overall	0.857
		Adj. Mean	141.2	137.7	147.0	M vs. L	0.828
		95% C.I.	(82.2,216.2)	(82.7,206.5)	(86.3,223.8)	H vs. L	0.735
	Enlisted Flyer	n	21	24	22	Overall	0.283
		Adj. Mean	229.0	202.6	174.2	M vs. L	0.438
		95% C.I.	(143.0,335.2)	(123.4,301.3)	(109.5,253.9)	H vs. L	0.114
	Enlisted Groundcrew	n	65	71	53	Overall	0.900
		Adj. Mean	215.9	206.4	209.9	M vs. L	0.650
		95% C.I.	(176.2,259.6)	(169.3,247.3)	(168.9,255.4)	H vs. L	0.794

TABLE 19-9. (continued)

Adjusted Exposure Index Analyses for Cell Surface Markers by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
Monocytes	Officer	n	62	63	54	Overall	0.988
		Adj. Mean	45.70	46.75	46.31	M vs. L	0.878
		95% C.I.	(24.95,83.69)	(26.56,82.31)	(25.21,85.06)	H vs. L	0.930
	Enlisted Flyer	n	21	25	23	Overall	0.605
		Adj. Mean	25.81	26.49	31.68	M vs. L	0.903
		95% C.I.	(14.30,46.57)	(14.86,47.21)	(19.07,52.61)	H vs. L	0.356
	Enlisted Groundcrew	n	65	74	53	Overall	0.836
		Adj. Mean	43.00	41.64	44.84	M vs. L	0.778
		95% C.I.	(34.22,54.03)	(33.52,51.72)	(35.28,54.00)	H vs. L	0.739
HLA-DR Cells	Officer	n	62	62	55	Overall	0.963
		Adj. Mean	552.6	563.9	564.9	M vs. L	0.819
		95% C.I.	(370.7,770.6)	(390.9,768.6)	(380.2,786.0)	H vs. L	0.807
	Enlisted Flyer	n	21	25	24	Overall	0.912
		Adj. Mean	501.9	479.5	504.8	M vs. L	0.729
		95% C.I.	(337.6,698.7)	(322.1,668.1)	(360.9,672.7)	H vs. L	0.966
	Enlisted Groundcrew	n	65	74	52	Overall	0.903
		Adj. Mean	591.0	584.4	571.9	M vs. L	0.864
		95% C.I.	(515.5,672.1)	(512.6,660.9)	(492.1,657.8)	H vs. L	0.654

TABLE 19-9. (continued)

Adjusted Exposure Index Analyses for Cell Surface Markers by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
T_4/T_8 Ratio	Officer	n	62	62	54	Overall	0.204
		Adj. Mean	1.326	1.575	1.285	M vs. L	0.152
		95% C.I.	(0.626,2.026)	(0.921,2.229)	(0.585,1.985)	H vs. L	0.816
	Enlisted Flyer	n	21	25	23	Overall	0.788
		Adj. Mean	1.675	1.539	1.552	M vs. L	0.527
		95% C.I.	(1.079,2.271)	(0.955,2.122)	(1.040,2.064)	H vs. L	0.583
	Enlisted Groundcrew	n	65	74	53	Overall	0.909
		Adj. Mean	1.833	1.878	1.827	M vs. L	0.716
		95% C.I.	(1.587,2.079)	(1.645,2.112)	(1.569,2.086)	H vs. L	0.965

TABLE 19-10.

Adjusted Exposure Index Analyses for Functional Stimulation Tests by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Contrast	p-Value
Unstimulated Response (PHA)	Officer	n	****	****	****	Overall	****[a]
		Adj. Mean	****[a]	****[a]	****[a]	M vs. L	****[a]
		95% C.I.	****[a]	****[a]	****[a]	H vs. L	****[a]
	Enlisted Flyer	n	21	25	24	Overall	0.731
		Adj. Mean	2,162	2,489	2,167	M vs. L	0.501
		95% C.I.	(941,4966)	(1195,5185)	(1088,4659)	H vs. L	0.991
	Enlisted Groundcrew	n	65	76	52	Overall	0.713
		Adj. Mean	1,893	2,000	2,067	M vs. L	0.579
		95% C.I.	(1366,2624)	(1433,2793)	(1481,2886)	H vs. L	0.427
PHA Net Response	Officer	n	****	****	****	Overall	****[a]
		Adj. Mean	****[a]	****[a]	****[a]	M vs. L	****[a]
		95% C.I.	****[a]	****[a]	****[a]	H vs. L	****[a]
	Enlisted Flyer	n	21	25	24	Overall	0.456
		Adj. Mean	276,274	240,021	251,070	M vs. L	0.222
		95% C.I.	(158,921, 393,628)	(136,445, 343,597)	(143,073, 359,068)	H vs. L	0.382
	Enlisted Groundcrew	n	65	76	52	Overall	0.482
		Adj. Mean	222,416	220,417	204,601	M vs. L	0.888
		95% C.I.	(175,692, 269,141)	(172,635, 268,198)	(156,815, 252,386)	H vs. L	0.261

TABLE 19-10. (continued)

Adjusted Exposure Index Analyses for Functional Stimulation Tests by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Medium	High	Contrast	p-Value
Pokeweed Net Response	Officer	n	62	63	55	Overall	0.674
		Adj. Mean	123,706	118,404	131,711	M vs. L	0.711
		95% C.I.	(69,007, 194,255)	(67,130, 184,129)	(74,319, 205,414)	H vs. L	0.596
	Enlisted Flyer	n	21	25	24	Overall	0.025
		Adj. Mean	173,897	164,642	111,772	M vs. L	0.737
		95% C.I.	(80,411, 302,996)	(89,936 274,089)	(44,741, 208,963)	H vs. L	0.014
	Enlisted Groundcrew	n	65	76	52	Overall	0.392
		Adj. Mean	105,624	121,674	110,807	M vs. L	0.180
		95% C.I.	(71,257, 146,732)	(83,779, 166,618)	(74,803, 153,863)	H vs. L	0.689
MLC Net Response	Officer	n	58	62	53	Overall	0.977
		Adj. Mean	95,550	98,079	97,973	M vs. L	0.847
		95% C.I.	(47,962, 159,377)	(51,645, 159,278)	(49,028, 163,692)	H vs. L	0.859
	Enlisted Flyer	n	20	25	22	Overall	0.491
		Adj. Mean	114,713	93,189	86,844	M vs. L	0.387
		95% C.I.	(35,112, 240,104)	(29,607, 192,257)	(24,482, 187,417)	H vs. L	0.249
	Enlisted Groundcrew	n	64	75	51	Overall	0.251
		Mean	61,403	78,259	69,881	M vs. L	0.097
		95% C.I.	(34,314, 96,320)	(46,477, 118,275)	(40,193, 107,728)	H vs. L	0.437

[a]Group-by-covariate interaction--adjusted mean, confidence interval, and p-value not presented.

Cell Surface Markers

Unadjusted analyses revealed very few significant results. Among enlisted groundcrew, the medium exposure level had a significantly lower mean total T cell count than the low exposure level (1,555 cells/mm^3 versus 1,759 cells/mm^3, p=0.032), and the high exposure level mean was marginally significantly (p=0.091) lower than the low exposure level mean (1,586 cells/mm^3 versus 1,759 cells/mm^3). Suppressor T cells, for enlisted groundcrew in the low exposure level, were marginally significantly higher than in the medium or high exposure levels (575.5, 502.3, 505.5 cells/mm^3, respectively: medium versus low, p=0.063, high versus low, p=0.097). For enlisted flyers, the trends with exposure level were steadily downwards for total T cells, helper T cells, B cells, and the T_4/T_8 ratio, and upwards for suppressor T cells and monocytes, but no contrasts were significant.

Adjusted analyses revealed marginally significant differences among exposure levels of enlisted groundcrew for total T cells (p=0.068) and suppressor T cells (p=0.088). For both total and suppressor T cells, the means for the medium and high exposure levels were much lower than those of the low exposure level. For total T cells, the adjusted means were: low, 1,737 cells/mm^3; medium, 1,533 cells/mm^3; and high, 1,558 cells/mm^3 (medium versus low: p=0.029, high versus low: p=0.085). For suppressor T cells, the adjusted means were: low, 558.6 cells/mm^3; medium, 480.8 cells/mm^3; and high, 483.7 cells/mm^3 (medium versus low p=0.044, high versus low p=0.081). A similar but less marked pattern was seen for helper T cells.

In summary, there was no consistent evidence of any significant dose-response pattern in an occupational category. For the enlisted flyer cohort, six of the seven variables revealed nonsignificant dose-response trends in the unadjusted analyses, but only two trends persisted after adjustment by the covariates.

Functional Stimulation Tests

Exposure index analyses were performed on PHA unstimulated responses, and net PHA, PWM, and MLC counts. For officers, the unadjusted mean PHA unstimulated response counts varied significantly among exposure levels (p=0.047). The means were 1,705 CPM, 1,428 CPM, and 1,809 CPM, respectively, for low, medium, and high exposure levels (medium versus low: p=0.071, high versus low: p=0.557). The PWM net count for enlisted flyers was significantly lower for the high versus the low exposure levels (55,480 CPM versus 92,847 CPM, p=0.011). The PHA net count had a downward trend with increasing exposure level for enlisted groundcrew. The PWM net count for officers had an increasing trend but there was no statistically significant difference among exposure levels.

In the adjusted analyses, officers had a significant exposure index-by-drink-year interaction (p=0.011) for PHA controls, and an exposure index-by-age interaction for the PHA net count (p=0.003) (see Table 19-11 for a summary of these interactions). Although the numbers were small, the high

TABLE 19-11.

Summary of Exposure Index by Covariate Interactions for Functional Stimulation Tests

Variable	Occupation	Covariate	p-Value
Unstimulated Response (PHA)	Officer	Drink-years	0.011
PHA Net Response	Officer	Age	0.003

exposure-level nondrinking officers had a lower mean PHA control count than the low exposure level (1,557 CPM versus 3,273 CPM, p=0.031), and the high exposure level officers with more than 100 drink-years had a higher PHA control count than the corresponding low exposure group (6,700 CPM versus 1,983 CPM, p=0.049). Officers born in or after 1942 had a lower PHA net count in the medium exposure level as contrasted with the low exposure level (153,534 CPM versus 261,397 CPM, p=0.002).

Other adjusted analyses revealed that enlisted flyers had a lower PWM net count in the high exposure level as compared to the low exposure level (111,772 CPM versus 173,897 CPM, p=0.014), as in the unadjusted analysis. Enlisted groundcrew in the medium exposure level also had a marginally significantly higher MLC net count as compared to the low exposure level (78,259 CPM versus 61,403 CPM, p=0.097).

In summary, there was no evidence for a strong dose-response relationship, but there was a trend for declining PWM and MLC net counts for enlisted flyers with increasing exposure level.

SKIN TESTING RESULTS

General

Four skin test antigens, mumps, Candida albicans, Trichophyton, and staph-phage-lysate, were intradermally administered to 76 percent (1,759) of the participants on the first day of the examination. Skin tests were not given to the remaining 24 percent of the population because they had been selected to give blood for the immunological tests on the second day of their examination. Candida albicans and Trichophyton tests were administered (0.1 ml) at a 1:1000 weight/volume dilution because of clinical concern that a 1:100 or higher concentration might induce significant skin reactions and cause morbidity in the active pilot population. Mumps was given at a dose of 2 complement-fixing units, and staph-phage-lysate was administered at a dose of 6-9 x 10^6 colony-forming units of Staph. aureus and 0.5 - 5 x 10^8 bacteriaphage plaque-forming units.

Three experienced technicians from the SCRF Allergy Division measured the size of both induration and skin erythema by the "pen method" at 24 and 48 hours after administration. Each reader was required to measure the skin reactions by a millimeter ruler and record length and breadth measurements at each of the four sites, refer exaggerated reactions to an allergist, collect medication use data, and sign the data form. The skin test data were interpreted by defined criteria, as given in Table 19-12. Other categories included: impairment noted, clinical correlation required; normal (versus abnormal) results; with medications noted; and refusal.

Of the 1,759 participants with skin tests, 269 were excluded from the analyses for the following reasons: 205 due to missing reader signature or failure of the participant to report for the 48-hour reading; 58 because of immunosuppressive medication, cancer chemotherapy, or x-ray therapy; 3 for impaired hypersensitivity requiring more tests; and 3 due to refusal. Readings at 24 hours were not analyzed since these readings occurred prior to peak response to the antigens.

Statistical Analyses and Interpretations

The initial analytical intent was to test Ranch Hand-Comparison group differences in skin test response by standard models, using both discrete and continuous data. In the preanalysis of the continuously distributed data (length by width measurement of the skin reactions), there was a suggestion of profound reader variation. This observation generated a series of contrasts between the readers prior to group testing.

Figures 19-1 through 19-6 show contrasts of the three skin test readers from the tests of mumps and Trichophyton. Each graph shows the individual plots of the 48-hour induration square area measurement versus the 48-hour

TABLE 19-12.

Clinical Interpretation Categories of Skin Test Results by Specific Measurement Criteria at SCRF

Clinical Interpretation Category	Measurement Criteria
Normal (Delayed Cutaneous Hypersensitivity Intact)	Length (L) induration @ 48 Hrs ≥10 mm Width (W) induration @ 48 Hrs ≥ 10 mm on <u>any one</u> of four skin tests
Probably Normal (Probably Intact Delayed Cutaneous Hypersensitivity)	L induration @ 48 Hrs ≥ 5-<10 mm W induration @ 48 Hrs ≥ 5-<10 mm on any one of four skin tests
Possibly Anergic	L, W induration <u>or</u> erythema @ 48 Hrs >0-<5 mm on any one or more of four skin tests
Anergic	L and W, induration at 48 hrs = 0 on all skin tests.

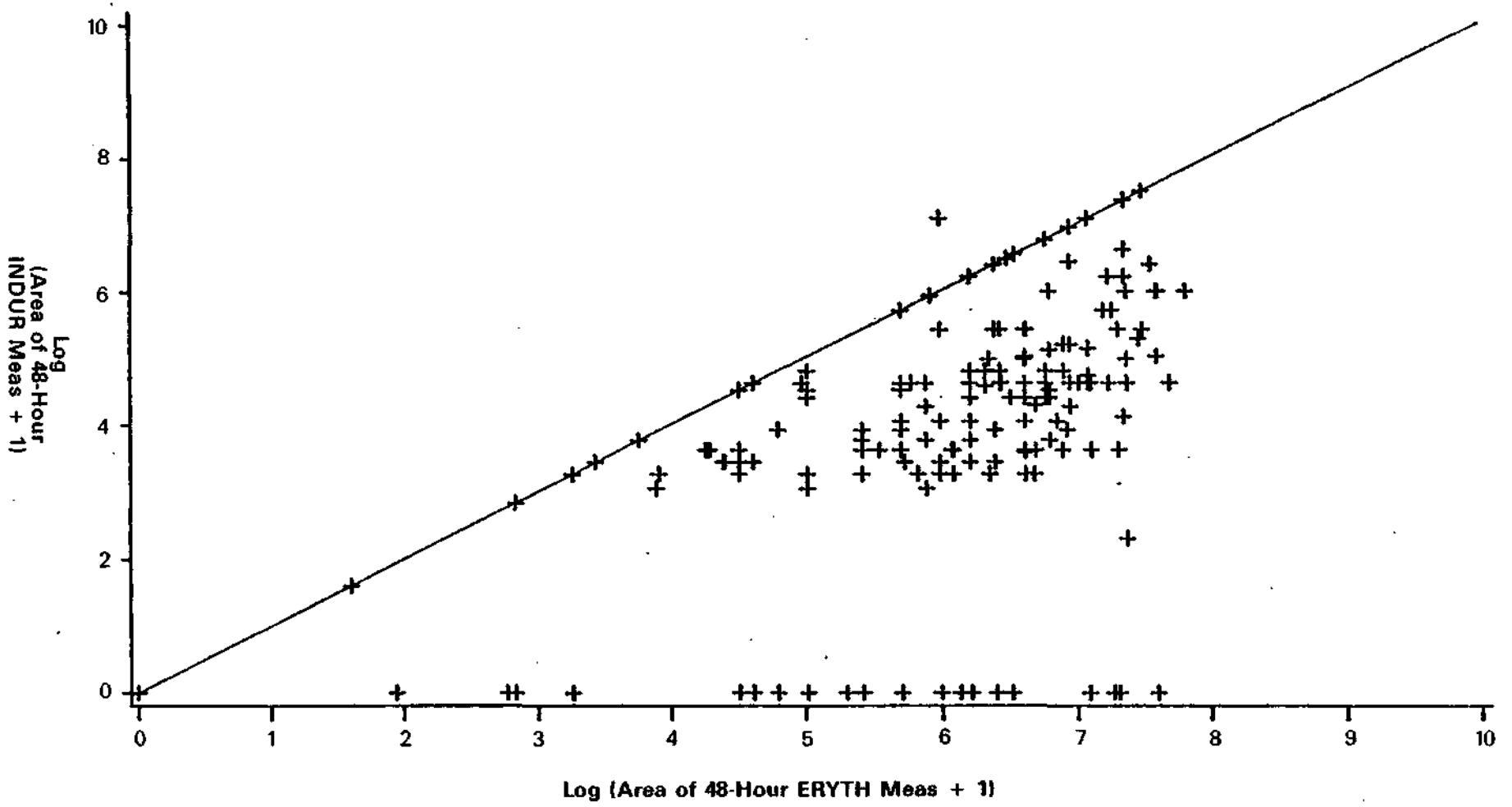

Figure 19-1.
Relationship of Induration Measurements to Erythema Measurements for the Mumps Skin Test
Reader 1 Results

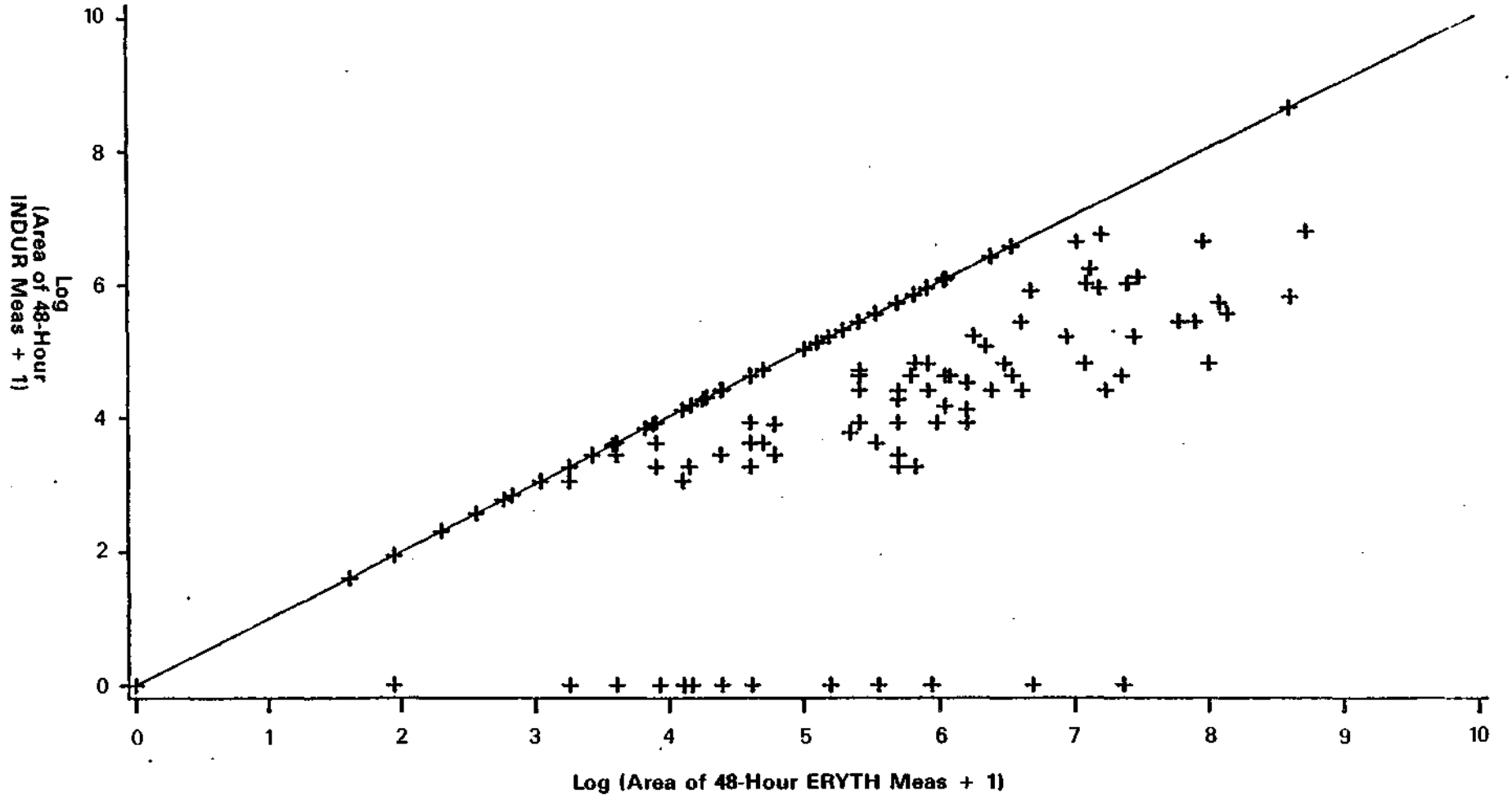

Figure 19-2.
Relationship of Induration Measurements to Erythema Measurements for the Trichophyton Skin Test.
Reader 1 Results

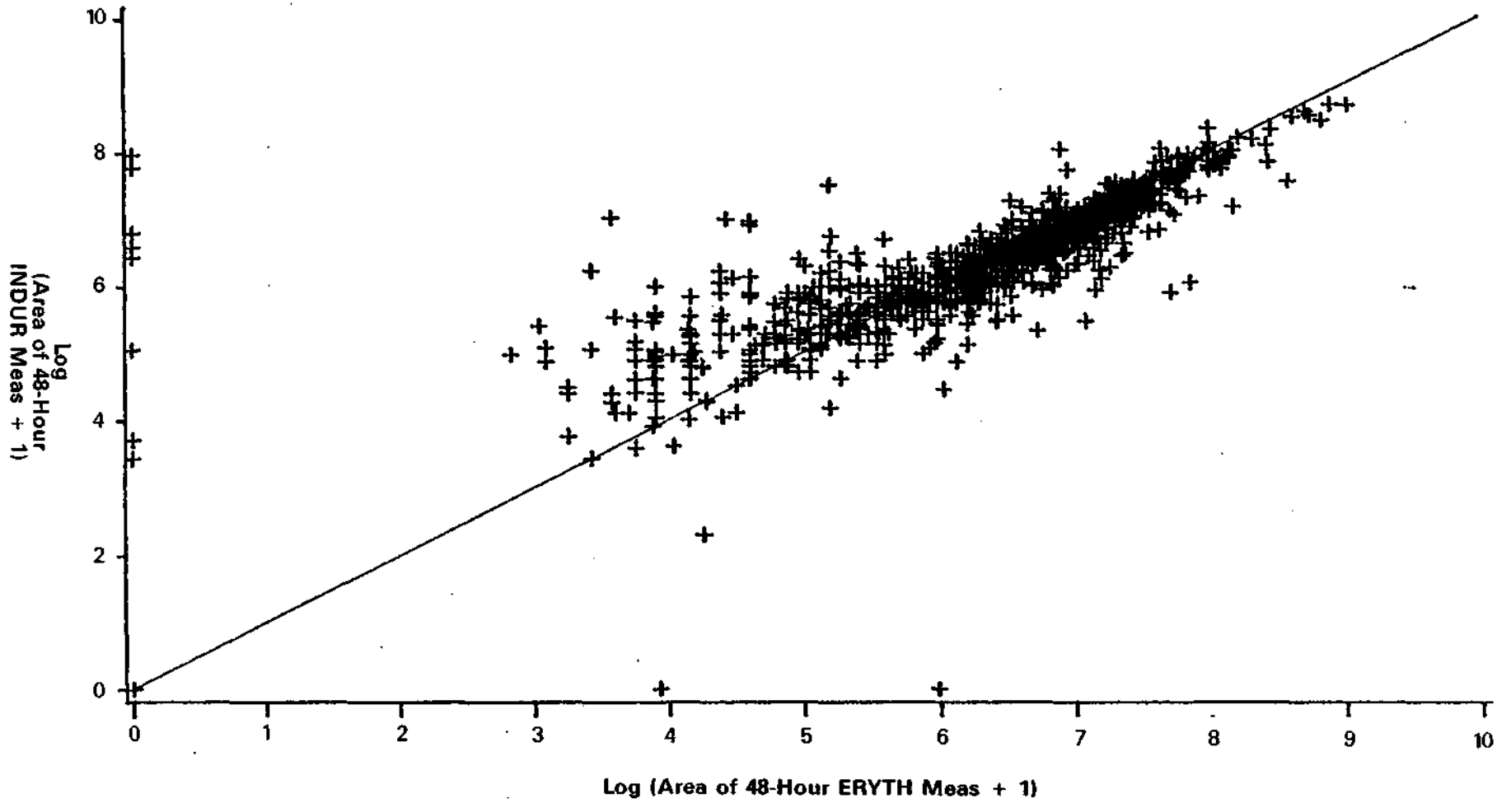

Figure 19-3.
Relationship of Induration Measurements to Erythema Measurements for the Mumps Skin Test
Reader 2 Results

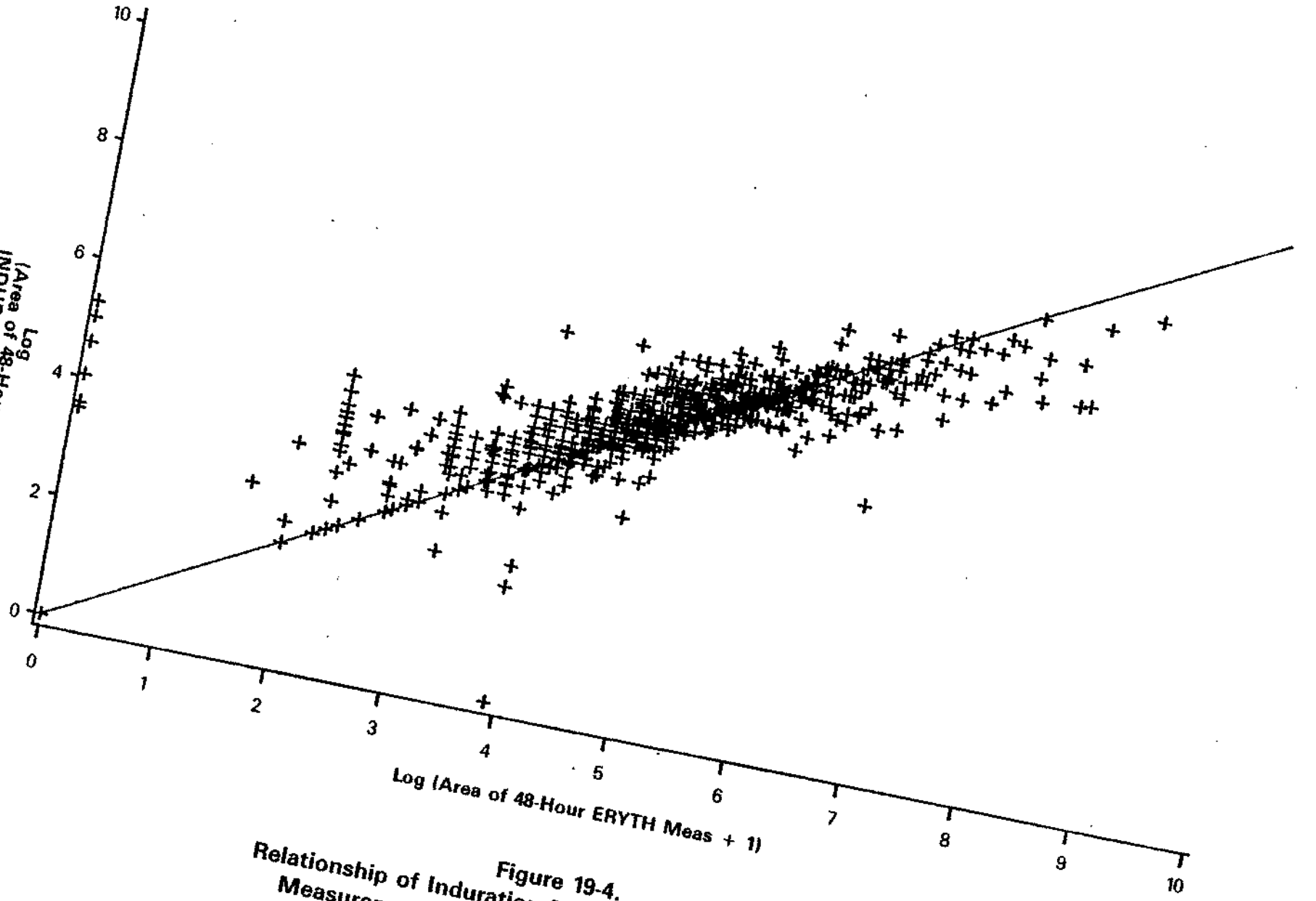

Figure 19-4.
Relationship of Induration Measurements to Erythema Measurements for the Trichophyton Skin Test Reader 2 Results

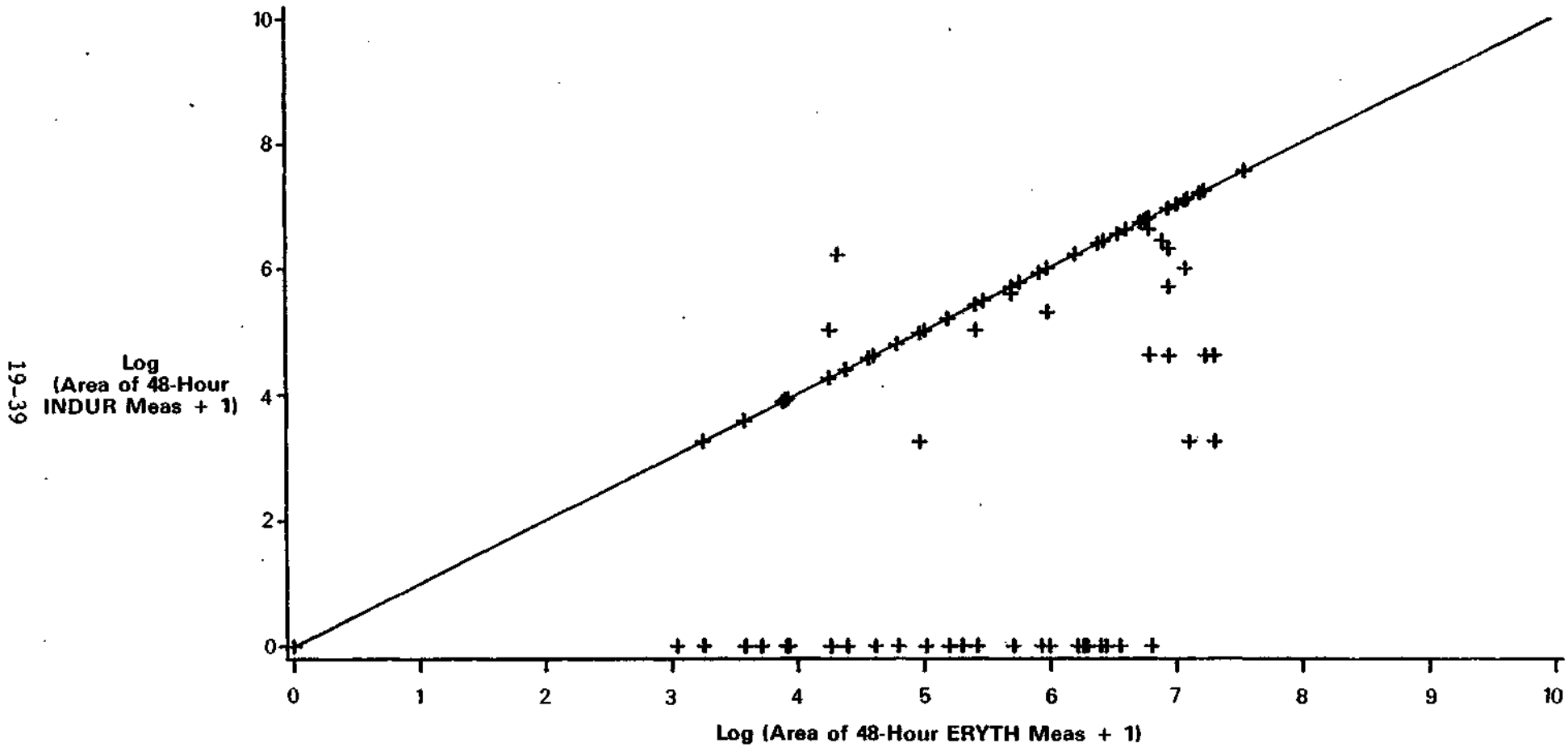

Figure 19-5.
Relationship of Induration Measurements to Erythema Measurements for the Mumps Skin Test
Reader 3 Results

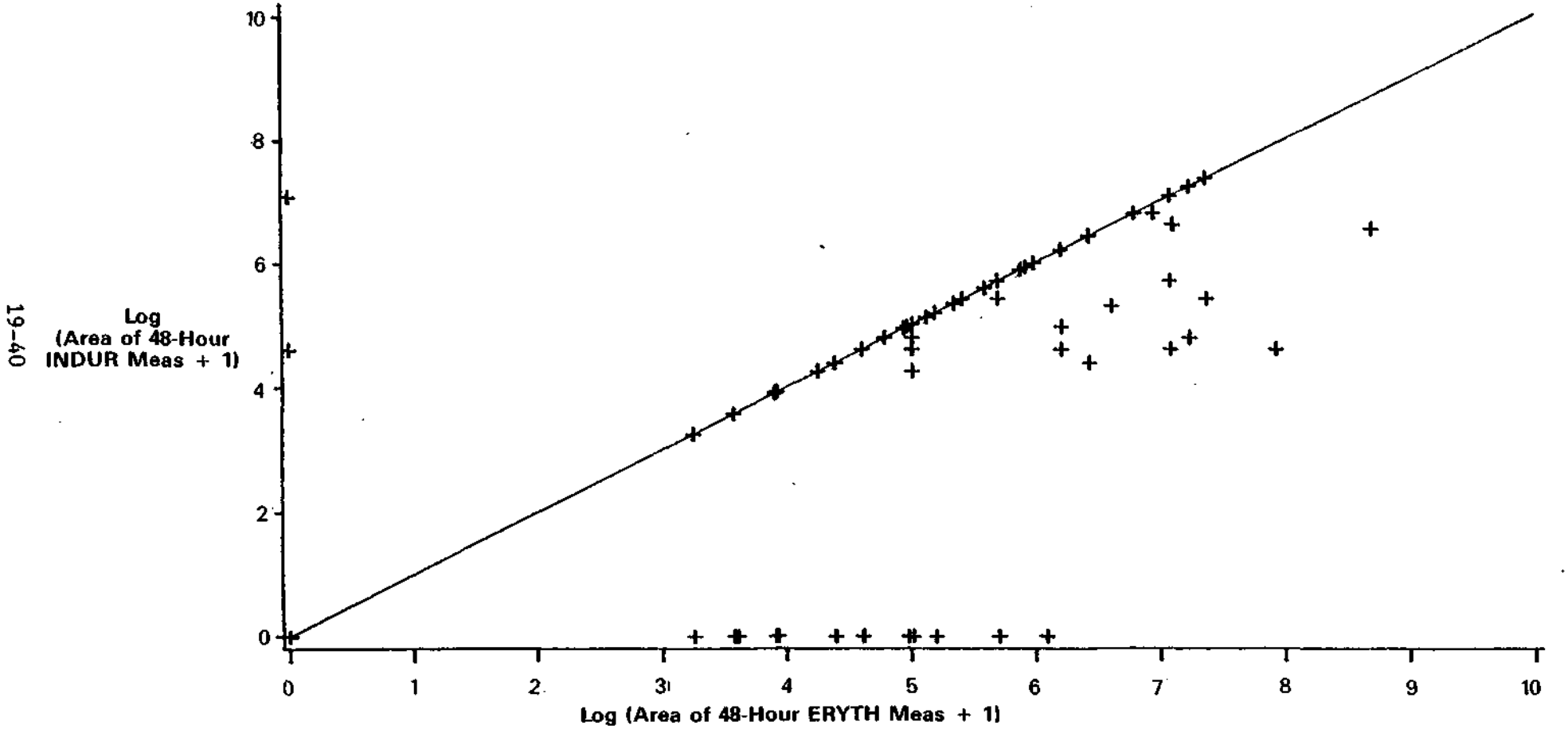

Figure 19-6.
Relationship of Induration Measurements to Erythema Measurements for the Trichophyton Skin Test
Reader 3 Results

square area erythema measurement by specific skin test and reader. These measurements are presented in log units to centralize the outlying values. These analyses were done because the size of induration rarely exceeds the size of the erythema reaction. Thus, each of the depicted graphs shows a line of values with the sizes of erythema equal to the size of induration; this line, and all values on, or to the lower right of the line, are labeled "clinically acceptable" values. All values above and to the left of the line, deemed "clinically unacceptable," are probably due to hurried measurements by inspection (rather than the pen method) or recording errors.

These figures demonstrated a marked difference in the occurrence of clinically unacceptable results between readers for comparable tests. Specifically, Reader 2's measurements revealed a higher proportion of clinically unacceptable results than those observed with Readers 1 and 3. Further, the graphs supported some variation in the clinically acceptable measurement values between Reader 1 and Reader 3. Because of these discordances, further analyses of the continuously distributed data were abandoned in favor of discretized analyses.

Categorical analyses were conducted on two parameters of the skin testing results, the area measurement relationship of induration to erythema, and the clinical interpretation of the skin test readings. Each of the three readers was compared for 48-hour measurements on the same skin test, categorizing the induration-erythema relationship as (1) Induration (I) equals Erythema (E) (both values equal to zero), (2) E greater than I, (3) I equals E, and (4) I greater than E. As previously noted, only the category of I greater than E was judged clinically unacceptable. An analysis of these four categories, by reader, for each of the four skin tests, showed a profound statistical difference ($p<0.001$) between the readers for all four skin tests. An average of the percentages for each category by reader is shown in Table 19-13, exemplifying the marked differences (a p-value is inappropriate due to the averaging).

TABLE 19-13.

Induration Erythema Relationships in Average Percentage Over Four Skin Tests, by Reader

In Percent

Reader	I=E=Zero*	E>I	I=E	I>E
1	26.2	53.9	19.8	0.1
2	7.0	42.3	20.7	30.0
3	24.1	35.4	39.6	0.9

*I:Induration
E:Erythema

These data show marked reader differences for the category I greater than E. The magnitude of clinically unacceptable results (30.0% on the average for four skin tests) for Reader 2 (visually shown in Figures 19-3 and 19-4) strongly suggested that this entire data set was invalid. Further, the data pattern from Reader 2 was shown to be uniform over time, confirming the existence of a consistent bias. In this light, the existence and magnitude of a reverse error for Reader 2, i.e., misreadings of I equals E equals 0, E greater than I, and I equals E, seem plausible, but unestimable. Of these three categories, I equals E equals 0 is the most clinically important (suggesting anergy), and Table 19-13 provides clear evidence of a negative bias, with Readers 1 and 3 showing over three times more average detection of anergy than Reader 2. Also of interest in Table 19-13 are the substantial differences in the categories E greater than I and I equals E for Readers 1 and 3. Analyses of the four skin tests by erythema-induration relationships showed statistically significant differences beween Readers 1 and 3 for all four tests ($p<0.001$ for mumps, Candida albicans, and Trichophyton, and $p=0.036$ for staph-phage-lysate).

The decision to remove Reader 2 data from subsequent analysis was agreed to by all the Principal Investigators, recognizing the minimal role of erythema as a contemporary indicator of anergy. This decision was based on the concern that an error in erythema measurement likely indicated an error in measurement of induration (the predominant indicator of anergy).

In preparation for the analysis of group data remaining from Readers 1 and 3, it was noted that the clinical interpretations (see Table 19-12) from these valid readings were inconsistent over time of the study. Specifically, 80 percent of relative anergy and anergy occurred in the first 10 of 81 groups of participants (or 2 1/2 months of the 9-month examination period). Further, the proportion of diagnoses of anergy between the allergists was disproportionate. The value of these analyses was therefore reduced.

SUMMARY AND CONCLUSIONS

Immunologic competence was measured by cell surface marker (phenotypic) studies and cell stimulation studies on 47 percent of the study population, and by a four antigen series of skin tests in 76 percent of participants to assess the delayed hypersensitivity response. Table 19-14 summarizes the results of all unadjusted and adjusted analyses on 11 primary variables spanning the first two of these three functional areas.

Cell surface marker studies were conducted for total T cells (T_{11}), helper T cells (T_4), suppressor T cells (T_8), B cells, monocytes, and HLA-DR cells; the ratio of T_4/T_8 cells was included in the analysis. Because of inherent significant day-to-day and batch-to-batch variation, all results (including functional stimulation studies) were adjusted for blood-draw day variation. Statistical testing of the seven phenotypic cell markers did not reveal any significant group differences (interactions excepted), either unadjusted or adjusted for the covariates of age, race, occupation, current smoking, lifetime smoking history (pack-years), current alcohol use, or lifetime alcohol use (drink-years). Similarly, none of the unadjusted or adjusted analyses of the functional stimulation studies (for phyto-hemagglutinin, pokeweed mitogen, or mixed lymphocyte culture) showed any

TABLE 19-14.

Overall Summary Results
of Unadjusted and Adjusted
Analyses of Immunological Variables

Variable	Unadjusted	Adjusted
Total T Cells (T_{11})	NS	****
Helper T Cells (T_4)	NS	NS
Suppressor T Cells (T_8)	NS	NS
B Cells	NS	****
Monocytes	NS	****
HLA-DR Cells	NS	****
T_4/T_8 Ratio	NS	NS
Unstimulated Response (PHA)	NS	NS
PHA Net Response	NS	NS
Pokeweed Net Response	NS	NS
MLC Net Response	NS	****

NS:Not significant (p>0.10).
****Significant group-by-covariate interaction.

statistically significant group differences. However, the adjusted analyses for total T cells, B cells, monocytes, HLA-DR cells, pokeweed mitogen, and net mixed lymphocyte culture stimulation showed some significant group-by-covariate interactions, precluding direct adjusted group contrasts. Overall, no discernible pattern was identified to suggest a detriment in any subgroup of either the Ranch Hands or Comparisons. Results were similar between the analyses of the total Comparison group and the analyses of the Original Comparisons.

The covariate effects of age, race, smoking, and alcohol use were generally profound on most variables in the phenotypic and stimulation studies. Consistently decreasing values of all cell markers and stimulated cells were associated with increasing age, whereas increased levels of smoking were usually associated with increases in the values of those variables. Blacks had consistently higher stimulated cell counts than nonblacks, but this effect was not observed for counts of T cells, B cells, or HLA-DR cells. Enlisted personnel generally had higher cell surface marker counts than officers.

Exposure index analyses of cell surface markers revealed no pattern consistent with a dose-response relationship. For enlisted groundcrew, the mean total T cell and suppressor T cell counts for the medium exposure level were significantly lower than those of the low exposure level, but were slightly lower than those of the high exposure level. The exposure index analyses of the functional stimulation tests revealed no consistent significant dose-response patterns for net PHA counts or net MLC counts. For net pokeweed counts, enlisted flyers in the high exposure level had a significantly lower adjusted count than enlisted flyers in the low exposure level, and a decreasing trend was apparent.

The delayed hypersensitivity response was assessed by the skin test antigens of mumps, Candida albicans, Trichophyton, and staph-phage-lysate. The 48-hour measurements of skin induration and erythema for the four tests showed marked inter-reader variation. Analyses showed that one of the three skin test readers too often measured induration larger than erythema (a clinically unacceptable finding), in an average of 30 percent of the readings, and did not yield measurements that detected a case of possible or overt anergy, whereas the other two readers found this condition in 5.6 percent of the participants. Remaining data from Readers 1 and 3, however, were found to vary significantly in clinical interpretation over duration of the examination. Consequently, all skin test data were declared invalid, and were not used in the assessment of group differences. The skin test reading problems led to the use of additional clinical quality control procedures for the AFHS followup examination begun in May 1987.

In conclusion, no significant group differences were judged present for the comprehensive cell surface marker or functional stimulation studies. The profound effects of age, smoking, and alcohol use were observed in these immunologic tests. The assessment of delayed hypersensitivity skin responses was precluded by poor data quality and excluded from further analysis. Overall, there was no indication of impaired immunologic competence in either group.

CHAPTER 19

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CHAPTER 20

PULMONARY DISEASE

INTRODUCTION

Pulmonary dysfunction and overt pulmonary disease are not recognized clinical entities resulting from exposure to chlorophenols or TCDD.

Acute exposure to chlorophenols, phenoxy herbicides, and TCDD, have caused the traditional acute symptoms of cough, nasal/lung irritation, shortness of breath, and, occasionally, bronchitis. These symptoms have been noted almost exclusively in industrial workers and not in individuals experiencing casual contact. Long-term sequelae arising from the acute symptom stage in ill individuals have not been generally known because of minimal followup and surveillance of the pulmonary symptoms.

Only one contemporary morbidity study has attributed pulmonary dysfunction to phenoxy herbicide and TCDD exposure.[1] The percent abnormal pulmonary parameters of forced expiratory volume (FEV), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1)/FVC ratio, and forced midexpiratory flow rate (FEF_{25-75}) were significantly higher in exposed workers who currently smoke, than in nonexposed workers who smoke. In considerable contrast, these test parameters were essentially equal in nonsmokers and former smokers of both the exposed and nonexposed groups. The effect of current smoking persisted after a logistic regression analysis adjusting for pack-years of cigarette smoking. Adjusted means of the test parameters FEV, FVC, and FEV_1/FVC also showed significant differences for current smokers but not for nonsmokers or former smokers.

As with other nonclassical clinical endpoints, prior investigators perhaps undervalued the incorporation of pulmonary disease and function into their study protocols.

Further, due to the profound effect of smoking on pulmonary function, great emphasis must be placed in the collection of highly accurate, detailed, and validated smoking data as an adjustment variable, a process that is not straightforward in today's environment of antismoking.

The only recent data comparable to this study are found in the 1984 AFHS Baseline Morbidity Report, which is reviewed below.[2]

Baseline Summary Results

The 1982 Baseline examination explored historical pulmonary disease by questionnaire and active pulmonary function by standardized spirometric technique at the physical examination. These areas were of significant interest because of routine operational inhalation of Herbicide Orange by all Ranch Hand flying crewmen as well as ground maintenance personnel (Baseline Report Chapter 1, Buckingham).

The questionnaire revealed no group differences for historical diagnoses of tuberculosis and fungal infections, pneumonia, cancer, or chronic sinusitis and upper respiratory disease. At the physical examination the unadjusted means for FEV_1 (percent predicted), FVC, and the FEV_1/FVC ratio were almost identical between the Ranch Hands and Comparisons. Adjusted mean values were not calculated due to significant interactions (age, group, and pulmonary function for FEV_1 and FVC; smoking with FEV_1/FVC).

Detailed exposure analyses showed two significant associations in the enlisted flyer and enlisted groundcrew strata, but neither was indicative of linear dose response. Attempts to adjust the means of the pulmonary function values for age and smoking revealed several interactions, but essentially negative results.

Overall, there were no pulmonary disease or pulmonary function data or associations of concern.

Parameters of the 1985 Pulmonary Examination

Because of the essentially negative pulmonary analyses from the Baseline examination, pulmonary function (spirometric) studies were not performed during the first followup examination. Collection of pulmonary data was limited to a questionnaire history of respiratory disease, physical examination of the thorax and lungs, and pulmonary abnormalities detected on a routine chest x ray.

Thus, the data analyses consist of group assessments of respiratory disease incidence, physical examination abnormalities, and the current prevalence of x-ray abnormalities. Covariate adjustments are made for age and smoking (yes, no, former, and pack-years). Minor numeric differences in the tables are due to rare missing dependent variable or covariable data. The analyses are based on 1,016 Ranch Hands and 1,293 Comparisons. No exclusions based on clinical conditions were made.

Mortality due to respiratory disease, as of 31 December 1985, in the Ranch Hand and the 1:5 matched Comparison cohort is summarized. Morbidity data are analyzed using linear and loglinear models.

RESULTS AND DISCUSSION

Mortality Experience

The mortality of the Ranch Hand and Comparison groups through 31 December 1985 was evaluated. There were seven deaths from respiratory system conditions in the Comparison group and none in the Ranch Hand group. This analysis was based on the 1:5 Ranch Hand to Comparison mortality study cohorts. Two of these deaths were Comparison flying officers, three were enlisted flyers, and the remaining two were enlisted groundcrew.

Unadjusted Morbidity Analyses

Analyses were performed on the history of respiratory illnesses as provided by the participants during the physical examination. The results of the

radiological and clinical examination of the lungs and chest were also analyzed. These unadjusted analyses are summarized in Tables 20-1 and 20-2.

As shown, no significant group differences were observed for history of asthma, bronchitis, pleurisy, pneumonia, or tuberculosis. Similar non-significant results were found in the evaluation of the clinical variables.

Parallel analyses were conducted using data from the Original Comparisons, with comparable results (Appendix R, Table R-1).

Adjusted Morbidity Analyses

Statistical adjustment for the effects of age and lifetime smoking did not alter the findings of group similarity seen in the unadjusted analyses. Lifetime smoking was categorized as nonsmoking (0 pack-years), moderate (greater than 0 to 10 pack-years) and heavy (greater than 10 pack-years). These results are shown in Table 20-3.

Lifetime smoking consistently exerts significant effects on nearly all historical illness and clinical examination variables, and age was an important factor for the history of pneumonia and the clinical assessment of thorax and lungs (representing an overall clinical assessment of normality/abnormality in the respiratory system), chest asymmetry, the presence of hyperresonance, rales, and the presence of x-ray abnormality.

There were significant or borderline significant group-by-pack-year interactions in analyses of a history of pleurisy and tuberculosis, for the presence of rales on examination, and for x-ray abnormality. There was also an interaction for asthma of borderline significance ($p=0.068$). A significant group-by-age interaction was seen for the presence of rales. The results of analyses stratified to clarify these interactions are shown in Table 20-4.

Nonsmoking Ranch Hands had significantly more asthma ($p=0.050$) than their nonsmoking Comparisons, while the history of asthma was not significantly different in either category of smokers. Pleurisy was significantly more frequent in moderately smoking Ranch Hands ($p=0.0001$), but bordered on being significantly increased in heavily smoking Comparisons ($p=0.060$). Analyses of a history of tuberculosis and the presence of rales was hampered by small numbers of cases in both groups (a total of 13 cases). The presence of several cells containing zeros makes interpretation of these analyses extremely difficult. Except in those strata with zero cells, no statistical significance was noted. In the analysis of x-ray abnormalities, the nonsmoking Ranch Hands had significantly less abnormality ($p=0.030$) than the nonsmoking Comparisons. Analyses of other strata did not reveal any significant group differences.

These adjusted analyses were performed on data from the Original Comparisons, with similar results (see Tables 20-2 and 20-3).

EXPOSURE ANALYSES

The pulmonary data from the Ranch Hands were analyzed using the exposure index as a covariate (categorized as high, medium, or low within each occupational stratum). The percent abnormality at each level of exposure for each clinical or historical variable is presented in Tables 20-5, 20-6, and 20-7.

TABLE 20-1.

Unadjusted Analyses of Reported History of Respiratory Illness by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Asthma	n	1,016		1,292			
	Abnormal	44	4.3	50	3.9	1.12 (0.74,1.70)	0.58
	Normal	972	95.7	1,242	96.1		
Bronchitis	n	1,015		1,292			
	Abnormal	129	12.7	168	13.0	0.97 (0.76,1.25)	0.84
	Normal	886	87.3	1,124	87.0		
Pleurisy	n	1,016		1,291			
	Abnormal	47	4.6	57	4.4	1.05 (0.71,1.56)	0.81
	Normal	969	95.4	1,234	95.6		
Pneumonia	n	1,016		1,291			
	Abnormal	195	19.2	245	19.0	1.01 (0.82,1.25)	0.89
	Normal	821	80.8	1,046	81.0		
Tuberculosis	n	1,015		1,292			
	Abnormal	7	0.7	6	0.5	1.49 (0.52,4.28)	0.48
	Normal	1,008	99.3	1,286	99.5		

TABLE 20-2.

Unadjusted Analyses of Radiological and Clinical Respiratory System Findings by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Thorax and Lungs	n	1,015		1,293			
	Abnormal	61	6.0	61	4.7	1.29 (0.90,1.86)	0.17
	Normal	954	94.0	1,232	95.3		
Asymmetrical Expiration	n	1,015		1,293			
	Abnormal	2	0.2	3	0.2	0.85 (0.17,4.45)	0.86
	Normal	1,013	99.8	1,290	99.8		
Hyperresonance	n	1,015		1,293			
	Abnormal	30	3.0	35	2.7	1.09 (0.67,1.79)	0.72
	Normal	985	97.0	1,258	97.3		
Dullness	n	1,015		1,293			
	Abnormal	2	0.2	1	0.1	2.55 (0.31,17.62)	0.43
	Normal	1,013	99.8	1,292	99.9		
Wheezes	n	1,015		1,293			
	Abnormal	24	2.4	21	1.6	1.47 (0.82,2.63)	0.20
	Normal	991	97.6	1,272	98.4		
Rales	n	1,015		1,293			
	Abnormal	6	0.6	7	0.5	1.09 (0.38,3.15)	0.86
	Normal	1,009	99.4	1,286	99.5		
X Ray	n	1,012		1,289			
	Abnormal	102	10.1	149	11.6	0.86 (0.66,1.12)	0.26
	Normal	910	89.9	1,140	88.4		

TABLE 20-3.

Adjusted Analyses of Respiratory Variables by Group*

Variable	Group: Ranch Hand Total	Group: Comparison Total	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
Asthma	1,012	1,290	1.16 (0.76,1.75)	0.57	PACKYR (p=0.023) GRP*PACKYR (Borderline: p=0.068)
Bronchitis	1,011	1,290	0.97 (0.76,1.25)	0.83	None
Pleurisy	1,012	1,289	****	****	GRP*PACKYR (p=0.0026)
Pneumonia	1,012	1,289	1.02 (0.82,1.26)	0.93	AGE (p=0.0001)
Tuberculosis	1,011	1,290	****	****	GRP*PACKYR (p=0.034)
Thorax and Lungs	1,011	1,291	1.27 (0.87,1.84)	0.19	AGE (p<0.0001) PACKYR (p<0.001)
Asymmetrical Expiration	1,011	1,291	0.81 (0.14,4.85)	0.85	AGE*PACKYR (p=0.036)
Hyperresonance	1,011	1,291	1.04 (0.63,1.73)	0.80	AGE (p<0.0001) PACKYR (p<0.0001)
Dullness	1,011	1,291	2.56 (0.31,17.66)	0.47	None
Wheezes	1,011	1,291	1.46 (0.80,2.64)	0.22	PACKYR (p<0.0001)
Rales	1,011	1,291	****	****	GRP*AGE (p=0.046) GRP*PACKYR (Borderline: p=0.070) AGE*PACKYR (Borderline: p=0.090)
X Ray	1,008	1,287	0.85 (0.65,1.11)	0.22	AGE (p<0.0001) PACKYR (p=0.0019) GRP*PACKYR (Borderline: p=0.060)

*Group-by-covariate interactions are described in Table 20-4.

**Abbreviations

PACKYR: Lifetime smoking history (pack-years)
GRP: Group

****Group-by-covariate interaction--relative risk, confidence interval, and p-value not presented.

TABLE 20-4.

Summary of Group-by-Covariate Interactions for Respiratory Variables

Variable	Interaction	Stratification	Statistic	Group: Ranch Hand Number	Group: Ranch Hand Percent	Group: Comparison Number	Group: Comparison Percent	Adj. Relative Risk (95% C.I.)	p-Value
Asthma	Group-by-Pack-Year	0	n	291		367			
			Abnormal	11	3.78	5	1.36	2.84 (1.00,7.89)	0.05
			Normal	280	96.22	362	98.64		
		>0-10	n	284		397			
			Abnormal	16	5.63	15	3.78	1.52 (0.75,3.10)	0.25
			Normal	268	94.37	382	96.22		
		>10	n	437		526			
			Abnormal	17	3.89	30	5.70	0.67 (0.37,1.23)	0.19
			Normal	420	96.11	496	94.30		
Pleurisy	Group-by-Pack-Year	0	n	291		366			
			Abnormal	8	2.75	8	2.19	1.27 (0.48,3.32)	0.64
			Normal	283	97.25	358	97.821		
		>0-10	n	284		397			
			Abnormal	18	6.34	8	2.02	3.29 (1.43,7.49)	<0.001
			Normal	266	93.66	389	97.98		
		>10	n	437		526			
			Abnormal	21	4.81	41	7.79	0.60 (0.35,1.02)	0.06
			Normal	416	95.19	485	92.21		

TABLE 20-4. (continued)

Summary of Group-by-Covariate Interactions for Respiratory Variables

Variable	Interaction	Stratification	Statistic	Group: Ranch Hand Number	Group: Ranch Hand Percent	Group: Comparison Number	Group: Comparison Percent	Adj. Relative Risk (95% C.I.)	p-Value
Tuberculosis	Group-by-Pack-Year	0	n	290		367			
			Abnormal	1	0.34	4	1.09	0.31 (0.06,2.26)	0.28
			Normal	289	99.66	363	98.91		
		>0-10	n	284		397			
			Abnormal	4	1.41	0	0.00	--	0.02
			Normal	280	98.59	397	100.00		
		>10	n	437		526			
			Abnormal	2	0.46	2	0.38	1.20 (0.21,2.04)	0.86
			Normal	435	99.54	524	99.62		
Rales	Group-by-Age	>1942	n	384		509			
			Abnormal	1	0.26	1	0.20	1.33 (0.14,12.78)	0.84
			Normal	383	99.74	508	99.80		
		1922-1942	n	600		741			
			Abnormal	5	0.83	6	0.81	1.03 (0.33,3.25)	0.96
			Normal	595	99.17	735	99.19		
		<1922	n	27		41			
			Abnormal	0	0.00	0	0.00	--	--
			Normal	27	100.00	41	100.00		

TABLE 20-4. (continued)

Summary of Group-by-Covariate Interactions for Respiratory Variables

Variable	Interaction	Stratification	Statistic	Group: Ranch Hand Number	Group: Ranch Hand Percent	Group: Comparison Number	Group: Comparison Percent	Adj. Relative Risk (95% C.I.)	p-Value
Rales	Group-by-Pack-Year	0	n	291		367			
			Abnormal	1	0.34	2	0.54	0.63 (0.09,5.26)	0.71
			Normal	290	99.66	365	99.46		
		>0-10	n	283		398			
			Abnormal	0	0.00	2	0.50	--	0.23
			Normal	283	100.00	396	99.50		
		>10	n	437		526			
			Abnormal	5	1.14	3	0.57	2.02 (0.51,7.67)	0.33
			Normal	432	98.86	523	99.43		
X Ray	Group-by-Pack-Year	0	n	290		365			
			Abnormal	15	5.17	36	9.86	0.50 (0.27,0.93)	0.03
			Normal	275	94.83	329	90.14		
		>0-10	n	282		398			
			Abnormal	28	9.93	32	8.04	1.26 (0.74,2.14)	0.39
			Normal	254	90.07	366	91.96		
		>10	n	436		524			
			Abnormal	59	13.53	81	15.46	0.86 (0.60,1.23)	0.40
			Normal	377	86.47	443	84.54		

-- No abnormals present in Comparison group.

TABLE 20-5.

Exposure Index Analysis Results for Officers
p-Values of Dependent Variable-by-Covariate Association[a,b]

Variable	D*EXP	D*AGE	D*PACKYR	D*EXP *AGE	D*EXP *PACKYR	D*AGE *PACKYR	D*EXP* AGE*PACKYR	Overall Abnormal	Overall Total	Overall Percent
Asthma								16	380	4.2
Bronchitis					0.08		0.009	52	380	13.7
Pleurisy		0.02						16	380	4.2
Pneumonia							0.04	75	380	19.7
Tuberculosis	(No Analysis; Only 3 Abnormal)									
Thorax and Lungs	0.05		0.02			0.06		17	380	4.5
Asymmetrical Exp.	(No Analysis; Only 2 Abnormal)									
Hyperresonance					0.07			9	380	2.4
Dullness	(No Analysis; Only 2 Abnormal)									
Wheezes								5	380	1.3
Rales	(No Analysis; Only 3 Abnormal)									
X Ray	0.09	0.01	0.06				0.08	34	380	8.9

[a]Dependent variable indicated by D in column headings.

[b]Abbreviations:

EXP: Exposure index.
PACKYR: Pack-years.

TABLE 20-6.

Exposure Index Analysis Results for Enlisted Flyers
p-Values of Dependent Variable-by-Covariate Association*

Variable	D*EXP	D*AGE	D*PACKYR	D*EXP *AGE	D*EXP *PACKYR	D*AGE *PACKYR	D*EXP* AGE*PACKYR	Overall Abnormal	Overall Total	Overall Percent
Asthma		0.07						6	175	3.4
Bronchitis							0.005	21	174	12.1
Pleurisy							0.08	9	175	5.1
Pneumonia				0.08				39	175	22.3
Tuberculosis	(No Analysis; Only 2 Abnormal)									
Thorax and Lungs	0.04							19	175	10.9
Asymmetrical Exp.	(No Analysis; 0 Abnormal)									
Hyperresonance	0.04				0.08			9	175	5.1
Dullness	(No Analysis; 0 Abnormal)									
Wheezes								7	175	4.0
Rales	(No Analysis; Only 1 Abnormal)									
X Ray	0.04							19	175	10.9

*Dependent variable indicated by D in column headings.

TABLE 20-7.

Exposure Index Analysis Results for Enlisted Groundcrew: p-Values of Dependent Variable by Covariate Association*

Variable	D*EXP	D*AGE	D*PACKYR	D*EXP* *AGE	D*EXP *PACKYR	D*AGE *PACKYR	D*EXP* AGE*PACKYR	Overall Abnormal	Overall Total	Overall Percent
Asthma				0.08			0.02	22	457	4.8
Bronchitis	0.08							55	457	12.0
Pleurisy				0.03				22	457	4.8
Pneumonia			0.01					81	457	17.7
Tuberculosis	(No Analysis; Only 2 Abnormal)									
Thorax and Lungs		0.06						25	456	5.5
Asymmetrical Exp.	(No Analysis; 0 Abnormal)									
Hyperresonance		0.007						12	456	2.6
Dullness	(No Analysis; 0 Abnormal)									
Wheezes				0.009	0.02			12	456	2.6
Rales	(No Analysis; Only 2 Abnormal)									
X Ray		0.0005						49	456	10.8

*Dependent variable indicated by D in column headings.

Two sets of analyses were performed on enlisted groundcrew data. In the first set of analyses, all three year-of-birth categories (born after 1942, born between 1922 and 1942, born before 1922) were used. In the second set of analyses, only those born between 1922 and 1942 and after 1942 were used, since only one enlisted groundcrew Ranch Hand was born before 1922. All testing results in the two sets of analyses were the same, except for the asthma-by-age interaction shown in Table 20-6.

Each of the dependent variable-by-exposure category interactions are noted by occupation category in Appendix R, Tables R-4 through R-18. These data are considered too sparse for meaningful interpretation.

SUMMARY AND CONCLUSIONS

A summary of the results on the analyses of reported history of respiratory illness and of radiological and clinical findings is given in Table 20-8.

Based on the 31 December 1986 mortality data, there were seven deaths from respiratory conditions in the Comparison group and none in the Ranch Hand group.

TABLE 20-8.

Overall Summary Results of Unadjusted and Adjusted Analyses of Pulmonary Disease

Pulmonary Disease	Unadjusted	Adjusted
Reported History of Respiratory Illness		
Asthma	NS	NS
Bronchitis	NS	NS
Pleurisy	NS	****
Pneumonia	NS	NS
Tuberculosis	NS	****
Radiological and Clinical Findings		
Thorax and Lungs	NS	NS
Asymmetrical Expiration	NS	NS
Hyperresonance	NS	NS
Dullness	NS	NS
Wheezes	NS	NS
Rales	NS	****
X Ray	NS	NS

NS: Not significant ($p>0.10$)
****Group-by-covariate interaction.

There were no group differences found for reported history of asthma, bronchitis, pleurisy, or tuberculosis based on the unadjusted analyses. Adjustments for age and lifetime smoking did not alter the findings of group similarity, although there was a significant group-by-pack-year interaction for pleurisy and for tuberculosis.

Similarly, there were no significant group differences in the unadjusted analyses for the radiological and clinical respiratory findings of thorax and lungs, asymmetrical expiration, hyperresonance, dullness, wheezes, rales, and x-ray interpretations. These findings were supported by the adjusted analyses, although there was a group-by-age interaction for rales.

The exposure index analyses revealed no consistent dose-response pattern.

Analyses of past history of respiratory illness and the clinical and radiological examination of the chest and lungs did not reveal any statistically significant differences between the Ranch Hand and Comparison groups suggestive of herbicide related disease. Several group-by-covariate interactions did exhibit statistical significance, but these findings did not indicate any consistent patterns suggesting different disease experience in the two groups.

REFERENCES

CHAPTER 20

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CHAPTER 21

INTERPRETIVE CONSIDERATIONS

This chapter reviews several scientific issues that should be considered when attempting to reach conclusions on a study of this size and complexity. These issues are critical to the interpretation of the data analyses in this report. Data patterns observed in many clinical chapters of this report are also summarized so that hypothesis testing of group differences may be placed in better perspective.

DIOXIN ENDPOINTS

Based upon data in this report, final conclusions on herbicide causality must consider results of the various clinical areas, reflected in the separate chapters. Each chapter introduction has attempted to highlight the major organ systems that are known or suspected to be significantly affected by the ingredients of Agent Orange with particular emphasis on the effects of dioxin. Categories of clinical endpoints and their generally accepted degree of association with dioxin are presented in Table 21-1. These associations are based on the scientific literature.

TABLE 21-1.

Summary Associations of Adverse Health Effects to TCDD Exposure Reported in the Literature

Degree of Association by Clinical Chapter

Confirmed	Highly Suspected	Moderately Suspected	Negative or Weakly Suspected
Dermatology Neurology Hepatic	Malignancy	General Health Immunology	Psychology Cardiovascular Hematology Endocrine Renal Pulmonary

It is recognized that alternative conclusions based on these patterns of association are possible within the framework of current knowledge, particularly for the highly and moderately suspected areas (malignancy, general health, immunology). However, for illustrative purposes, two extremes are presented: multiple adverse findings in the Ranch Hand group for the areas

of dermatology, neurology, hepatic (discussed in Chapter 13), and cancer would suggest a case for TCDD causality, whereas multiple adverse findings in the weakly suspected areas, and not in any of the confirmed areas, would be difficult to ascribe to an overall TCDD causation.

The aspects of biological plausibility and specificity require balanced interpretation across clinical chapters, with careful attention placed on nonsignificant findings as well as significant findings. The chapters in this report should be viewed as artificial boundaries for convenience of presentation, and should not discourage consideration of their relatedness, or of the individual variables within them.

EXPOSURE

Approximately 600 exposure index analyses have been conducted in this study, underscoring attempts to associate increasing proportions of various abnormalities to estimates of increasing exposure.

To determine whether the results of the exposure analyses varied by chance, several perspectives were taken. Of the 255 adjusted exposure analyses (excluding 39 with interactions), 13 were statistically significant, a figure which is the expected number (based on $\alpha = 0.05$). It is recognized that this contrast is a crude yardstick, considering the relatedness of the dependent variables, statistical power, disproportionate representation of chapter variables, and the presence of interactions. The six possible patterns of exposure response (increasing, decreasing, V-shaped with fewer abnormalities at the low exposure level than the high exposure level, V-shaped with more abnormalities at the low exposure level than at the high exposure level, inverted V-shaped with fewer abnormalities at the low exposure level than the high exposure level, and inverted V-shaped with more abnormalities at the low exposure level than at the high exposure level) were tabulated (regardless of statistical significance) for the clinical chapters of dermatology, neurology, psychology, and renal. As noted in Table 21-1, two of these chapters contain clinical variables that have had confirmed associations to TCDD exposure, and two chapters have had negative or weakly suspected associations to TCDD. Of the 126 exposure analyses in these four chapters, 21 (or one-sixth) showed the primary pattern of interest, an increase--exactly the number expected. Taken together, these analyses suggest that statistically significant exposure analyses may have occurred due to chance among the data set, and that the pattern of dose-response may also have been random. These inferences, or that the exposure index was unrelated to actual exposure, together with the acknowledged limitations of the exposure index, indicate that estimated exposure may only be weakly relied upon to assert a causal relationship. Based upon the current exposure index calculations, either of the above inferential alternatives is possible.

The use of serum dioxin levels (see Chapter 23, Future Directions) in the next report will clarify the exposure calculations of this report and the Baseline Report. Thus, from an interpretive context, final conclusions on dose-response, and the implications to herbicide causation are based on current knowledge available for this report. These conclusions could change with future analyses using a factual exposure concept.

TYPES OF MEASUREMENTS

This report includes all types of measures traditionally used in morbidity followup epidemiologic studies, e.g., self-reports, structured interview responses, medical record data, physician findings, scalar measurements, biopsy results, laboratory determinations, morbidity indices, and mortality results. At many points in this report, various terms have been used to qualitatively describe the data and analyses arising from the measurement processes. In particular, the terms "subjective," "objective," "continuous," and "categorical," and "constructed indices" have been used to connote differences in data or data sets that are important in making statements of inference.

From the perspective of the Study Protocol, significant group differences for subjective historical variables, not mirrored by significant group differences in medical record findings or physician/laboratory testing, may be viewed as preliminary evidence of over-reporting by a group. The opposite finding of significant group differences for physical examination variables in the absence of reported symptoms may support the primary conclusion of significant subclinical group differences. Either of these alternatives may greatly affect an overall inference of herbicide causality. Hence, the descriptive phrases "subjective data" and "objective data" have not been used as value judgments of the worth of the data, but simply as inferential qualifiers.

This report contains numerous comments on the differences in results between analyses of continuous versus categorical data from the same variable (exclusively laboratory data). Because the statistical power is stronger for detecting mean shifts than categorical differences, it was anticipated that very small mean shifts might be more easily discerned than differences in proportions of abnormalities between the two groups. Both methods of examining the data reveal important aspects of the distribution. Inferentially, when both types of analyses were done, greater weight has been given to significant group differences when analyses of both data forms agree. Lesser weight was given to significant differences seen in only one analysis, and least weight to significant shifts in means if both group means were within normal range, and the mean difference was not supported by other statistical findings in related variables (e.g., hepatic test battery). Consistent patterns of findings within an organ system, or between related organ systems, is required to strongly suggest an inference of causality.

Several summary indices were constructed in this report, e.g., dermatology index, cranial nerve function index, and anatomic categories of abnormal peripheral pulses, and are similar to some indices in the 1984 Baseline Report. They were formed by summing or grouping related abnormalities for the purposes of assessing increased numbers and/or showing group directionality of overall results. They should not be strongly considered in final inferences because they are artificially derived.

BASELINE-FOLLOWUP EXAMINATION DIFFERENCES

A common difficulty of followup studies is the inherent variation in measurement systems from one observation period to the next. To the maximum extent possible, the USAF has restricted clinical variation by requiring the use of identical laboratory equipment for most clinical chemistries, by the

use of 50 samples from the Baseline serum bank to evaluate interexamination laboratory differences, and by the use of carefully prescribed written clinical procedures that allow little room for variation. Nonetheless, some interexamination variability must be expected, but in the presence of blindness to group membership, there is no reason to expect biases in the results with respect to either the Ranch Hand or Comparison groups.

This report has cited classical longitudinal analyses to assess changes in variables between the examinations by group. Of 21 variables examined, 5 showed statistically significant group differences in the changes between examinations. Four of these significant results were attributed to actual changes over time, while the other (e.g., sedimentation rate) was believed due to a change in laboratory methodology.

Other less refined longitudinal contrasts consisting of narrative discussions of Baseline results versus followup results have been presented in all chapters. Interpretive caution is required in assessing examination similarities or differences because of the slight changes in cohort composition between the examinations (see Chapter 2, Population), the use of slightly different statistical models and modeling strategy (see Chapter 7, Statistical Methods), and sometimes the use of the Original Comparison group. The relative contribution of these changes was not explored mathematically, but is believed to have played a minimal role in accounting for any large group shifts between examinations.

In the context of comparing results between examinations, there has been a subtle but consistent observation that group differences have substantially narrowed over the 3-year period, either by decreased findings in the Ranch Hands, increased findings in the Comparisons, or a combination of both mechanisms. In general, several broad interpretations are possible: any bona fide herbicide effect decreases over time, that the convergence is largely attributable to unquantifiable factors, that both examinations have produced chance results, or that these observations have been affected by the slight shifts in cohort composition and modeling strategy.

Several segments of this report have noted marked differences in the prevalence rates of abnormalities found at the Baseline and followup specialty examinations, e.g., the dermatology and neurology clinical assessments. The followup dermatological examination detected substantially more abnormalities than the Baseline examination, whereas far greater numbers of neurological abnormalities were noted at the Baseline examination than at the followup for some variables. These examination variances were affected by differences in "clinical sensitivity" between the examining teams, although clearly other factors (such as a true change in disease-abnormality status or slight cohort differences) contributed. The phrase "clinical sensitivity" refers to the inherent differences in clinical styles and interpretations of possible abnormalities that often prevail. Because of examiner blindness to exposure status, and because of the judgment that the interexamination variation was within the artful bounds of accepted medical practice, no bias was thought to have resulted from this inherent variation.

STUDY BIASES

Each reviewer of this report must reach a conclusion on whether the results of this study have been seriously flawed by the design, the operation

of significant biases, or both. The Protocol authors believe that the comprehensive multifaceted design is the chief strength of this study, although it is recognized that each and every published phase of the study must invite renewed inspection of fundamental scientific aspects of the study design.

It is believed that, with the exception of skin test readings, all data in this study were collected accurately and validly, and that blindness to group membership was well maintained throughout the collection process. This opinion is important from an inferential perspective in that both misclassification of data (tending to dilute true group differences) and bias in data (creating a false group effect) most likely did not occur appreciably in this study. Thus, it is believed that both the magnitude and direction of the group results found in this study reflect truth to the maximum degree possible, within the inherent boundaries of statistical models to account for all important adjusting variables.

GROUP INTERACTIONS: PATTERN RECOGNITION

Many of the adjusted analyses in this report have demonstrated significant group-by-covariate interactions, requiring stratified analyses to determine the nature of significant group differences. All significant two- and three-factor interactions have been included in the main text or in appendices. The analysis of followup data has found substantially more interactions than the analysis of Baseline data, due primarily to the larger number of covariates used in the followup analyses.

Several related viewpoints have aided in the overall interpretation of group-by-covariate interaction in the report. In the presence of a significant interaction, a direct conclusion on main group effects cannot be made, and the focal point of interpretation resides with the covariate stratum containing the significant group effect (or a reversal in nonsignificant group effects across strata). Past this point, however, there appears to be little consensus in how to best place the interaction into inferential context. Further interpretations appear to be largely individualistic.

No consistent pattern has emerged to support a finding of impairment in the Ranch Hands for any specific stratum of one or more covariates. In fact, of all the two- and three-factor interactions encountered, only one was thought to have possible biologic relevance. Other interactions may have such relevance, but the reason was not apparent. As with tests of group differences, significant interactions may occur by chance, but the method to calculate an expected number of group-by-covariate interactions, unfortunately, remains an open research question.

Because of the possible diverse interpretations of interactions, all significant two- and three-factor interactions involving group with statistically significant strata are presented in Table 21-2 for detailed inspection. No particular covariate or group pattern is noted, although the variables in psychology and gastrointestinal showed Ranch Hands at a relative detriment, while the interactions in the cardiovascular chapter indicated detrimental findings in the Comparisons.

Most variables without interactions in this report have shown remarkable concordance between unadjusted and adjusted results, both in terms of absolute value of relative risk and of statistical significance.

TABLE 21-2.

Summary of Significant Covariate Strata (or Covariate Level Difference) Found Within Significant Two- and Three-Factor Group-by-Covariate Interactions by Clinical Chapter and Dependent Variable (Group Direction and p-Value)

Clinical Chapter	Dependent Variable	Covariate Stratum	RH>C	C>RH	p-Value
General Health	Self-Perception of Health	Enlisted Groundcrew	*		0.003
Malignancy	Basal Cell Carcinoma (Verified Interval)	Enlisted Flyer	*		0.019
	Systemic Cancer (Verified plus Suspected, Interval)	Enlisted Flyer	*		0.042
	Basal Cell Carcinoma (Verified plus Suspected, Lifetime)	Intermediate Skin Reaction to Sun	*		0.038
	Systemic Cancers (Verified, Lifetime)	Enlisted Flyer	*		0.019
	Systemic Cancer (Verified plus Suspected, Lifetime)	Enlisted Flyer	*		0.004
Neurology	Pin Prick	Impaired (Diabetic Class)		*	0.021
Psychology	Paranoia	Born Before 1942	*		0.027
	Schizophrenia	High School	*		0.033
	Social Introversion	Combat Index--Low	*		0.002
	Validity	Black		*	0.038
	Total CMI	High School	*		<0.001
Gastrointestinal	SGOT	1-4 Drinks per Day	*		0.010
	Alkaline Phosphatase	Exposed to Ind. Chems.	*		<0.001
	Direct Bilirubin	Exposed to Ind. Chems.	*		0.035
	Triglycerides (cont.)	Born In or Before 1922	*		0.039
	Triglycerides (disc.)	Officer	*		0.035
	Uroporphyrins	BUN≤14		*	<0.001

TABLE 21-2. (continued)

Summary of Significant Covariate Strata (or Covariate Level Difference)
Found Within Significant Two- and Three-Factor Group-by-Covariate Interactions
by Clinical Chapter and Dependent Variable
(Group Direction and p-Value)

Clinical Chapter	Dependent Variable	Covariate Stratum	RH>C*	C>RH	p-Value
Dermatology	Dermatology Index	Pre-SEA Acne: 1 vs. 0		*	0.004
Cardiovascular	Systolic Blood Pressure	Black/53 Yrs Old		*	0.006
	ECG (Overall)	0 Pack-years		*	0.038
	ECG (Arrhythmia)	7 Pack-years/10% Body Fat		*	0.018
	Posterior Pulses (Manual)	Enlisted Flyer	*		0.032
	Leg Pulses (Manual)	Officer/21% Body Fat		*	0.026
	Peripheral Pulses (Manual)	Officer		*	0.030
Hematology	WBC	Nonblack/30 Pack-years/ 35 Yrs Old	*		<0.001
	WBC	Black/Officer/35 Yrs Old		*	0.003
	WBC	Black/EFL/35 Yrs Old		*	0.050
	PLT	Nonblack/30 Pack-years and 1 pack/day	*		0.014
	PLT	Black/30 Pack-years and 1 pack/day	*		0.007
Renal	Urinary Protein	Normal (Diabetic Class)	*		0.018
	Urinary WBC	Nonblack/Born In or After 1942	*		0.001
	BUN	Black		*	0.017
	Urine Specific Gravity	Nonblack/Enlisted Groundcrew	*		<0.001
Endocrinology	Testosterone	<10% Body Fat		*	0.012
	Testosterone	10-25% Body Fat	*		0.023
	Differential Cortisol	Black/Born In or After 1942		*	0.003

TABLE 21-2. (continued)

Summary of Significant Covariate Strata (or Covariate Level Difference)
Found Within Significant Two- and Three-Factor Group-by-Covariate Interactions
by Clinical Chapter and Dependent Variable
(Group Direction and p-Value)

Clinical Chapter	Dependent Variable	Covariate Stratum	RH>C*	C>RH	p-Value
Immunology	Total T Cells	Black		*	0.039
	B Cells	Nonblack/0 Pack-years		*	0.004
	Monocytes	Enlisted Groundcrew/ 4 Drinks/Day	*		0.003
Pulmonary	Pleurisy	1-10 Pack-years	*		<0.001
	Tuberculosis	1-10 Pack-years	*		0.020
	X-ray	0 Pack-years		*	0.030
	Total Interactions: 43		26	17	

*Relative risk greater than one, or Ranch Hand mean greater than Comparison mean.

CLASSICAL COVARIATES

Many of the dependent variables in this report are known to be significantly affected by risk factors also measured in this study. The use of these covariates in the adjusted analyses has served to clarify Ranch Hand-Comparison group differences in the presence of significant covariate group differences. Such adjustments, whether by a single covariate, multiple covariates, or covariate interactions, have given results on group differences generally quite similar to the unadjusted analyses both in terms of relative risk and statistical signficance. In fact, in only one instance in this report has an unadjusted result of $p \geq 0.10$ changed to a value of $p \leq 0.05$ in the adjusted analysis. The covariates used in this study were not effect modifiers (which may be synergistic with exposure and also be equally distributed between groups). Consistent effects were observed for almost all of the classical covariates of age, race, occupation, education, alcohol, smoking, percent body fat, and glucose tolerance. In only a few instances were unexpected effects noted, e.g., personality type, wine consumption, and a few smoking and alcohol "inversions."

The overall covariate effects observed in this study indeed reflect the mainstream of results found in well-conducted epidemiologic studies, and lend credence to the validity of the clinical endpoints and covariate values in this report.

MULTIPLE COMPARISONS

As noted in Chapter 7, Statistical Methods, the problem of multiple comparisons is complex and not easily adjudicated because of the total number of statistical tests, the number of tests performed on each dependent variable, and the biologic relatedness of many of the variables. A conscious effort has been made to expand inferential interest to borderline group associations ($0.05 < p \leq 0.10$) thereby increasing the probability of the acceptance of a false association. Each chapter summary has carefully flagged all borderline associations to provide expanded summary statements for possible inclusion in deriving final conclusions. Additional confidence in the final acceptance or rejection of an overall herbicide effect would be warranted if the majority of borderline associations were in the same consistent direction as the significant associations.

Multiple analyses on the same variable have been conducted in this report. Continuous and categorical data have been subjected to both unadjusted and adjusted analyses, and multiple adjusted analyses were sometimes conducted with different covariates or slightly different covariate sets. The question arises as to which results best reflect the truth when different results are found. In general, the following approach has been followed: the statistical significance of both continuous and categorical analyses is convincing, while significance for only the continuous analysis must be viewed in terms of the biologic relevance of the mean shift detected.

Overall, the multiple comparison issue is due to repeated hypothesis testing for group, exposure, and interaction strata differences. The calculation of expected numbers of significant associations for these tests is difficult (if not impossible) because of the relatedness of the dependent variables, the relatedness of the covariates, and the often difficult analytic decisions that arise in a "step-down, best model" strategy. Thus,

the final assessment of whether the frequency of significant associations does not meet, or exceeds expectation, must remain an interpretive judgment of each reader.

CAUSALITY

The AFHS is an inferential assessment of observed group differences. The inference of herbicide causality will be determined by a balanced judgment of the following factors: biological plausibility, consistency, specificity, coherence, time relationships, and strength of association. Except for aspects of association strength, most of these causality factors have been discussed in the preceding sections of this chapter. Nearly every statistically significant group difference in this report has only been of moderate to weak strength. Highly significant p-values ($p<0.001$) were not found for main group associations, but were observed for covariate tests. A few strata in the group interactions were highly significant. Most of the statistically significant estimated relative risks were below the value of 2.0 (a traditional boundary of interest in epidemiology). The few relative risks above 2.0 generally had very wide confidence intervals due to low proportions of detected abnormalities. Weakly significant associations, in particular, are cause to reassess the element of chance and the possible presence of other causality factors before a final conclusion of cause and effect is determined.

CHAPTER 22

CONCLUSIONS

INTRODUCTION

This chapter summarizes the conclusions drawn from the statistical analyses that have been conducted on the Air Force Health Study data base. The followup study, which began in 1985, was the logical extension of the 1982 Baseline study, building upon the strengths of the Baseline study and utilizing the data collected at both the Baseline and the followup. The high level of Government support and outstanding participation of the study subjects that characterized the Baseline study were maintained through this first followup.

STUDY PERFORMANCE ASPECTS

Of the living Baseline study participants, 99.2 percent were located and asked to participate in the followup. Participation in the followup physical examination and questionnaire was very high. Of the fully compliant Baseline participants, 971 of the 1,045 Ranch Hands (92.9%) and 1,139 of the 1,224 Comparisons (93.1%) participated in the followup. Thus, there was no group difference in compliance of the Baseline participants at the followup. Overall, the 2,309 participants in the followup (1,016 Ranch Hands and 1,293 Comparisons) represented a loss of 159 individuals and a gain of 199 since Baseline. One percent of the fully compliant Baseline population died between 1982 and the 1985 followup examination.

The bias/compliance analyses suggested that there had been no change between Baseline and the followup in the way replacements volunteered for entry into the study, and that no additional bias had been introduced at the followup due to scheduling differences. Although replacements were not health-matched at Baseline as they were at the followup, they were similar to refusals with respect to reported health, medication use, and income level. The results supported the use of the total Comparison group in the main analyses presented in this report.

POPULATION CHARACTERISTICS

Overall, the Ranch Hands and Comparisons reported similar social and behavioral characteristics. No significant differences were found in age, educational background, religious preference, current military status, and income level. Significantly more Ranch Hands smoked cigarettes at the time of the followup examination than did Comparisons, but there was no significant difference between groups on past cigarette, cigar, and pipe use and on recent and past use of marijuana. A much higher percentage of participants

reported past marijuana use at the followup than at Baseline. This difference was most likely due to a greater level of confidentiality afforded by the questionnaire technique. Risk taking behavior, assessed by questions on potentially dangerous recreational activities, revealed borderline significance. Slightly more Comparisons were scuba divers and more Ranch Hands raced motor vehicles. The difference in scuba diving was also significant at Baseline.

Patterns of Results

Both the chapter conclusions and the final conclusions of this report have been predicated upon concepts of consistency, specificity, coherence, strength, and plausibility as they apply to the interpretation of group differences. In particular, careful consideration has been given to a variety of data and patterns of results that have emerged from the clinical evaluations. Specifically, there were few differences in the proportions of abnormalities between groups; the positive associations have not aggregated in the clinical areas of prime dioxin concern, nor have they been of serious clinical importance; the unadjusted results have been remarkably concordant with the adjusted results, both in terms of relative risk and p value; the analyses using the Original Comparison set have largely mirrored the results found with the total Comparison group; many of the group differences noted at Baseline have disappeared at the followup examination, and only a few new associations have emerged; almost all of the covariates have acted as expected in the adjusted analyses; and the exposure index analyses and the group-by-covariate interactions have not demonstrated biological patterns of concern and appeared to be more likely due to chance than not. Due to the acknowledged limitations of the exposure index used in this report (and considering the potential use of dioxin body burden levels at the next followup), dose-response relationships have not been emphasized in reaching final conclusions.

The overall pattern of these findings indicates that this followup study cannot be viewed as alarming from the traditional perspectives of clinical medicine or epidemiology. This study, in fact, demonstrates similarity in current health status between the Ranch Hand and Comparison groups.

CLINICAL ASPECTS

General Health

The nonspecific assessment of general health showed relatively close similarity between the two groups. Ranch Hands rated their health as fair or poor more frequently, but this difference was found only in the enlisted groundcrew and not in the officers nor enlisted flyers. The perception of health in both groups had improved since Baseline. Physician-rated appearance of relative age was not found to be significantly different at the followup in contrast to the Baseline finding that a higher percent of Ranch Hands than Comparisons looked younger than their stated age. The categorical analysis of sedimentation rate showed that the Ranch Hands had more abnormalities than the Comparisons. These results were not supported by the continuous analysis of mean sedimentation rates and were opposite to the

Baseline results, which showed that younger Comparisons had elevated sedimentation rates. The categorical analysis of percent body fat showed no significant differences between the two groups, which was consistent with Baseline. However, the continuous analysis found that the Ranch Hands had a significantly lower mean percent body fat using age, race, and occupation as covariates. The detailed exposure analyses revealed no consistent exposure effects, and this result was consistent with the Baseline analysis. No longitudinal difference was found on perception of health. A significant group difference was found over time for the longitudinal analysis of sedimentation rate due to the change in the findings between the two examinations, possibly related to a change in laboratory methodology.

Malignancy

Skin and systemic cancers, both suspected and verified by medical records, showed no significant group differences for the Baseline-followup interval (1982-1985). However, for all neoplasms combined (malignant, benign, and uncertain), a borderline significant excess in the Ranch Hand group was noted in an unadjusted analysis. The analyses of interval cancers revealed group interactions for verified and verified plus suspected basal cell carcinoma and verified plus suspected systemic cancers. Nonsignificant findings were observed for verified and verified plus suspected sun exposure-related cancers. Verified systemic cancers did not differ significantly between groups.

The analyses of lifetime cancer found significant results for verified basal cell carcinoma and verified sun exposure-related skin cancers. Group interactions were noted for systemic cancer categories and for verified plus suspected basal cell carcinoma. The higher rate of basal cell carcinoma in the Ranch Hands versus the Comparisons found at Baseline was nonsignificant for the followup interval, but due to the effect of the larger number of Baseline cases and the significant confounding of average residential latitude, the adjusted analysis of lifetime basal cell carcinoma emerged as statistically significant.

There were several disparities in the distribution of testicular, colon, and smoking-related tumors in the groups. Further, one case of soft tissue sarcoma and one possible lymphoma (both in Ranch Hands) were diagnosed in the interval, balancing the two similar cases found in the Comparison group at Baseline. Considering that the systemic cancer curves are in their early stages for both groups, with perhaps insufficient latency, the cancer results of the followup examination should not be viewed as disturbing, but as cause for continued monitoring.

Neurological Assessment

None of the 27 neurological variables demonstrated a significant group difference, although several variables had relative risks which were greater than one. There was no group difference in reported neurological illnesses for the interval or for a lifetime history. Of the cranial nerve variables, speech and tongue position were marginally significant, with the Ranch Hands at a slight detriment. The analyses of peripheral nerve function showed no significant differences between the Ranch Hands and the Comparisons. In the analysis of central nervous system function, hand tremor was found to be of borderline significance, with the Ranch Hands faring slightly worse than the Comparisons. A borderline significant group interaction (Ranch Hand hand tremor by insecticide exposure) may have had biological and operational

significance. Overall, substantially fewer neurological abnormalities were detected at the followup examination than at the Baseline examination. The exposure analyses showed only occasional statistically significant results, although no consistent pattern with increasing exposure was evident. In the longitudinal analysis of the Babinski reflex, a significant change over time was observed. This was due to a nonsignificant finding in the Ranch Hands at the followup, which differed from the significant adverse finding at Baseline. The covariates of age, alcohol history, and diabetes showed classical effects with many of the neurological measurements. Overall, the followup examination results were quite similar to the Baseline findings.

Psychological Assessment

The reported and verified data on lifetime psychological illnesses showed no significant differences between groups. Distributional tests of the 14 Minnesota Multiphasic Personality Inventory (MMPI) scales, stratified by occupation, revealed that only 2 of the 42 results approached significance. For the total Cornell Medical Index (CMI), separate distributional tests were conducted with stratification by age, race, occupation, education, and current drinking status; a significant difference was found for one statum of each of the covariates. In all cases, the mean of the Ranch Hand distribution was greater than the mean of the Comparisons. The analysis of the 14 MMPI scales showed that there was a significant difference between the two groups for denial and masculinity/femininity, with more abnormalities in the Comparisons than the Ranch Hands. The results of the analyses for hysteria were of borderline significance, with more abnormalities in the Ranch Hands. There were more abnormalities in the Ranch Hands than the Comparisons for social introversion, which was of borderline significance. Differences in the total CMI and A-H area subscore were found to be significant, with more abnormalities in the Ranch Hands. There was no significant difference between the two groups on the Halstead-Reitan Battery impairment index, a measure of the functional integrity of the CNS. The exposure index analyses did not reveal any pattern consistent with a dose-response relationship. As expected, the effects of age, educational level, and alcoholic history showed profound effects on many of the psychological measurements.

Gastrointestinal Assessment

Although the followup gastrointestinal assessment disclosed more statistically significant findings than the Baseline examination, the abnormalities were distributed equally between the two groups, and there was no clinical, statistical, or exposure pattern consistent with an herbicide-related effect on health. No historical or biochemical evidence was found to suggest an increased likelihood of porphyria cutanea tarda (PCT) in the Ranch Hand group. Only sparse and nonsignificant liver disorders were reported for the interval between Baseline and followup. Also, for the lifetime history of liver disorders, there were no significant differences between groups. Further, there were no significant group differences in reported lifetime peptic ulcer disease. A review of digestive system mortality showed a relative excess in the Ranch Hands but a relative lack of malignant neoplasms. The results of the physical examination showed a borderline increase of hepatomegaly in the Ranch Hand group. There was a significantly lower mean serum glutamic-pyruvic transminase (SGPT) level, a greater mean alkaline phosphatase level, and a lower mean uroporphyrin level in the Ranch

Hand group. The analysis of coproporphyrin was of borderline significance, with the mean of the Ranch Hands in excess of the mean of the Comparisons. No group differences were found for serum glutamic-oxaloacetic transminase (SGOT), gamma-glutamyl transpeptidase (GGTP), total and direct bilirubin, lactic dehydrogenase (LDH), cholesterol, or triglycerides. The numerous group-by-covariate interactions did not disclose any consistent subgroup patterns detrimental to the Ranch Hands. These findings were generally consistent with the results of the 1982 assessment. The longitudinal analyses for SGOT, SGPT, and GGTP showed no significant differences between results by group over time.

Dermatological Evaluation

No significant group differences were identified in the dermatological evaluation. None of the questionnaire data showed an increased likelihood of past chloracne, as determined by anatomic patterns of acne, and no cases were diagnosed in the physical examination. Analyses were conducted on six dermatologic disorders (comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation) and on a composite variable of 16 other minor conditions (the latter not generally associated with chloracne). Exposure index analyses did not reveal consistent patterns suggestive of a dose-response relationship. The longitudinal analysis, based on a composite dermatology index, showed no significant differences between the results over time. Substantially more dermatologic abnormalities were detected at the followup examination than at the Baseline examination. In general, however, the followup results were consistent with the findings at Baseline.

Cardiovascular Evaluation

Overall there was general similarity in the cardiovascular health of the Ranch Hands and the Comparisons. Of the 27 cardiovascular variables, there was a significant difference for only one, verified heart disease, with an excess in the Ranch Hand group. This finding was largely unsupported by other cardiac measurements. The cardiovascular assessment was based on reported and verified heart disease; the measurement of central cardiac function by systolic blood pressure, abnormal heart sounds, and ECG findings; and the evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Doppler recordings of five peripheral pulses were similar in both groups, a finding which was in marked contrast to the Baseline examination that found significant pulse deficits in the Ranch Hand group. This change was most likely due to a required 4-hour abstinence from tobacco prior to the pulse measurements. Overall, the exposure analyses were unsupportive of any meaningful dose-response relationship. The longitudinal analyses confirmed the change in pulse abnormalities in the Ranch Hand group over time, but showed no significant group change in overall ECG findings between the examinations.

Hematological Evaluation

The hematological evaluation found that neither group manifested an impairment of the hematopoietic system, consistent with similar findings at

the Baseline. The evaluation was based on eight peripheral blood variables: red blood cells (RBC), white blood cells (WBC), hemoglobin (HGB), hematocrit concentration (HCT), corpuscular volume (MCV), corpuscular hemoglobin (MCH), corpuscular hemoglobin concentration (MCHC), and platelet count (PLT). Both the discrete and categorical analyses revealed no significant group differences. The covariate effects of age, race, occupation, and smoking history were highly significant for many of the variables. Two group-by-covariate interactions in the analyses of mean differences did not appear to have a meaningful interpretation. The exposure index analyses did not support any plausible dose-response relationship. The longitudinal analyses of MCV, MCH, and PLT found significant differences only for PLT between the Baseline and the followup, with the Ranch Hands exhibiting a slight decline in mean level from Baseline and the Comparisons showing an opposite change.

Renal Assessment

None of the six renal variables of reported kidney disease, urine protein, occult blood, urine white blood cell count, blood urea nitrogen, and urine specific gravity showed a significant difference between the two groups based on the unadjusted analyses. In the adjusted analyses of the laboratory variables, however, there were significant group-by-covariate interactions that did not yield a consistent pattern to suggest a renal detriment to either group. The finding of group equivalence for past kidney disease was in contrast to the Baseline examination, which found significantly more reported disease in the Ranch Hand group. The difference in findings is more likely due to a change in questionnaire wording than to a true change in renal health. Like the Baseline findings, the exposure index analyses showed very little evidence of a dose-response relationship. In the longitudinal analyses of blood urea nitrogen, there was no significant group difference in the change between the examinations.

Endocrine Assessment

In general, the endocrine health status of the Ranch Hands and the Comparisons was reasonably comparable. The examination found no significant differences between the two groups for past thyroid disease, or thyroid and testicular abnormalities determined by palpation. In the analyses of the seven laboratory values (T_3 % Uptake; thyroid stimulating hormone [TSH]; testosterone; initial, second, and differential cortisol; and postprandial glucose), significant differences were found for TSH and testosterone, with higher mean levels in the Ranch Hands. These analyses were not supported by the categorical analyses. The thyroid test results were conflicting with respect to an assertion of hypothyroidism in the Ranch Hands (a possible dioxin effect). Mean levels of testosterone were significantly elevated in the Ranch Hand group as contrasted with the Comparisons in the 10-25 percent body fat category. The effects of personality score and percent body fat on the differential cortisol levels were not fully expected. Although tests of 2-hour postprandial mean values showed no significant group differences, comparable categorical tests revealed that significantly fewer Ranch Hands had impaired glucose levels, but conversely, had more (nonsignificant) diabetic levels of glucose. Analyses of the composite diabetes indicator (history plus 2-hour postprandial results) did not disclose significant group differences. The exposure index analyses suggested that the enlisted flyers in the medium exposure level were significantly different from those in the

low exposure level for differential cortisol, postprandial glucose, and testosterone. The corresponding high to low contrasts were not significant. The longitudinal analyses were based on T_3 % Uptake, TSH, and testosterone, and revealed only symmetrical and nonsignificant changes in the Ranch Hand and Comparison groups over the time interval.

Immunological Evaluation

Overall, there were no significant group differences or any indication of impaired immunological competence in either group based on comprehensive cell surface marker and functional stimulation studies. Six cell surface markers (total T cells, helper T cells, suppressor T cells, B cells, monocytes, HLA-DR cells, and a constructed helper/suppressor ratio variable) and three functional stimulation studies (PHA, pokeweed, and mixed lymphocyte culture) were conducted on 47 percent of the study population. No significant differences were revealed for five of these variables. In the analyses of the other five variables, there were significant group-by-covariate interactions, but no discernible pattern was identified to suggest a detriment in any subgroup of either group. Skin test assessments of delayed hypersensitivity were characterized by inter-reader variation and shifting diagnostic criteria for anergy. The skin test data were judged invalid and were not subjected to statistical testing for group differences. No consistent pattern of immunological deficits could be associated with increasing levels of herbicide exposure in the Ranch Hand group.

Pulmonary Disease

The pulmonary assessment did not reveal any statistically significant differences between the Ranch Hand and Comparison groups that were suggestive of an herbicide-related disease. The analyses consisted of group assessments of respiratory disease incidence, physical examination abnormalities, and the current prevalence of x-ray abnormalities. There were no significant differences between the Ranch Hands and Comparisons for history of asthma, bronchitis, pneumonia, or for six of seven clinical variables (excluding rales) determined by x-ray or auscultation. Analyses of history of pleurisy, history of tuberculosis, and rales showed significant but inconsistent group-by-covariate interactions. These findings did not indicate any patterns suggesting a different disease experience in the two groups. The exposure index analyses did not reveal any consistent pattern suggestive of an increasing dose response.

CONCLUSION

The results of the first followup study in 1985 have shown a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the Baseline Study in 1982. The 1985 examination results provide reassuring evidence that the current state of health of the Ranch Hand participants is unrelated to herbicide exposure in Vietnam. Continued close medical surveillance of these military populations is strongly indicated. This followup report concludes that there is not sufficient plausible or consistent scientific evidence at this time to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group.

CHAPTER 23

FUTURE DIRECTIONS

The scope and complexity of the AFHS has required gradual refinement and correction to meet the challenges of changing technology and scientific direction, and to ensure continued participation of all enrolled members. This chapter outlines some of the changes incorporated in the fifth-year followup examination and identifies several areas of future work expected to significantly augment the study.

FIFTH-YEAR FOLLOWUP EXAMINATION

Since the fifth-year followup examination was initiated prior to the full analysis of the data from the third-year examination, most modifications were founded upon quality control issues and the desire to make the clinical content of the examination more responsive to the medical needs of the participants.

Clinical quality control enhancements were made to improve measurement techniques. The digit preference noted in systolic and diastolic blood pressure readings led to the use of automated blood pressure recording; all other parameters of the blood pressure readings (e.g., sitting position, three recordings, nondominant arm at heart level) were not changed.

The problem in skin test reading was met by a rigorous quality control plan that included the following elements: refresher training for readers; a required reading of the four skin tests of all participants by both readers, each blind to the results of the other; a required reread of 10 percent of all tests by each of the readers, each blind to the previous reading; and a required weekly report citing numbers and proportions of participants with possible anergy, reversal of induration-erythema measurements, and untoward skin reactions or other reading problems (e.g., participant refusal).

In addition, new skin test forms were developed to facilitate accurate recording and transcription; specific clinical criteria were formulated to require consultation by an allergist; and the skin test measurement criterion for possible anergy, consistent with current World Health Organization guidelines, was adopted for the clinical interpretation of all skin test readings. It is anticipated that this clinical quality control program will standardize both readings and interpretations, and will produce a uniformly superior data set.

EXPOSURE INDEX REFINEMENTS

Since the development of the Study Protocol and the analysis of the 1982 Baseline data, there has been concern among some scientists and the principal

investigators over the accuracy and validity of the exposure estimates. It is unclear whether statistically significant differences in some variables between the Ranch Hand and Comparison groups, unsupported by dose-response estimates, have been due to chance, or whether true differences are obscured by an inadequate exposure index or group misclassification.

In mid-1986, strong correlations between dioxin levels in fat tissue and serum were demonstrated by the CDC and other institutions. Because of these results, the Air Force is currently engaged in a collaborative study with CDC to determine whether serum dioxin levels vary significantly in the Ranch Hand population. Approximately 200 AFHS volunteers have supplied a pint of blood to be analyzed for dioxin at the CDC laboratories. If clear and meaningful exposure findings are evident from this study, several additional studies are feasible: testing can be expanded to the entire study population and a meaningful exposure index based on total current TCDD body burden may be developed; and by means of archived AFHS serum samples from the Baseline study, it may be possible to calculate a reasonably precise half-life of TCDD in humans. These expanded studies will allow the estimation of body burdens of TCDD at the time of departure from SEA (assuming the absence of intervening vocational and recreational exposures).

If, in fact, these potential studies become reality within the next 2 years, the fifth-year followup study data will be statistically analyzed using a more appropriate exposure index. In anticipation of this advance, the AFHS is currently collecting 280 to 350 ml of blood from all volunteers attending the fifth-year followup study.

ADDITIONAL ANALYSES AND STUDIES

As in the 1984 Baseline Report, not all of the measured dependent variables were subjected to statistical analysis (e.g., prothrombin, leutinizing hormone, follicle stimulating hormone), largely because they were not within the bounds of the Air Force-prescribed analyses. Exploration of many of the unanalyzed variables is contemplated as time and resources permit. Similarly, many analytic opportunities to define possible symptom-clinical sign clusters or syndromes by multivariate analysis of variance techniques were passed over due to time and charter. Particularly challenging as an area of future work may be the changing relationships of some immunological variables over time and the biological impact of these changes on the induction of diseases such as cancer. Likewise, future efforts to define shifting cardiovascular disease patterns are a logical extension of the rich longitudinal data base of the AFHS. Such efforts await future analysis and publication.

The assessment of possible selection and participation bias has been addressed in a comprehensive manner in this report (see Chapter 5). The analyses and discussion suggest that statistical use of the total Comparison group (versus the Original Comparison group) is justified in this report, and that the impact of selection and participation biases have been minimal. As the followup studies continue, it is anticipated that a wealth of data on

compliance-participation factors will be available for continued comprehensive bias analyses. In particular, it is hoped that more complete data will exist to examine the true differences in current health status between refusals and their replacements. As the data set grows over time, the bias analyses will become more complex and will have to deal with changing motivations of the participants to continue in this study. Such bias analyses and assessments will always be of great importance to this study as they ultimately set the bounds for an inference on herbicide causality.